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FRED HUTCHINSON CANCER RESEARCH CENTER
UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE

Previous version: 05/05/2015
Current version: 03/02/2016

Title of Protocol: **The Effect of Antiangiogenic Therapy with Pazopanib Prior to Preoperative Chemotherapy for Subjects with Extremity Soft Tissue Sarcomas: A Randomized Study to Evaluate Response by Imaging**

Investigator List:

Principal Investigator	**Professional Title**	**Phone Number**
Darin Davidson, MD	Assistant Professor of Orthopedics and Sports Medicine, University of Washington	(206) 543-3690
Co-Principal Investigator		
Robin Jones, MD	Affiliate Professor of Medicine, University of Washington Affiliate Member, Fred Hutchinson Cancer Research Center	(206) 288-7439
Eve Rodler, MD	Affiliate Assistant Professor of Medicine, University of Washington Affiliate Assistant Member, Fred Hutchinson Cancer Research Center	(206)-288-7438
Co-Investigators		
Andrew Shields, MD	Clinical Assistant Professor, University of Washington	
Elizabeth Loggers, MD, PhD	Assistant Professor of Medicine, University of Washington Assistant Member, Fred Hutchinson Cancer Research Center	(206) 288-6975
Lee Cranmer, MD, PhD	Associate Professor, University of Washington Associate Member, Fred Hutchinson Cancer Research Center	(206) 288-7439
Gabrielle Kane, MD	Associate Professor, Radiation Oncology, University of Washington	(206)-598-7362
Rosa Yeh, Pharm. D.	Director, Pharmacokinetics Lab SCCA Affiliate Investigator, FHCRC	(206)288-7396
Seth Pollack, M.D.	Assistant Professor, University of Washington Assistant Member, Fred Hutchinson Cancer Research Center	(206)-667-6629

Biostatistician:

Brenda F. Kurland	Associate Member, Fred Hutchinson Cancer Research Center	(206)-667-2804

Research Staff: **Phase I Program (206) 288-7551**
Emergency Contact: **Operator at UWMC (206) 598-6190**

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1.0 INTRODUCTION

This document is a clinical research protocol and the described study will be conducted in compliance with the IRB approved protocol, associated Federal regulations and all applicable IRB requirements.

This is a randomized study in patients with intermediate/high grade adult soft tissue sarcoma of the extremity or chest wall which will utilize an oral angiogenesis inhibitor versus placebo followed by neoadjuvant chemotherapy. The primary objective is to use FDG-PET to evaluate early response to antiangiogenic therapy with pazopanib. This will be correlated with pharmacokinetic analysis of pazopanib. Standard RECIST response to therapy will be measured and compared with FDG-PET results. The study will provide preliminary data on the relative contributions of pazopanib and chemotherapy with doxorubicin and ifosfamide as measured by changes in SUV by FDG-PET. Secondary objectives include: analyzing the safety of sequential pazopanib and neoadjuvant chemotherapy; measuring histologic response at the time of surgery as a surrogate marker of outcome; and evaluating tumor and serum biomarker response. The hypothesis is that the addition of pazopanib to preoperative chemotherapy with doxorubicin and ifosfamide will increase the overall response rate which could ultimately translate into an improvement in outcome for patients with resectable soft tissue sarcoma. The results of this study will inform the design and feasibility of a larger trial which would incorporate pazopanib as neoadjuvant therapy.

FDG-PET will be performed pre-treatment, after pazopanib, and after neoadjuvant chemotherapy to provide correlative, exploratory pharmacodynamic data on the anti-tumor effect of adding antiangiogenic inhibition to chemotherapy. Biomarker studies will also be performed including plasma measurement of VEGF and soluble VEGFR2 (sVEGFR2). Quantitative enzyme-linked immunosorbent assays (ELISA) for VEGF and sVEGFR2 will be performed on plasma and tumor extracts. Plasma will also be collected for micro RNA.

This is a pilot study to test the hypothesis that antiangiogenic therapy with pazopanib will enhance the response rate of front line chemotherapy agents as measured by radiologic response and tumor necrosis. This would provide the rationale to undertake a larger Phase II trial, randomizing patients to neoadjuvant chemotherapy with or without pazopanib, with progression-free and overall survival as end points.

2.0 BACKGROUND

2.1 Soft Tissue Sarcoma Adjuvant and Neoadjuvant Chemotherapy

Soft tissue sarcomas account for less than 1% of all solid tumors in adults. They encompass a complex heterogeneous group of tumors likely arising from pluripotential mesenchymal stem cells. Although most patients present with localized disease which allows good local control by surgical resection and radiation, approximately 50% die from subsequent metastatic disease.[1,2] There is a strong need to develop new treatments which will improve outcome for this group of patients.

