A Phase II Study of Pazopanib as Front-Line Therapy in Patients with Non-Resectable or Metastatic Soft Tissue Sarcomas Who Are Not Candidates for Chemotherapy

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Principal Investigator Signature Page

Principal Investigator:	Brian A. Van Tine, M.D., Ph.D.	
	Signature of Investigator	Date
	Printed Name of Investigator	
	By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/HRPO procedures, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.	

Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
BID	Bis in die (twice a day)
BP	Blood pressure
CBC	Complete blood count
CFR	Code of Federal Regulations
CMP	Comprehensive metabolic panel
CR	Complete response
CRF	Case report form
CST	Central standard time
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DBP	Diastolic blood pressure
DSMC	Data and Safety Monitoring Committee
DVT	Deep venous thrombosis
ECG (or EKG)	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
HRPO	Human Research Protection Office (IRB)
INR	International normalized ratio
IRB	Institutional Review Board
IULN	Institutional upper limit of normal
LFT	Liver function tests
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRP	Office of Human Research Protections
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetic
PR	Partial response
PT	Prothrombin time

QASMC	Quality Assurance and Safety Monitoring Committee
QD	Quaque die (every day)
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
SAE	Serious adverse event
SBP	Systolic blood pressure
SCC	Siteman Cancer Center
SD	Stable disease
TKI	Tyrosine kinase inhibitor
TSH	Thyroid stimulating hormone
UPC	Urine protein creatinine
UPN	Unique patient number
VEGF	Vascular endothelial growth factor
WUSM	Washington University School of Medicine

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1.0 BACKGROUND AND RATIONALE

1.1 Soft Tissue Sarcomas

Soft-tissue sarcomas make up approximately 1% of adult malignancies and encompass approximately 70 different histologic subtypes [1]. Most of these tumors are genetically complex and are highly unlikely to share a common mutation or alteration in signaling that would allow for treatment with an inhibitor to one molecule across all subtypes. Surgery is usually the first line of treatment in localized disease, while radiation or chemotherapy can be used in local disease that is unresectable due to size or location. Cytotoxic chemotherapy remains the standard of care for advanced and metastatic disease. Doxorubicin is the most active single agent with a response rate of approximately 20-25% [2]. In some instances, patients may not be a candidate for either one of these therapies based on age or other comorbidities leaving no viable treatment options. Prognosis is dismal in the metastatic setting with a median survival of less than 12 months even with therapy.

1.2 Pazopanib

Pazopanib is a multitargeted tyrosine kinase inhibitor that has been shown to have efficacy in sarcoma patients. Preclinical data has demonstrated comparable inhibitory effects of pazopanib against a number of targets including VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, and c-Kit [3]. In a phase II study published in JCO in 2009, Sleijfer et al. demonstrated that pazopanib is well-tolerated in patients with relapsed or refractory advanced soft-tissue sarcoma [4]. Further, there is data from a phase III study of pazopanib in previously treated metastatic soft tissue sarcoma patients which demonstrated a progression free survival of 4.6 months for pazopanib vs. 1.6 months for placebo. Overall survival in the pazopanib group was 12.5 months [5].

1.3 Rationale

Pazopanib is FDA approved as a second line and beyond treatment for metastatic soft tissue sarcoma. There is a population of elderly and debilitated soft tissue sarcoma patients that are not fit for standard first line chemotherapy that is doxorubicin based. As pazopanib is well tolerated with minimal side effects, we propose a phase II study to evaluate pazopanib as a first-line agent in patients with non-resectable or metastatic disease who are not candidates for cytotoxic chemotherapy.

1.4 Background of Correlative Studies

Sleijfer et al. recently published a translational study in which they evaluated whether cytokine levels in the patients enrolled in EORTC 62043, the phase II study of pazopanib in soft tissue sarcoma, correlated with PFS and OS. They measured levels of several cytokines at baseline and 12 weeks after beginning pazopanib therapy and demonstrated that baseline levels were not predictive, but that high sVEGFR2 and low PIGF were associated with a more favorable PFS at 12 weeks (OR 0.636, 95% CI 0.413-

0.977, P=0.039) and (OR 1.081, 95% CI 1.007-1.160, P=0.0318) respectively. There was also a trend toward high sVEGFR2 at week 12 and increased OS and a statistically significant association between low PIGF levels at week 12 and longer OS (HR 1.061, 95% CI 1.025-1.099, P=0.0009) [6].

We propose to measure sVEGFR2 and PIGF levels at baseline, 4 weeks, 8 weeks, and 12 weeks to both verify the results of Sleijfer et al and to determine if there is an even earlier correlation that can be detected between levels of these cytokines and PFS as well as OS which may allow us to better predict treatment response early on in therapy

In addition, plasma pazopanib concentrations will be determined immediately prior to the first dose of each dose escalation, then after steady-state is reached at 800 mg QD (after at least 10 days of 800 mg QD administration). These PKs will only be performed in the first 10-20 patients enrolled at Washington University.

2.0 OBJECTIVES

2.1 Primary Objective

To determine the clinical benefit rate (CR + PR + SD) in patients with soft tissue sarcoma not candidates for chemotherapy treated with first-line pazopanib at 16 weeks.