The role of neoadjuvant and/or adjuvant chemotherapy in adult soft tissue sarcomas is controversial. A 1997 individual patient meta-analysis published in the Lancet of all randomized clinical trial data showed a significant 10% improvement in local and distant disease free survival at 9.4 years follow-up for patients who received adjuvant chemotherapy versus those who underwent surgery alone. The meta-analysis failed to show a significant benefit in terms of overall survival[3] but a subgroup analysis suggested that patients with extremity sarcomas had a 7% improvement in overall survival, which was significant. It is possible that the benefits of chemotherapy were underestimated in this meta-analysis since patients with low grade lesions who would not be expected to benefit from chemotherapy were included and less than 5% of patients received ifosfamide, which was found to be an active agent in soft tissue sarcoma in later studies. A subsequent Italian Phase III study involving 104 patients with high grade, large (> 5 cm) resectable or recurrent extremity and limb girdle sarcomas evaluated adjuvant chemotherapy with epirubicin and ifosfamide versus observation.[4] At 5 years follow-up there was an absolute overall survival benefit of 19% favoring the chemotherapy arm which was significant. When the study was updated at 90 months, the intent-to-treat analysis no longer showed a statistically significant overall survival benefit.[5] An updated meta-analysis which included the meta-analysis from 1997 as well as 4 modern studies showed a significant improvement in overall survival benefit for chemotherapy, with an odds ratio of 0.56 for anthracycline-ifosfamide combination therapy. [6]

The sole randomized trial conducted in the neoadjuvant setting showed no survival advantage in those patients treated with a doxorubicin/ifosfamide based-regimen versus no chemotherapy.[7] However, this trial was small and may have been underpowered to show a survival benefit. In addition, lower doses of doxorubicin (50 mg/m^2) and ifosfamide (5/gm/m^2) for each cycle were administered, compared to what would now be considered optimal dosage of these drugs.

There are practical and theoretical advantages to offering neoadjuvant chemotherapy for patients with large high-risk extremity sarcomas. Neoadjuvant chemotherapy may act in the early systemic treatment of micrometastases and improve outcome for subgroups of patients. In one retrospective study combining data from Dana Farber and Memorial Sloan Kettering, neoadjuvant chemotherapy with doxorubicin and ifosfamide provided a disease specific survival benefit for patients with tumors larger than 10 cm. [8] In some cases neoadjuvant chemotherapy can downsize tumors and improve resectability. Neoadjuvant chemotherapy allows the tumor to be used as a measure of response *in-vivo*, by performing imaging studies before and after treatment. Finally, there is prognostic value to treatment induced pathologic necrosis. A study by Eilber and colleagues from UCLA utilizing neoadjuvant chemotherapy and radiation therapy showed that soft tissue sarcoma patients having 5% or less residual viable tumor (at least 95% tumor necrosis) after therapy at the time of surgery had a significantly lower risk for local recurrence and improved overall survival.[9]

While chemotherapy in adult soft tissue sarcoma may improve outcome for some patients with localized disease, there is a compelling need to develop better control of soft tissue sarcoma dissemination by systemic approaches. Even doxorubicin and ifosfamide, the two most active agents in soft tissue sarcoma, result in frequent tumor recurrence and progression after initial responsiveness.

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2.2 Antiangiogenic Therapy in Sarcoma

Angiogenesis, the growth of new vessels from pre-existing vasculature, is essential for tumor progression. Since the time that tumor angiogenesis was initially postulated by Folkman in 1971, several basic and clinical studies have shown that the growth, invasion and metastatic potential of solid tumors is dependent on angiogenesis.[10-13] In the past two decades, inhibitors of angiogenesis have been developed for clinical use and recently have shown clinical benefit in combination with chemotherapy [14,15] and as monotherapy in certain solid tumors [16-18].

Soft tissue sarcomas express vascular endothelial growth factor (VEGF) which is a key mediator of angiogenesis.[19, 20] In one study of 115 patients with soft tissue sarcoma, the concentration of VEGF in the tumor tissue was found to be an independent prognostic factor for disease outcome.[21] Tumors associated with local recurrence or metastasis in this study showed a significantly higher tissue VEGF concentration than those without either. In addition, VEGF blood levels in patients with soft tissue sarcomas are elevated compared with healthy controls and correlate with outcome. [19,22-24]. Other angiogenic factors such as platelet-derived growth factor (PDGF) are likely involved in the pathogenesis of soft tissue sarcoma.[25] Thus, there is a rationale for targeting angiogenesis in soft tissue sarcoma. Recent clinical trials have provided preliminary evidence to support this scientific rationale. Sunitinib malate and sorafenib, both small molecule inhibitors whose targets include VEGF receptors and PDGF receptor, have shown activity in several soft tissue sarcoma subtypes as monotherapy in Phase II studies.[26,27]

2.3 Pazopanib in Sarcoma

Pazopanib is an oral angiogenesis inhibitor that potently inhibits the tyrosine kinase activity of VEGF, platelet-derived growth factor receptor (PDGFR) and c-KIT. [28,29,30] In murine studies, pazopanib inhibited VEGF-induced VEGFR2 phosphorylation, tumor angiogenesis and the growth of human tumor xenografts. In a Phase I study, pazopanib was well tolerated which prompted further studies. Recently, pazopanib gained FDA approval for the treatment of patients with advanced renal cell carcinoma based on the results of a Phase III trial which demonstrated that the agent improved progression-free survival and tumor response compared with placebo in this population of patients.[31]

Promising results of a Phase II study conducted by the European Organization for the Research and Treatment of Cancer (EORTC) in advanced soft tissue sarcoma have been published.[32] In this study 142 patients with intermediate- or high-grade disease received pazopanib 800 mg orally daily. The progression-free rate at 12 weeks was 44% in leiomyosarcoma patients, 49% in synovial sarcoma patients, and 39% in other subtypes, which compares favorably with historical controls treated with second-line chemotherapy. The median duration of response was longer than 1 year. The most common toxicities were hypertension, fatigue, hypopigmentation, and nausea. Mild myelosuppression and liver enzyme elevations were encountered. In light of the anti-tumor activity demonstrated in this trial, a double-blind, placebo-controlled, Phase III trial of pazopanib has been initiated in patients with angiogenesis-naïve, metastatic soft tissue sarcoma who had progressive disease after several lines of treatment. [57] Results showed a significant improvement in median

progression-free survival for pazopanib versus placebo, 12.6 months versus 10.7 months, respectively.

Given the scientific rationale for combining conventional chemotherapy with inhibitors of the VEGF receptor pathway [33] we are interested to evaluate further the potential benefit of adding pazopanib to standard front-line cytotoxic agents that have activity in sarcoma, doxorubicin and ifosfamide.

2.4 Study Agent - Pazopanib

Pazopanib is a potent and selective, orally bioavailable, adenosine triphosphate competitive, small molecule inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, -2, and -3, platelet-derived growth factor receptor (PDGFR)-α, -β, and c-KIT tyrosine kinases (TKs).[34] In human umbilical vein endothelial cells (HUVECs), pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation and was 3- to 400-fold selective for VEGFRs compared to 23 other kinases tested. Pazopanib showed significant growth inhibition of a variety of human tumor xenografts in mice, and also inhibited angiogenesis in several different models of angiogenesis. Because angiogenesis is necessary for the growth and metastasis of solid tumors, and VEGF is believed to have a pivotal role in this process, pazopanib treatment may have broad-spectrum clinical utility.

Mechanism of Action

Pazopanib inhibits VEGFR-1, -2, and -3 with concentrations causing 50% inhibition (IC_{50}) values of 10, 30, and 47 nM, respectively, and inhibits PDGFR-α, -β, and c-KIT with IC_{50} values of 71, 84, and 74 nM, respectively [34,35,36].

Preclinical Pharmacology, Toxicology , Pharmacokinetics, and Drug Metabolism

Refer to the Investigator's Brochure 2016.

Clinical Experience

Approximately 8600 subjects with cancer have been enrolled in clinical studies of pazopanib as of September 2015. In October 2009, the FDA approved pazopanib tablets for the treatment of subjects with advanced renal cell carcinoma (RCC) and soft tissue sarcoma (STS). In addition, several clinical studies evaluating pazopanib in non-small cell lung cancer (NSCLC), ovarian cancer, breast cancer, cervical cancer, hepatocellular cancer (HCC), multiple myeloma (MM), and glioma are in progress or have been completed.

Clinical Efficacy

In a randomized, parallel assignment, double-blind, placebo-controlled study evaluating safety, efficacy and PFS of subjects with soft tissue sarcomas, statistically significant improvements in PFS were observed in the pazopanib arm when compared with subjects taking placebo. The median PFS in the placebo arm was 7.0 weeks and in the pazopanib arm was 20.0 weeks with corresponding HR or 0.35 as assessed by independent radiology review. Soft tissue sarcoma sub-types included in this trial included synovial (48.6%), adipocytic (26.3%) and "other" sarcomas (39%). [34]

In a randomized, double-blind, placebo-controlled phase III study evaluating the efficacy and safety of pazopanib monotherapy in treatment-naive and cytokine-pretreated subjects

with advanced RCC, the median progression-free-survival (PFS) was significantly prolonged with pazopanib compared with placebo in the overall study population (9.2 vs. 4.2 months). The objective response rate (RR) was 30% with pazopanib and only 3% with placebo [37]. In subjects with ovarian cancer, 31% of subjects experienced a CA-125 response to pazopanib, with a median time to response of 29 days and median duration of response of 113 days (Investigator's Brochure, 2010). In a phase II trial of subjects with early-stage NSCLC, 86% of subjects experienced a reduction in tumor volume after short-term, preoperative use of pazopanib (~2-6 weeks) as assessed by high-resolution CT scanning [38]. Interim results from a phase II study of pazopanib in subjects with recurrent or metastatic breast invasive breast cancer showed that the clinical benefit rate was 26% [39]. The median TTP was 3.7 months, and 50% of subjects with measurable target lesions had some decrease in size. PFS at 3 and 6 months was 55% and 28%, respectively. Preliminary results from a randomized study in subjects with first-line advanced ErbB2-positive advanced or metastatic breast cancer showed that a higher response rate (36.2% vs. 22.2%) was observed in subjects on combination lapatinib 1000 mg once daily + pazopanib 400 mg once daily compared to monotherapy lapatanib 1500 mg once daily [40]. In a randomized phase II study of pazopanib vs. lapatinib vs. the combination of pazopanib/lapatinib in advanced and recurrent cervical cancer, there was a 34% reduction in risk for progression in subjects receiving pazopanib relative to lapatinib. The median PFS was 17.1 weeks in the lapatinib group and 18.1 weeks in the pazopanib group [41]. Interim analysis of data from 26 subjects showed that pazopanib has both a favorable toxicity profile and promising clinical activity in subjects with advanced and progressive differentiated thyroid cancers [42]. Five confirmed partial responses (PRs) (19%) were reported. Pazopanib has not shown efficacy in phase II studies conducted in MM or glioma.[34]