2.2 Secondary Objectives

1. To determine the rate of progression-free survival (PFS) in patients with soft tissue sarcoma not candidates for chemotherapy treated with first-line pazopanib.
2. To determine the rate of overall survival (OS) in patients with soft tissue sarcoma not candidates for chemotherapy treated with first-line pazopanib.
3. To evaluate the quality of life of patients with soft tissue sarcoma not candidates for chemotherapy treated with first-line pazopanib.
4. To correlate serum sVEGFR2 and PICG levels with outcomes.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Histologically confirmed diagnosis of nonresectable or metastatic soft tissue sarcoma. The following histologies are excluded: embryonal rhabdomyosarcoma, chondrosarcoma, osteosarcoma, Ewing tumors, primitive neuroectodermal tumors, gastrointestinal stromal tumors, dermatofibrosarcoma protuberans, inflammatory myofibroblastic sarcoma, and mixed mesodermal tumors of the uterus.

2. Evaluable disease by imaging or physical exam OR measurable disease defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan, as ≥ 20 mm by chest x-ray, or ≥ 10 mm with calipers by clinical exam.

3. Not a candidate for chemotherapy as determined by the treating physician.

4. Age ≥ 18 years

5. ECOG performance status ≤ 2 (see Appendix A).

6. Normal bone marrow and organ function as defined below:
   a. Absolute neutrophil count ≥ 1,500/mcl
   b. Platelets ≥ 100,000/mcl
   c. Hemoglobin ≥ 9.0 g/dL
   d. PT or INR ≤ 1.2 x IULN (if not receiving anticoagulation therapy)
   e. PTT ≤ 1.2 x IULN (if not receiving anticoagulation therapy)
   f. Total bilirubin ≤ 1.5 x IULN or ≤ 3.0 x IULN with normal AST and ALT in patients with Gilbert's disease
   g. AST(SGOT)/ALT(SGPT) ≤ 2.5 x IULN
   h. Creatinine ≤ 1.5 mg/dL OR creatinine clearance ≥ 30 mL/min/1.73 m^2 for patients with creatinine levels above 1.5 mg/dL
   i. UPC < 1 (in like units) or, if UPC ≥ 1, 24-hour urine protein < 1 g; use of urine dipstick for renal function assessment is not acceptable.

   Notes:
   Subjects may not have had a transfusion within 7 days of screening assessments.
   Concomitant elevation of bilirubin and AST/ALT above the IULN is not allowed.
   Patients receiving anticoagulation therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation.

7. Ability to swallow and retain oral tablets.

8. Women of childbearing potential must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

9. Ability to understand and willingness to sign an IRB approved written informed consent document.

3.2 Exclusion Criteria

1. Eligible for cytotoxic chemotherapy.

2. Prior systemic therapy for this type of sarcoma. Neoadjuvant or adjuvant therapy more than two years prior would not apply.

3. Prior treatment with any VEGFR tyrosine kinase inhibitor.

4. Administration of any non-oncologic investigational drug within 30 days or 5 half-lives (whichever is longer) prior to the first dose of pazopanib.

5. Use of a strong CYP3A4 inhibitor less than 14 days prior to initiation of study treatment (please refer to Section 5.2.5 and Appendix F).

6. A history of other malignancy ≤ 5 years previous with the exception of basal cell or squamous cell carcinoma of the skin which were treated with local resection only or carcinoma *in situ* of the cervix.

7. Known brain metastases.

8. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to pazopanib or other agents used in the study.

9. Any ongoing toxicity from prior anti-cancer therapy that is > grade 1 and/or that is progressing in severity (except alopecia).

10. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, uncontrolled seizure disorder, or psychiatric illness/social situations that would limit compliance with study requirements.

11. Corrected QT interval (QTc) > 480 msecs.

12. History of any one or more of the following cardiovascular conditions within the past 6 months: cardiac angioplasty or stenting, myocardial infarction, unstable angina pectoris, coronary artery bypass graft surgery, symptomatic peripheral vascular disease, class III or IV congestive heart failure as defined by the New York Heart Association (see Appendix B).

13. Poorly controlled hypertension (defined as systolic blood pressure of ≥ 140 mmHg or diastolic blood pressure of ≥ 90 mmHg). Note: initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. Following antihypertensive medication initiation or adjustment, blood pressure must be reassessed three times at approximately 2-minute intervals. At least 24 hours must have elapsed between antihypertensive medication initiation or adjustment and blood pressure measurement. These three values should be averaged to obtain the mean diastolic and systolic blood pressures, which must be < 140/90 mmHg in order for a patient to be eligible for the study.

14. Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding, including (but not limited to) active peptic ulcer disease, known intraluminal metastatic lesions 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 or intra-abdominal abscess within 28 days prior to beginning study treatment.

15. Clinically significant gastrointestinal abnormalities that may affect absorption of pazopanib, including (but not limited to) malabsorption syndrome or major resection of the stomach or small bowel.

16. History of cerebrovascular accident including transient ischemic attack, pulmonary embolism (PE) (including asymptomatic or previously treated PE), or untreated deep venous thrombosis within the past 6 months. Patients with DVT who are being treated with therapeutic anti-coagulating agents are eligible.

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

18. Evidence of active bleeding or bleeding diathesis.

19. Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels that increase the risk of pulmonary hemorrhage. Note: lesions infiltrating major pulmonary vessels (contiguous tumor and vessels) are excluded; however, the presence of a tumor that is touching but not infiltrating (abutting) the vessels is acceptable (CT with contrast is strongly recommended to evaluate such lesions). Large protruding endobronchial lesions in the mail or lobar bronchi are excluded; however, endobronchial lesions in the segmented bronchi are allowed. Lesions extensively infiltrating the main or lobar bronchi are excluded; however, minor infiltrations in the wall of thee bronchi are allowed.