Safety

The randomized, phase III study in STS subjects provided a key comparison of safety with pazopanib compared to placebo.[34] The most common AEs reported in ≥20% of subjects in the pazopanib arm were fatigue (65%), diarrhea (59%), nausea (56%), weight decreased (51%), hypertension (42%), anorexia (40%), hair color change (depigmentation; 39%), and vomiting (34%), tumor pain (30%), dysguesia (28%), gastrointestinal pain (24%), headache (23%), musculoskeletal pain (23%), myalgia (23%), and dyspnea (20%). Most of the events were grade 1 or 2. A higher number of grade 3 AEs were reported in the pazopanib arm (63%) compared with the placebo arm (28%). The most frequent grade 3 AEs in the pazopanib arm were increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), hypertension, and diarrhea. The frequency of grade 4 and grade 5 AEs was similar between the pazopanib and placebo arms: grade 4 in 7% and 6%, respectively; grade 5 in 4% and 3%, respectively.

When pazopanib was compared with sunitinib in 1102 subjects (554 subjects taking pazopanib and 548 subjects taking sunitinib), the frequency of AEs was similar (>99% in both). The safety profiles observed between the treatment arms were different, with greater frequency of diarrhea (63% pazopanib, 57% sunitinib) and hypertension (47% pazopanib, 41% sunitinib). Subjects who took pazopanib when compared with subjects taking sunitinib experienced lower frequency of fatigue, nausea, dysguesia and palmar-plantar erythrodysesthesia (PPE) syndrome. Grade 3 and 4 reported adverse events were similar between treatment arms, adding no comparative risk. However, grade 3 AEs of increased

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ALT; increased ASP and headache occurred more frequently in the pazopanib arm when compared with the sunitinib arm. [34]

A comprehensive review of all completed and ongoing pazopanib clinical trials with a cut-off date of September 2015, lists 15 most commonly occurring serious AEs (SAEs).[34] Vomiting and diarrhea are the most commonly reported SAEs across all the pazopanib studies. As a consequence of this, dehydration is also seen with pazopanib treatment. For most reports, the AEs resolved after supportive treatment such as antiemetics, antidiarrheal agents, and IV fluids. GI perforation is commonly associated with VEGF pathway inhibitors. This may manifest as abdominal pain which is not uncommon in cancer subjects for many reasons. Of the 42 subjects in pazopanib trials with SAEs of abdominal pain, only three had a documented underlying intestinal perforation. In July 2006, the DCTD, NCI, issued an Action Letter to investigators using pazopanib describing the occurrence of bowel perforations in subjects on pazopanib clinical trials.

The most common (≥1%) AEs leading to permanent discontinuation of study drug were increased ALT, increased AST, proteinuria, fatigue, and hepatotoxicity. Of these AEs, increased ALT, increased AST and proteinuria occurred in a higher proportion of subjects taking pazopanib.

Dyspnea is also frequently seen in pazopanib-treated subjects and may reflect the underlying disease under treatment. Anemia is commonly seen in cancer subjects in association with chemotherapy, hemorrhage, or infection. The SAEs of pyrexia were attributed to multiple causes: concurrent infections, the underlying malignancy, hepatic events, other concomitant medications, and unknown causes. Hepatic events are thought to be on-target tyrosine kinase inhibitor (TKI) class effects, as hepatic enzyme elevations have been seen with other agents of this class. Careful clinical evaluation is, therefore, warranted in subjects with hepatic abnormalities. Pazopanib is not recommended in subjects with severe hepatic impairment (defined as total bilirubin >3✕ULN regardless of any level of ALT) as there is insufficient data in these subjects. Pneumonia can be a complication of chemotherapy or can result from debilitation and advanced disease. Review of the 33 SAEs showed the presence of an underlying cause other than pazopanib in 19 of the 30 subjects. Fatigue and asthenia are commonly reported and have multiple causes.

Hypertension observed with pazopanib is a known class effect. There have been 30 SAEs of hypertension and 3 SAEs of hypertensive crisis in pazopanib clinical trials. There were 28 subjects who were effectively treated with antihypertensive medication initiation or dose adjustment, while 4 had no such treatment. Although there were 29 SAEs of pleural effusion, the body of data does not suggest that any of these cases were due to pazopanib. There have been 24 SAEs of pulmonary embolism (PE) reported in pazopanib trials. This is of particular relevance since other members of this class have been associated with PE and other venous thromboembolic events.