20. Recent hemoptysis (≥ ½ teaspoon of red blood within 8 weeks before first dose of pazopanib).

21. Pregnant and/or breastfeeding. Patient must have a negative serum pregnancy test within 14 days of study entry.

22. Known HIV-positivity. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility by Washington University
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

Once the patient has been entered in the Siteman Cancer Center database, the WUSM coordinator will forward verification of enrollment and the UPN via email.

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below and scanning and emailing it to the research coordinator listed in the *Siteman Cancer Center Clinical Trials Core Protocol Procedures for Secondary Sites* packet at least one business day prior to registering patient:

1. Your name and contact information (telephone number, fax number, and email address)
2. Your site PI's name, the registering MD's name, and your institution name
3. Patient's race, sex, and DOB
4. Three letters (or two letters and a dash) for the patient's initials
5. Currently approved protocol version date
6. Copy of signed consent form (patient name may be blacked out)
7. Planned date of enrollment
8. Completed eligibility checklist, signed and dated by a member of the study team
9. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center Database

Registrations may be submitted Monday through Friday between 8am and 5pm CT. Urgent late afternoon or early morning enrollments should be planned in advance and coordinated with the Washington University research coordinator. Registration will be confirmed by the research coordinator or his/her delegate by email within one business day. Verification of eligibility and registration should be kept in the patient chart.

All patients at all sites must be registered through the Siteman Cancer Center database at Washington University.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. Patients will also be identified by first, middle, and last initials. If the patient has no middle initial, a dash will be used on the case report forms (CRFs). All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

5.1 Agent Administration

Pazopanib will be started at a dose of 200 mg BID for four days, then escalated to a dose of 400 mg BID for four days (if tolerated), then escalated once more to a dose of 800 mg QD for the duration of participation (if tolerated) or until dose reduction, if necessary. Pazopanib should be taken orally without food at least one hour before or two hours after a meal. One cycle of pazopanib is 28 days. 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 dose is missed, the subject should take the dose as soon as possible, but only if there are 12 or more hours remaining 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 vomiting occurs after taking pazopanib, the subject should not take a replacement dose for that dose, but should resume taking pazopanib at the next scheduled dose. If vomiting persists, the subject should be instructed to notify the investigator.

Please note that a Monday or Thursday start is recommended to avoid weekend blood draws for pharmacokinetic testing.

5.2 General Concomitant Medication and Supportive Care Guidelines

Patients should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates, when appropriate.

Anti-emetics (such as prochlorperazine, lorazepam, ondansetron or other 5-HT3 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. Although acetaminophen at doses of $\leq$ 2 g/day is permitted, it should be used with caution in subjects with impaired liver function.

5.2.1 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.

5.2.2 Hypoglycemic Therapy

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[31]. Such changes may require an adjustment in the dose of hypoglycemic and/or insulin therapy. Subjects should be advised to report symptoms of hypoglycemia (e.g., confusion, visual disturbances, palpitations, sweating). Serum glucose should be tested during treatment with pazopanib as outlined in the protocol and as clinically indicated.

5.2.3 Use of Statins

Concomitant use of pazopanib and simvastatin increases the risk of ALT elevations. If a patient receiving concomitant simvastatin develops ALT elevations, follow guidelines for pazopanib dose modification and discontinue simvastatin. Insufficient data are available to assess the risk of concomitant administration of alternative statins and pazopanib.

5.2.4 Medications that Raise Gastric pH

In a drug interaction trial in patients with solid tumors, concomitant administration of pazopanib with esomeprazole, a proton pump inhibitor, decreased the exposure of pazopanib by approximately 40% (AUC and Cmax). Therefore, concomitant use of pazopanib with drugs that raise gastric pH should be avoided. IF such drugs are needed, short-acting antacids such as Tums, Rolaids, Maalox, and Mylanta should be considered in place of proton pump inhibitors and H2 receptor antagonists. Separate antacid and pazopanib dosing by several hours to avoid a reduction in pazopanib exposure.

5.2.5 Medications to Use with Caution

In vitro data indicate that pazopanib is a potential inhibitor for CYP3A4, CP2C8,

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 should 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 Torsade de Pointes)
- Immune modulators: cyclosporine, tacrolimus, sirolimus (potential increased risk for nephrotoxicity and neurotoxicity)
- Miscellaneous: quetiapine, risperidone, clozapine, atomoxetine.

The results from *in vitro* studies suggested 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 should be used with **CAUTION**.

Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations. Co-administration of strong CYP3A4 inhibitors is prohibited (see Section 5.2.5); 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, carbamezepine, phenobarbital, oxcarbazepine
- HIV antivirals: efavirenz, nevirapine
- Antibiotics: rifampin (rifampicin), rifabutin, rifapentene
- Miscellaneous: St. John's Wort, modafinil, pioglitazone

5.2.6 Prohibited Medications

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 study. **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

Refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/

In vitro studies suggested that pazopanib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Therefore, absorption and subsequent elimination of pazopanib may be influenced by products that affect P-gp and BCRP.

Concomitant treatment with strong inhibitors of P-gp or BCRP should be avoided due to risk of increased exposure to pazopanib. Selection of alternative concomitant medicinal products with no or minimal potential to inhibit P-gp or BCRP should be considered.

5.3 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative serum pregnancy test within 14 days prior to the first dose of pazopanib.

Female patients are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for 28 days following the last dose of pazopanib.

If a patient is suspected to be pregnant, pazopanib should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient becomes pregnant during therapy or within 28 days after the last dose of pazopanib, the investigator must be notified in order to facilitate outcome follow-up.

5.4 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

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

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious non-compliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason other than withdrawal of consent will be followed as indicated in the study calendar.