In addition, there have been reports of cardiac and cerebral ischemic events, GI perforation or hemorrhage, pulmonary hemorrhage, cerebrovascular hemorrhage, QT prolongation, and Torsades de Pointes in pazopanib clinical trials.

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Laboratory abnormalities

In both treatment arms (placebo vs. pazopanib), most on-therapy hematology grade shifts were Grade 1 or Grade 2. A higher proportion of subjects in the pazopanib arm had grade shifts for neutrophils, platelets and WBCs compared with the placebo arm. Chemistry grade shifts that occurred more frequently in the pazopanib arm included hyperglycemia, hyperkalemia, hypoglycemia and hyponatremia. Transaminase elevations were also more common on pazopanib than placebo. Thirteen subjects experienced ALT elevations of >8✕ULN, and of these, 5 subjects experienced ALT elevations of >20✕ULN.

Clinical Pharmacokinetics

The oral bioavailability of pazopanib reflects absorption that is limited by solubility above doses of 800 mg once daily [34,43] Increases in doses above 800 mg to 2000 mg, in the fasted state will not result in increased systemic exposure. Geometric mean pazopanib $t_{½}$ values ranged from 18.1-52.3 hours. The mean $t_{½}$ was 30.9 hours in the 800 mg once daily group, in phase 2 and 3 trials. Oral absorption is significantly enhanced when dosed with food; therefore, it is recommended to administer pazopanib on an empty stomach, at least 1 hour before or 2 hours after a meal. Age, body weight, gender, and race have no significant influence on pazopanib PK.

Potential Drug Interactions

Pazopanib is metabolized primarily by CYP3A4, and systemic exposure to pazopanib is altered by inhibitors and inducers of this enzyme. The concomitant use of strong CYP3A4 inhibitors should be avoided. Grapefruit may also increase plasma concentrations of pazopanib and should be avoided. CYP3A4 inducers such as rifampicin may decrease plasma concentrations; therefore, an alternative concurrent medication with none or minimal enzyme induction should be used.

Concommitant medications that have narrow therapeutic windows ***and*** are substrates of CYP3A4, CYP2D6 or CYP2C8 should be used with caution. If possible, medications that are not substrates for these enzymes and/or do not have narrow therapeutic windows should be substituted.

Pazopanib is a substrate for P-glycoprotein (P-gp) and BCRP transporters.

Dose Selection

Pharmacodynamic data indicate that pazopanib, at a monotherapy dose of 800 mg once daily, results in effects consistent with inhibition of the VEGF receptors and angiogenic factors.[34] Concentration-effect relationships were observed between trough plasma pazopanib concentrations and the development of hypertension as well as the percent change from baseline to the nadir of soluble VEGFR2 (sVEGFR2), a marker of VEGFR inhibition. Decreases in sVEGFR2 have been correlated with increased clinical benefit in RCC with other small molecule TKIs.[44] The trough plasma pazopanib concentrations associated with the EC_{50} in both concentration-effect relationships were similar (15.3 mcg/mL for hypertension and 21.3 mcg/mL for sVEGFR2). Pazopanib monotherapy has been approved as an 800 mg once daily dose for the treatment of advanced RCC in the US.

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2.5 Dose Rationale

In this study, subjects will receive pazopanib 800 mg or placebo orally daily for 14 days (the "Run-in" period) followed by preoperative chemotherapy. Doses will be taken fasting (at least one hour before and/or 2 hours after dose).

Subjects who respond to pazopanib during the Run-in period will have the option to continue pazopanib 800 mg orally daily for one year following surgery and completion of any adjuvant chemotherapy. Refer to **Section 11.3** for details.

2.6 Chemotherapy

Pre-operative chemotherapy will consist of doxorubicin and ifosfamide administered on an inpatient basis. The regimen will consist of doxorubicin 75 mg/m^2 administered by continuous intravenous infusion over 3 days with ifosfamide 2 gm/m^2 administered intravenously over 4 hours daily for 5 days with IV fluid and Mesna, every 21 days for 2 to 4 cycles, depending on clinical and radiologic response. Patients may also receive 2 to 4 cycles of post-operative chemotherapy, (up to 6 cycles total of neoadjuvant plus adjuvant chemotherapy).

2.7 Imaging Studies to Determine Early Response to Therapy in Soft Tissue Sarcoma

Chemotherapy may improve the chance for a cure in patients with high risk sarcomas (intermediate to high grade, $\geq$ 5 cm), but does not benefit every patient and is associated with toxicities.[3,4] Identifying sarcoma patients who are likely to benefit from neoadjuvant and/or adjuvant systemic treatment has been challenging. In most current trials of anticancer drugs, the objective radiographic response of tumor to treatment, as defined by the international Response Evaluation Criteria in Solid Tumors (RECIST), is used as a surrogate measure for therapeutic benefit.[45] The assessment of soft tissue sarcoma response to chemotherapy is difficult, however, because sarcomas are heterogeneous tumors and consist of varying degrees of cellularity, fibrous septa, stroma, and necrosis. The beneficial effects of a therapy which is successful at eradicating neoplastic cells may be masked by a tumor mass that does not shrink or even grows due to necrosis or intratumoral hemorrhage.[46] Standard radiologic response defined by a change in the size of the tumor to preoperative chemotherapy has not correlated consistently with histologic results at surgery or with survival.[47-49]