5.5 Duration of Follow-up

After cessation of study treatment, patients will be followed every 3 months until death. Either phone contact or review of the Social Security Death Index is acceptable to monitor for overall survival. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

As a general rule, if dose reduction of pazopanib is necessary, the dose should be reduced stepwise by 200 mg at each step, and the patient should be monitored for approximately 10 to 14 days at each dose level. If toxicity does not abate during this monitoring time, the pazopanib may need to be interrupted and/or the dose further decreased with continued monitoring for an additional 10-14 days at each dose level, and so on.

If the toxicity has abated with reduction of the dose and dose re-escalation is considered safe by the investigator, the pazopanib dose can then be increased step-wise back to the pre-event dose (in 200 mg increments, after monitoring for 10-14 days at each dose level to ensure that toxicity did not recur or worsen).

Dose Modification Algorithms for Potential Treatment-Related Adverse Events

AE Terms & Descriptions	Dose Modification Algorithms
Hypertension	
(A). Asymptomatic and persistent SBP of ≥140-<170 mmHg, or DBP ≥90-<110 mmHg, or a clinically significant increase in DBP of 20 mmHg (but still below 110 mmHg).	Step 1. Continue pazopanib at the current dose. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[a] blood pressure (BP). If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
(B). Asymptomatic SBP ≥170 mmHg, or DBP ≥110 mmHg, or failure to achieve well-controlled BP within 2 weeks in scenario (A).	Step 1.Consider reducing or interrupting pazopanib, as clinically indicated. Step 2. Adjust current or initiate new antihypertensive medication. Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Step 4. Once BP is well-controlled, restart pazopanib dose-reduced by 200 mg if it was interrupted.
(C). Symptomatic hypertension or recurring SBP ≥170 mmHg, or DBP ≥110 mmHg, despite modification of antihypertensive medication(s)	Step 1. Interrupt pazopanib. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 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. Step 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.
Proteinuria	
UPC <3	Continue pazopanib at the current dose; monitor as clinically indicated
UPC ≥3 or 24-h urine protein ≥3g	Step 1. Interrupt pazopanib. Step 2. Weekly UPC or 24-hr urine protein monitoring until

AE Terms & Descriptions	Dose Modification Algorithms
	UPC is <3 or 24-hr urine protein is <3 g. Then restart pazopanib dose-reduced by 200 mg. Step 3. If UPC ≥3 or 24-h urine protein ≥3g recurs, repeat steps 1 and 2 Step 4. If UPC ≥3 or 24-hr urine protein ≥3 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 consider whether further treatment with pazopanib is appropriate. For other grade 1 hemorrhage/bleeding event, continue pazopanib at the current dose; monitor as clinically indicated.
Grade 2	Step 1. If pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue pazopanib and continue follow-up per protocol. Otherwise, interrupt pazopanib until the AE resolved to ≤ grade 1. Step 2. Restart pazopanib; consider reducing dose and monitor as clinically 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	Step 1. Interrupt pazopanib. Step 2. Initiate and monitor anticoagulation as clinically indicated. Step 3. Resume pazopanib at reduced 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 should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment. When treating with warfarin, international normalized ratio (INR) should 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	

AE Terms & Descriptions	Dose Modification Algorithms
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	Step 1. Interrupt pazopanib until toxicity resolves to ≤ grade 2. Step 2. Restart pazopanib dose-reduced by 200 mg and monitor as clinically indicated. If no recovery to ≤ grade 2 or recurrent grade 3 or 4 thrombocytopenia, discontinue pazopanib and follow-up per protocol
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)	Continue pazopanib with current dose.
Grade 2 Skin changes with pain; limiting instrumental activities of daily living (peeling, blisters, edema, bleed, hyperkeratosis)	Step 1. Hold pazopanib. Step 2. Treat as clinically appropriate. Step 3. Upon resolution to grade 1 or better, restart pazopanib with a dose reduction to 400 mg. Step 4. If recurrent, consider a further dose reduction to 200 mg or discontinuation.
Grade 3 Severe skin changes with pain and limiting self-care activities of daily living	Discontinue pazopanib
Other Clinically Significant Drug-Related Adverse Events[b]	
Grade 1	Continue pazopanib; monitor as clinically indicated.
Grade 2 or 3, if clinically significant	Step 1. Interrupt pazopanib until toxicity resolves to ≤ Grade 1. Step 2. Restart pazopanib dose-reduced by 200 mg and monitor as clinically indicated.
Grade 4	Discontinue pazopanib and continue follow-up per protocol. (study drug can be interrupted for up to 28 days)
Prolongation of QTc Interval: If the QTc is prolonged, the ECG should be manually read to ensure accuracy of the reading. The values below refer to manually-read ECGs.	
QTc ≥ 480-500 msec	Continue pazopanib; monitor as clinically indicated.
QTc ≥ 500 msec	Discontinue pazopanib and continue follow-up per protocol.

a. Well-controlled BP defined as SBP <140 mmHg and mean DBP <90 mmHg.

b. AEs are graded according to NCI Common Terminology Criteria for Adverse Events v4.0 (NCI CTCAE v4)

Guidelines for Management of Treatment Emergent Hepatotoxicity

Event	Dose Modification Algorithms
(A). ALT of ≤ 3.0 x ULN	Continue pazopanib at current dose with full panel LFTs[a] monitored as per protocol.
(B). ALT >3.0 x ULN to ≤8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[b] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	Step 1. Continue pazopanib at current dose levels. Step 2. Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT is reduced to grade 1.
(C). ALT >8.0 x ULN **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:** Step 1. Interrupt pazopanib until toxicity resolves to ≤ grade 1 or baseline. Report the event to Novartis as an SAE **within 24 hours** of learning of its occurrence. Make every reasonable attempt to have subjects return to the clinic within 24 to 72 hours for repeat liver chemistries and liver event follow up assessments. Step 2. Liver imaging and other laboratory investigations should be considered as clinically appropriate. Step 3. Monitor subject closely for clinical signs and symptoms; perform full panel LFTs [a] weekly or more frequently if clinically indicated until ALT is reduced to grade 1. Step 4. If the subject is benefiting from the study treatment, re-treatment with pazopanib at 400 mg may be considered if ALL following criteria are met: - ALT reduced to Grade 1 - 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:** 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 is reduced to grade 1.

Event	Dose Modification Algorithms
(D). ALT >3.0 x ULN **with** concomitant elevation in bilirubin[b] (defined as total bilirubin ≥2.0 x ULN; with direct bilirubin >35%) or **with** hypersensitivity symptoms (e.g., fever, rash).	**Liver Event Stopping Criteria:** Step 1. Discontinue pazopanib immediately; report the event to Novartis as an SAE **within 24 hours** of learning of its occurrence. Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries and liver event follow up assessments. Step 2. Consult a gastroenterologist / hepatologist and perform the following assessments to identify potential co-factors: - Eosinophil count - Viral serology for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus (IgM antibody, heterophile antibody, or monospot testing) - Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies. - Serum creatinine phosphokinase for possible muscle injury caused LFT elevation - Liver imaging - Consider toxicological blood screen for possible contributing chemical/medical entities Step 3. 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 grade 1.
For isolated total bilirubin[b] elevation without concurrent ALT increases (defined as ALT < 3 X ULN).	Step 1. Isolated hyperbilirubinemia (i.e., in the absence of elevated ALT 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. Step 2. If bilirubin is >1.5 x ULN in the absence of ALT elevation, fractionation of bilirubin elevation should be performed. If bilirubin is >35% direct (conjugated), further evaluation for underlying cause of cholestasis should be performed.

a. Full panel LFTs include: AST, ALT, alkaline phosphatase, and total bilirubin. Coagulation tests should be performed as clinically indicated.
b. Serum bilirubin fractionation should 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 should be promptly reported as an SAE.

Please see Section 7.8 for adverse event reporting instructions for hepatotoxicity.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 7.2.

The FDA requires that all serious and unexpected adverse events be reported as outlined in Section 7.4. In addition, any fatal or life-threatening adverse experiences where there is a reasonable possibility of relationship to study intervention must be reported.

Novartis requires that all serious adverse events be reported as outlined in Section 7.9.

7.1 Definitions

7.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website: http://www.hhs.gov/ohrp/policy/advevntguid.html

7.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

All unexpected SAEs must be reported to the FDA.

7.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

Events that are both serious AND unexpected must be reported to the FDA.

7.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Life-threatening adverse experiences must be reported to the FDA.

7.1.5 Unanticipated Problems

Definition:

- 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;
- related or 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
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

7.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

7.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Local IRB pre-approval of all protocol exceptions must be obtained prior to the event. For secondary sites, the Washington University PI will issue approval of the exception, but it must also be submitted to the local IRB with documentation of approval forwarded to Washington University. Washington University IRB approval is not required for protocol exceptions occurring at secondary sites.

7.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

7.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

7.4 Reporting Requirements for Secondary Sites

The research team at each secondary site is required to promptly notify the Washington University PI and research coordinator of all reportable events (as described in Section 7.6) within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event. This notification may take place via email if there is not yet enough information for a formal written report (using either an FDA MedWatch form if required or an institutional SAE reporting form if not). A formal written report must be sent to the Washington University PI and research coordinator within **10 working days** of the occurrence of the event or notification of the secondary site's PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification of the secondary site's PI of the event.

The research team at a secondary site is responsible for following its site's guidelines for reporting applicable events to its site's IRB according to its own institutional guidelines. The research team at Washington University is responsible for reporting all applicable events to the FDA.

7.5 Reporting to Secondary Sites

The Washington University PI (or designee) will notify the research team at each secondary site of all reportable events that have occurred at other sites within **10 working days** of the occurrence of the event or notification of the PI of the event. This includes events that take place both at Washington University and at other secondary sites, if applicable.

7.6 Reporting to Novartis

A serious adverse event (SAE) is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the patient's general condition

- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

The principal investigator has the obligation to report all serious adverse events to the IRB and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E) (For patients taking Pazopanib / Novartis drugs).

To ensure patient safety, every SAE, regardless of suspected causality, occurring

- after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment/participation
- after protocol-specified procedures begin (e.g., placebo run-in, washout period, double-blind treatment, etc.) and 30 days after the patient has stopped study treatment
- after the start of any period in which the study protocol interferes with the standard medical treatment given to a patient (e.g., treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication) and until 30 days after the patient has stopped study treatment

All Events must be reported to Novartis within 24 hours of learning of its occurrence. Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax to **(fax: 877-778-9739)** within 24 hours to the oncology Novartis DS&E department with the provided FAX cover sheets.

This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. The end date of the first event must be provided.

The original copy of the SAE Report and the fax confirmation sheet must be kept within the Trial Master File at the study site.

Follow-up information is sent to the same fax number as the original SAE Report Form was sent, using a new fax cover sheet, stating that this is a follow-up to the previously reported SAE, and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Pazopanib Investigator Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a DS&E associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

7.7 Timeframe for Reporting Required Events

Reportable adverse events will be tracked for 30 days following the last day of study treatment.