FDG-PET: Positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG), is a tool for evaluation of treatment response in sarcoma. In neoadjuvant therapy for high grade localized sarcomas, serial FDG-PET is a sensitive method to assess early response to therapy; pretreatment standardized uptake value (SUV) and change in SUV predict outcome.[50,51] Eary and colleagues first used FDG-PET in sarcomas and demonstrated the relationship between the quantitative value of the FDG metabolic rate of tumor and the semi-quantitative measure of tumor uptake, the SUV.[52] Eary and colleagues showed that a higher tumor maximum SUV at diagnosis correlated with a greater risk for disease progression and death from disease in patients with soft tissue or bone sarcomas.[50] In a later study, Schuetze and colleagues found that the pretreatment tumor maximum SUV and change in maximum SUV after neoadjuvant chemotherapy independently identified

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sarcoma patients at high risk of tumor recurrence.[51] Forty-six patients with high-grade localized extremity sarcomas were studied. Those with a baseline tumor maximum SUV of 6 or greater and less than a 40% decrease in FDG uptake after chemotherapy were at high risk for systemic disease recurrence, estimated to be 90% at 4 years. In contrast, those whose tumors had a 40% or more decline in the tumor maximum SUV after chemotherapy, were at significantly lower risk of recurrent disease and death following surgery and radiation. Interestingly, in this study the histologic response to chemotherapy did not correlate with patient outcome.

In this randomized study subjects will undergo baseline staging scans including FDG-PET. After the 14 day Run-in period of pazopanib versus placebo, and prior to commencement of preoperative chemotherapy, subjects will undergo repeat FDG-PET. After 2 cycles of chemotherapy FDG-PET will be repeated.

If results of this trial can be confirmed in larger trials, then this could establish that changes in tumor SUV in response to antiangiogenic therapy and to chemotherapy may distinguish those patients who are likely to benefit from these systemic therapies from those who will not.

2.8 Risks/Benefits

Subjects will have a 2:1 chance of being randomized to receive pre-operative pazopanib during a Run-in period. The potential benefits include early assessment of response to antiangiogenic therapy and possible enhanced tumor cell kill. Subjects who respond to pazopanib during the Run-in period (defined in **Section 11.3**) will have the option to continue pazopanib for one year, following surgical resection of their tumor. Antiangiogenic therapy may improve outcome for patients with high risk resectable soft tissue sarcoma, but this remains unproven. Benefits of chemotherapy include a potential improvement in disease free survival and overall survival compared to no systemic therapy. Risks of the study include side effects associated with pazopanib and with chemotherapy as described in **Section 10**.

3.0 STUDY OBJECTIVES

3.1 Primary Objectives

- To determine the absolute values and changes in standardized uptake values (SUV) by FDG PET before and after a 14 day Run-in period of pazopanib versus placebo, and to compare this to the change in SUV following pre-operative chemotherapy.
- To evaluate the correlation between antiangiogenic activity and pazopanib drug exposure.
- To assess the response rate by RECIST criteria after the 14 day Run-in period of pazopanib versus placebo and compare this to the response rate following pre-operative chemotherapy.

3.2 Secondary Objectives

- To examine the activity of antiangiogenic therapy with pazopanib combined with pre-operative chemotherapy for high risk extremity soft tissue sarcomas as measured by:
  Histological necrosis at surgery
  Change in plasma and tumor biomarker assays of angiogenesis
- To evaluate the safety of sequential treatment with pazopanib and pre-operative chemotherapy with doxorubicin and ifosfamide.

4.0 STUDY DESIGN

4.1 Description of Study

This is a multi-center randomized blinded study with 2:1 randomization of pazopanib versus placebo prior to neoadjuvant chemotherapy with doxorubicin and ifosfamide for adult soft tissue extremity sarcomas.

4.2 Endpoints

4.2.1 Primary Endpoints

- Absolute values and changes in standardized uptake values (SUV) of tumors measured by FDG-PET pre- and post receipt of pazopanib versus placebo, and post receipt of 2 cycles of preoperative chemotherapy
- Tumor response by RECIST criteria
- Correlation of pazopanib trough concentration with the change in SUV from FDG PET and change in RECIST measurements on MRIs

4.2.2 Secondary Endpoints

- Safety profile
- Pathologic response at the time of surgery as measured by % tumor viability
- Progression free survival and overall survival
- Change in plasma and tumor angiogenic biomarker levels pre- and postneoadjuvant therapy.

4.3 Study Procedures

The study procedures outlined in Appendix A are discussed in this section, with the exception of Treatment **(Section 7)**. Screening will occur within approximately 14 days prior (unless otherwise noted) to the first day of dosing (pazopanib versus placebo, Run-in period, Day 1). For procedures performed at Screening and repeated, the later procedure performed prior to dosing will serve as a baseline for clinical assessment.