8.0 PHARMACEUTICAL INFORMATION

8.1 Pazopanib

8.1.1 Pazopanib Description

GW786034 (pazopanib) is a vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor (TKI) manufactured by Novartis for oncology indications (as an oral formulation) and for ophthalmology indications (eye drops and low dose oral). Pazopanib has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with advanced renal cell carcinoma (RCC) (New Drug Application [NDA] #022465).

Chemical Name: 5-[[4-[(2,3-Dimethyl-2H-indazol-6-yl)methylamino]-2-pyrimidinyl]amino]-2-methylbenzenesulfonamide monohydrochloride

Molecular Formula: $C_{21}H_{23}N_7O_2S \bullet HCl$
Molecular Weight: 473.99 g/mol (monohydrochloride salt); 437.53 g/mol (free base)

8.1.2 Pharmacokinetics and Drug Metabolism

Pazopanib is absorbed orally with median time to achieve peak concentrations of 2 to 4 hours after the dose. Daily dosing at 800 mg results in geometric mean AUC and Cmax of 1,037 mcg·hr/mL and 58.1 mcg/mL (equivalent to 132 μM), respectively.

8.1.3 Supplier(s)

Pazopanib will be provided to the sites by Novartis Pharmaceuticals Corporation using a separate drug supply request form.

8.1.4 Dosage Form and Preparation

Pazopanib is supplied as 200 mg and/or 400 mgtablets. Tablets are packaged in a sealed bottle with an affixed content label identifying the product.

8.1.5 Storage and Stability

Store at room temperature between 20°C and 25°C; excursions permitted to 15°C to 30°C.

8.1.6 Administration

Pazopanib should be taken orally without food at least one hour before or two hours after a meal. Dosing will be as described in Section 5.1.

8.1.7 Safety Information

Information on safety, side effects and adverse events can be found in the most current Pazopanib Investigator Brochure.

9.0 CORRELATIVE STUDIES

9.1 Quality of Life

Quality of life will be measured using the FACT-G7 validated survey (Appendix D) at baseline, C1D15, and on Day 1 of each cycle.

9.2 Biomarkers

Fill 3 red top SST (Tiger) tubes (8.5 mL each) with blood to measure levels of sVEGFR2 and PIGF at the following time points:

- Baseline
- C2D1
- C3D1
- C4D1

Invert the tubes gently 10 times. Let the tubes stand at room temperature to coagulate for 30-60 minutes. Centrifuge within one hour of collection at 1600g for 15 minutes. Store tubes at -70°C or cooler until shipment.

SHIP FROZEN IN BATCHES TO:
Dr. Brian Van Tine – Research lab
4515 McKinley Building, 3rd Floor
4523 Clayton Avenue
St. Louis, MO 63110

9.3 Pharmacokinetics

Twenty mL of blood will be drawn at the following time points to measure plasma pazopanib concentrations:

- Baseline (prior to initiation of treatment)
- Cycle 1 Day 5 (prior to escalation to 400 mg BID)
- Cycle 1 Day 9 (prior to escalation to 800 mg QD)
- Cycle 2 Day 1

Blood should be collected in 2 EDTA purple top tubes and 1 red top tube. DNA (for future use), serum, and whole cells should be prepared and frozen down prior to shipment using standard laboratory techniques. Samples should be labeled with the corresponding patient's study ID number, initials, and date of collection.

These PKs will only be performed in the first 11 patients enrolled at Washington University. This testing was completed as of amendment 4.

SHIP FROZEN IN BATCHES TO:
Dr. Brian Van Tine – Research lab
4515 McKinley Building, 3rd Floor
4523 Clayton Avenue
St. Louis, MO 63110

10.0 STUDY CALENDAR

Screening assessments must be performed no more than 14 days prior to start of study treatment, except scans which may take place up to 28 days prior to the start of treatment. After the start of study treatment, there is a ± 7 day window for all exams, scans, labs and procedures to be performed. Please note, there is also a ± 7 day window for treatment and for routine office visits.

	Screening	**D1 of each cycle**	**C1D5**	**C1D8**	**C1D9**	**C1D15 and C2D15**	**End of every even-numbered cycle**	**EOT**	**F/U[1]**
Informed consent	X								
PE, H&P, PS	X	X						X	
VS	X	X		X				X	
CBC	X	X		X				X	
CMP	X	X		X				X	
LFTs[2]	X	X[2]		X[2]		X[2]		X	
Pregnancy test[3]	X							X	
UPC	X	X[4]						X	
TSH, FT4	X	X[5]							
PT/PTT, INR	X							X	
ECG	X	X[6]							
ECHO[10]	X								
CT scan	X						X	X	
Pazopanib		X ---------- X[7]							
FACT-G		X[8]				X[8]			
Blood for biomarkers		X[9]							
Collect/review drug diary		X							
Toxicity assessment	X	X						X	

1. Every 3 months until death.
2. Monitor serum liver tests (total bilirubin, ALT/AST) before initiation of treatment with pazopanib and on C1D15, C2D1, C2D15, C3D1, C4D1, C5D1, and as clinically indicated (± 3 days). Periodic monitoring should continue after C5.
3. Women of childbearing potential only.
4. D1 of each cycle through C6, then D1 of every even-numbered cycle thereafter.
5. Monitor between every 8 to every 16 weeks.
6. C2D1, C4D1, C7D1, and then every 16 weeks (D1 of every 4th cycle) until EOT.
7. To be taken PO each day. Each cycle is 4 weeks long. See Section 5.1 for dosing instructions.
8. Baseline (prior to C1D1), C1D15, and D1 of every cycle thereafter.
9. Baseline (prior to C1D1), C2D1, C3D1, and C4D1.
10. Baseline (prior to C1D1) and periodic reassessment as needed and/or as indicated. Consistent diagnostic imaging should be used throughout study.

11.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Registration Form Eligibility Form On-Study Form	Prior to starting treatment
Treatment Form Pill Diary	Every cycle
QOL Form	Baseline C1D15 Day 1 of every cycle thereafter
Correlatives Form	Baseline C1D5 C1D9 C2D1 C3D1 C4D1
Toxicity Form	Continuous
Treatment Summary Form	Completion of treatment
Follow Up Form	Every 3 months until death
Tumor Measurement Form	Baseline, end of every even numbered cycle, and end of treatment
MedWatch Form	See Section 7.0 for reporting requirements

Any queries generated by Washington University must be responded to within 28 days of receipt by the participating site. The Washington University research team will conduct a regular review of data status at all secondary sites, with appropriate corrective action to be requested as needed.

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response 8 weeks after initiation of pazopanib and then every 8 weeks thereafter. In addition to a baseline scan, confirmatory scans should also be obtained not less than 8 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest

diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm 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).

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

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

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

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

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

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

12.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

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

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

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:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- 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.
- 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 should 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.

12.4 Response Criteria

12.4.1 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.

12.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and

normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

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

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

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

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

12.4.3 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
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 should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
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		

12.4.4 Duration of Response

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

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

12.4.5 Progression-Free Survival

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

12.4.6 Response Review

It is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion.

13.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Data and Safety Monitoring Committee (DSMC) will meet to review toxicity data at least every 6 months following the activation of the first secondary site. The report will be prepared by the statistician with assistance from the study team and will be submitted to the Quality Assurance and Safety Monitoring Committee (QASMC). This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual including numbers from participating sites
- Protocol activation date at each participating site
- Average rate of accrual observed in year 1, year 2, and subsequent years at each participating site
- Expected accrual end date and accrual by site
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities at all participating sites
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Until such a time as the first secondary site activates this protocol, a semi-annual DSM report to be prepared by the study team will be submitted to the QASM Committee beginning 6 months after study activation at Washington University.

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

A DSMC will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. Like investigators, DSMC members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMC will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMC must also be disclosed.

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMC at http://www.siteman.wustl.edu/uploadedFiles/Research_Programs/Clinical_Research_Resources/Protocol_Review_and_Monitoring_Committee/QASMCQualityAssurcance.pdf

14.0 AUDITING

Since Washington University is the coordinating center, each site will be audited annually by Siteman Cancer Center personnel (QASMC) unless the outside institution has an auditing mechanism in place and can provide a report. The outside sites will be asked to send copies of all audit materials, including source documentation. The audit notification will be sent to the Washington University Research Patient Coordinator, who will obtain the audit materials from the participating institution.

Notification of an upcoming audit will be sent to the research team one month ahead of the audit. Once accrual numbers are confirmed, and approximately 30 days prior to the audit, a list of the cases selected for review (up to 10 for each site) will be sent to the research team. However, if during the audit the need arises to review cases not initially selected, the research team will be asked to provide the additional charts within two working days.

Additional details regarding the Auditing Policies and procedures can be found at http://www.siteman.wustl.edu/uploadedFiles/Research_Programs/Clinical_Research_Resources/Protocol_Review_and_Monitoring_Committee/QASMCQualityAssurcance.pdf

15.0 STATISTICAL CONSIDERATIONS

15.1 Sample Size

This is a single arm phase II trial. A single-stage design requires a total of 56 eligible patients to be enrolled in order to provide 81.64% power to test the desired 16 week clinical benefit rate (CBR) > 35% against an unfavorable CBR < 20% based on the exact binomial method at 5% significance level (actual significance level = 4.32%). Clinical benefit rate is defined as CBR = CR + PR + SD lasting ≥ 16 weeks. If 17 or more patients benefit at the end of the trial, the treatment regimen yields a higher clinical benefit rate and warrants further investigation.

15.2 Statistical Analysis

Clinical benefit rate will be calculated with 95% confidence interval (CI) based on the Wilson score method and compared to the pre-specified unfavorable CBR of 20% based on one-sided exact binomial test. The serum levels of sVEGFR2 and PIGF at each time point will plotted and Pearson or Spearman's correlation coefficient will be calculated to explore their relationship. PFS and OS in the overall cohort of patients and by dichotomized sVEGFR2, PIGF and their combinations at each time point will be

analyzed and plotted by the Kaplan-Meier method with 95% CI. PFS and OS probabilities, overall and by group will be reported with 95% CI at desired time point. Cox proportional hazard model will be used to report resulting hazard ratio and Wald test P-values on sVEGFR2 and PIGF in continuous format.

16.0 MULTICENTER REGULATORY REQUIREMENTS

Washington University requires that each participating site sends its informed consent document to be reviewed and approved by the Washington University Regulatory Coordinator (or designee) prior to IRB/IEC submission.

Site activation is defined as when the secondary site has received official written documentation from the coordinating center that the site has been approved to begin enrollment. At a minimum, each participating institution must have the following documents on file at Washington University prior to study activation:

- Documentation of IRB approval of the study in the form of a letter or other official document from the participating institution's IRB. This documentation must show which version of the protocol was approved by the IRB.
- Documentation of IRB approval of an informed consent form. The consent must include a statement that data will be shared with Washington University, including the Quality Assurance and Safety Monitoring Committee (QASMC), the DSMC (if applicable), and the Washington University study team.
- Documentation of FWA, signed FDA Form 1572 (if applicable), and signed and dated the CVs of all participating investigators.
- Protocol signature page signed and dated by the investigator at each participating site.