Informed Consent
Signed informed consent will be obtained from the subject or the subject's legally acceptable representative by the principal investigator or a co-investigator (the “Investigator”) before any study-specific procedures are undertaken.

The Investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed, signed, and dated by the subject and by the person who administered the informed consent. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's research chart.

Research analysis of plasma samples and surgical tumor tissue will be performed once the subject has signed and dated the informed consent, approved by the IRB of record, after the nature of the testing has been explained and the subject has had the opportunity to ask questions. The informed consent must be signed before the testing is performed or tumor tissue and plasma samples are used for analysis.

Medical History

The following information will be collected during the Screening Visit:

- Complete medical history, including documentation of any clinically significant medical condition
- Oncology history, including primary cancer diagnosis
  - Pathology of primary tumor
  - Stage of tumor (location, size, grade and depth)

At each visit, the subject's medical history will be reviewed and any changes from baseline will be recorded. On Run-in period, Day 1 any changes observed from the screening assessments, prior to dosing, will be recorded in the subject's medical history. All medication (prescription or over-the-counter, including vitamins and/or herbal supplements) will be recorded beginning with the Screening Visit and continued for the duration of the study.

Physical Examination

A complete physical examination will be performed at Screening, including height. A symptom-directed physical examination including weight will be performed at all other visits unless indicated otherwise. Clinically significant physical examination findings after the administration of the first day of dosing will be recorded as adverse events.

12-lead Electrocardiogram (ECG)

A resting 12-lead ECG will be performed at the Screening Visit, unless performed for standard of care within 14 days. The investigator or a designee will sign and date the ECGs, determine if any findings outside normal physiological variation are clinically significant (in consultation with a cardiologist if necessary), and document this on the ECG report. ECGs will also be performed at the initiation of pazopanib maintenance therapy, Cycle 1 Day 1 and Cycle 2 Day 2.

Vital Signs

Vital sign determinations of heart rate, blood pressure and body temperature will be measured at all visits unless indicated otherwise.

Pregnancy Test

For female subjects of childbearing potential, a serum pregnancy test will be performed at the Screening Visit and a urine pregnancy test will be done at the Run-in period Day 1 visit prior to the first dose of pazopanib versus placebo. Subjects considered not of childbearing potential must be documented as being surgically sterile or post-menopausal (for at least 1 year). The test results must be reviewed and determined to be negative prior to dosing. If the urine pregnancy test is positive at Cycle 1 Day 1, it should be confirmed by a serum pregnancy test. The test may be repeated at the discretion of the Investigator at any time during the study. Should the subject become pregnant or suspect she is pregnant while participating in this study, she should inform the Investigator immediately. The Principal Investigator should be notified and will be responsible for contacting the representative at Novartis.

Clinical Laboratory Tests
All subjects will undergo the laboratory assessments outlined in **Appendix A**. After Cycle 1 Day 1, clinical laboratory tests should be performed within 72 hours surrounding the scheduled study visit date. Any laboratory value outside the reference range that is considered clinically significant by the investigator will be followed as appropriate. Clinically significant laboratory values will be recorded as adverse events if they meet the criteria as specified in **Section 7.7**.

Tumor Assessments (Radiologic)
Baseline staging scans including a positron emission tomograph with a built-in CT component (FDG-PET), MRI of the primary tumor, and diagnostic CT chest are required at Screening (within approximately 14 days of the Run-in Period, Day 1). After the 14-day Run-in period of pazopanib versus placebo, and prior to commencement of preoperative chemotherapy, subjects will undergo repeat FDG-PET and MRI of the primary tumor. After 2 cycles of chemotherapy, FDG-PET and MRI of the primary tumor will be repeated.

CT of the chest without contrast will be performed approximately every 3 months for the first year following surgery and MRI (or CT) of the primary site of the tumor will be performed every 6 months.

ECOG Performance Status
The ECOG performance status will be assessed at Screening, Run-in Period Day 1 and Day 1 of each subsequent cycle, Final Visit, and at the 30-day Follow-up Visit. See **Appendix B** for ECOG criteria.

Pharmacokinetic Studies
Trough level (22-24 hrs after pazopanib dosing): A blood sample (4 mL K2EDTA purple top blood collection tube) will be drawn to assess the trough plasma pazopanib concentration during the 14 day Run-in period of pazopanib monotherapy, after completion of adjuvant chemotherapy, and every 3 months thereafter until completion of pazopanib maintenance therapy. During the Run-in period, the trough level will be drawn twice during Days 10 through 14: 1) one trough on any of Days 10-14 and 2) on the day of the FDG PET after the Run-in period, 22-24 hours after the patient's last dose of pazopanib versus placebo. After completion of surgery/adjuvant chemotherapy, the trough will be drawn once during each of the following periods: 1) Week 2 (Days 10-15 after restarting pazopanib), Weeks 3-4 after

restarting pazopanib, and then every 3 months for 1 year). If all trough levels are drawn, a total of 8 samples are possible in a single subject.
An optional full intensive pharmacokinetic visit will be performed in consenting patients during Weeks 2-4 in subjects following surgery/adjuvant chemotherapy. Blood (4 mL K2EDTA purple top blood collection tube) will be obtained at the following timepoints: immediately before pazopanib dosing (within 5 minutes before giving pazopanib on the day of PK dosing) and 1, 2, 3, 4, 6, 8 hour timepoints (+/- 10 minutes) , and 24 hrs (range 22 to 24 hours) after dosing (a total of 8 samples/subject).