The coordinating center is responsible for disseminating to the participating sites all study updates, amendments, reportable adverse events, etc. Protocol/consent modifications and IB updates will be forwarded electronically to the secondary sites within 4 weeks of obtaining Washington University IRB approval. Activated secondary sites are expected to submit protocol/consent/IB modifications to their local IRBs within 4 weeks of receipt, unless otherwise noted. Upon the secondary sites obtaining local IRB approval, documentation of such shall be sent to the Washington University study team within 2 weeks of receipt of approval.

Documentation of participating sites' IRB approval of annual continuing reviews, protocol amendments or revisions, all SAE reports, and all protocol violations/deviations/exceptions must be kept on file at Washington University.

The investigator or a designee from each institution must participate in a regular conference call to update and inform regarding the progress of the trial.

17.0 REFERENCES

1. Wilky BA, Meyer CF, Trent JC. Pazopanib in sarcomas: expanding the PALETTE. *Curr Opin Oncol* 2013; **25**(4): 373-8.
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4. Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). *J Clin Oncol* 2009; **27**(19): 3126-32.
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6. Sleijfer S, Gorlia T, Lamers C, et al. Cytokine and angiogenic factors associated with efficacy and toxicity of pazopanib in advanced soft-tissue sarcoma: an EORTC-STBSG study. *Br J Cancer* 2012; **107**(4): 639-45.

APPENDIX A: ECOG Performance Status Scale

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

APPENDIX B: New York Heart Association (NYHA) Functional Classification

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs, etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20-100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

The Criteria Committee of the NYHA, Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

APPENDIX C: Medication Diary – Cycle 1

Today's Date: _____ Cycle 1 Agent: Pazopanib

Patient Name: _____ Study ID# 201501057

1. Take pazopanib by mouth under fasting conditions (at least one hour before or two hours after a meal).
2. Take pazopanib with a glass of water and drink the glass of water in as little time as possible.
3. Record the date, time and amount of drug taken. Write "1-200mg", "2-200mg", "3-200mg", or "4-200mg."
4. If you forgot to take your dose, do not take that dose. Restart pazopanib at the next scheduled dose.
5. If you vomit or notice any side effects, list in the comments section. Do not re-take a dose after vomiting.
6. Return this form and used pill bottles to your study coordinator when you go to your next appointment.

Important Dosing Instructions: Slowing increase the dose when you first start taking pazopanib.
First 4 days (Cycle 1, Days 1-4): Take **one 200-mg pill** in the morning, and **one 200-mg pill** in the evening.
Next 4 days (cycle 1, Days 5-8): Take **two 200-mg pills** in the morning, and **two 200-mg pills** in the evening.
Cycle 1, Day 9 and beyond: Take **four 200-mg pills** in the morning. *Do not take drug in the evening*.
Dose changes: If you experience side effects, you may be asked to discontinue or reduce the dose.

Day	Date	Morning		Evening		Comments
		Pill # and mg	Time Taken	Pill # and mg	Time Taken	
1						
2						
3						
4						
5						
6						
7						
8						
9				[redacted]		
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						

23				[redacted]	
24					
25					
26					
27					
28					

APPENDIX D: Medication Diary – Cycle 2 & Beyond (200 mg)

Today's Date: _____ Cycle:_____ Agent: Pazopanib

Patient Name: _____ Study ID# 201501057

1. Take pazopanib by mouth under fasting conditions (at least one hour before or two hours after a meal).
2. Take pazopanib with a glass of water and drink the glass of water in as little time as possible.
3. Record the date, time and amount of drug taken. Write "4-200mg", "3-200mg", "2-200mg" or "1-200mg."
4. If you forgot to take your dose, do not take that dose. Restart pazopanib at the next scheduled dose.
5. If you vomit or notice any side effects, list in the comments section. Do not re-take a dose after vomiting.
6. Return this form and used pill bottles to your study coordinator when you go to your next appointment.

Important Dosing Instructions: Take **____ 200-mg pills** in the morning or appropriate dose as instructed by physician.
Do not take drug in the evening.
Dose changes: If you experience side effects, you may be asked to discontinue or reduce the dose.

Day	Date	Morning		Comments
		Pill # and mg	Time Taken	
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
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Medication Diary – Cycle 2 & Beyond (200 mg and/or 400 mg)

Today's Date: _____ Cycle:_____ Agent: Pazopanib

Patient Name: _____ Study ID# 201501057

1. Take pazopanib by mouth under fasting conditions (at least one hour before or two hours after a meal).
2. Take pazopanib with a glass of water and drink the glass of water in as little time as possible.
3. Record the date, time and amount of drug taken. Write "2-400mg" or 3-200mg, 2-200mg or 1-200mg.
4. If you forgot to take your dose, do not take that dose. Restart pazopanib at the next scheduled dose.
5. If you vomit or notice any side effects, list in the comments section. Do not re-take a dose after vomiting.
6. Return this form and used pill bottles to your study coordinator when you go to your next appointment.

Important Dosing Instructions: Take _____ **400-mg pills and** _____ **200-mg pills** in the morning. *Do not take drug in the evening*.
Dose changes: If you experience side effects, you may be asked to discontinue or reduce the dose.

Day	Date	Morning		Comments
		Pill # and mg	Time Taken	
1				
2				
3				
4				
5				
6				
7				
8				
9				
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APPENDIX E: FACT-G7

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4