Biomarker Studies
Plasma will be collected for measurement of VEGF and soluble VEGFR2 (sVEGFR2) at baseline, after the 14 day Run-in period of pazopanib, after completion of neoadjuvant chemotherapy and approximately every 3 months thereafter until completion of pazopanib maintenance therapy, when indicated. Quantitative enzyme-linked immunosorbent assays (ELISA) for VEGF and sVEGFR2 will be performed on plasma and tumor extracts.

Plasma will also be collected for micro RNA at baseline, after the 14 day Run-in period of pazopanib, following neoadjuvant chemotherapy and every 3 months thereafter until completion of pazopanib maintenance therapy, when indicated.

5.0 SUBJECT SELECTION

5.1 Inclusion Criteria

5.1.a Histologically or cytologically confirmed soft-tissue sarcoma, excluding alveolar and embryonal rhabdomyosarcoma, well- and dedifferentiated adipocytic sarcomas, Ewing's, osteosarcoma, or gastrointestinal stromal tumor. AJCC (6^{th} Edition) Stage III or T2a Stage II or Stage IV-treatment naive patients planned for resection of the primary tumor, with resectable metastatic disease.

5.1.b Measurable disease greater than 5 centimeters in greatest dimension. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter for non-nodal lesions and short axis for nodal lesions to be recorded) by chest x-ray, CT scan, MRI or with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

5.1.c Intermediate or high grade lesions: 2 or 3 on a scale of 1-3 or grades 2 to 4 on a scale of 1-4.

5.1.d Sarcoma located on upper (includes shoulder) or lower (includes hip) extremities or on the body wall.

5.1.e Life expectancy of greater than 6 months.

5.1.f ECOG performance status ≤1 (Karnofsky ≥80%; see **Appendix B**).

5.1.g No prior chemotherapy, radiotherapy, or antiangiogenic therapy.

5.1.h Age ≥ 18 years

5.1.i No significant organ dysfunction with initial labs:

ANC	≥ 1500 /μL
Hgb	≥ 9.0 g/dL
Platelets	≥ 100,000 /μL
Creatinine	≤ 1.5 x ULN
Bilirubin	≤ 1.5 mg/dL
AST/ALT	≤ 1.5 x ULN

PT/INR/PTT within 1.2 X the upper limit of normal unless a subject is receiving Coumadin and has stable INR which is in range for the desired level of anticoagulation

5.1.j Normal cardiac function: LVEF ≥ 50%

5.1.k Blood pressure (BP) no greater than 140 mmHg (systolic) and 90 mmHg (diastolic) for eligibility. Initiation or adjustment of BP medication is permitted prior to study entry provided that the average of three BP readings on baseline assessment prior to enrollment is less than 140/90 mmHg.

5.1.l Eligibility of subjects receiving any medications or substances known to affect or with the potential to affect the activity or pharmacokinetics of pazopanib will be determined following review of their cases by the Principal Investigator (see **Section 7.4** for further information).

5.1.m Women of child-bearing potential and men must agree to use adequate contraception.

5.1.n A female is eligible to enter and participate in this study if she is of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) or if she is of childbearing potential, if she fits the criteria in **Appendix C**.

5.1.o Ability to understand and the willingness to sign a written informed consent document.

5.2. Exclusion Criteria

5.2.a Subjects with known brain metastases and/or unresectable sarcoma.

5.2.b Uncontrolled intercurrent illness including, active serious infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac ventricular arrhythmia requiring anti-arrhythmic therapy, serious hepatic impairment, or psychiatric illness/social situations that would limit compliance with study.

5.2.c Pregnant or lactating women.

5.2.d Subjects with no additional active malignancy within the last 3 years.

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5.2.e Subjects receiving other investigational agents.

5.2.f Subjects with a history of allergic reactions attributed to compounds of similar chemical or biologic composition to pazopanib or other agents used in the study.

5.2.g Subjects who have both bilirubin >ULN *and* AST/ALT >ULN

5.2.h Subjects with a urine protein/creatinine ratio greater than 1.

5.2.i Subjects with a baseline QTc of equal to or greater than 480 msecs or other significant ECG abnormalities.

5.2.k Certain medications that act through the CYP450 system are specifically prohibited in subjects receiving pazopanib and others should be avoided or administered with extreme caution and require PI approval.

- **Strong inhibitors of CYP3A4** such as ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinivir, ritonavir, saquinavir, telithromycin, voriconazole may increase pazopanib concentrations and **are prohibited.** Grapefruit juice is also an inhibitor of CYP450 and should not be taken with pazopanib.

- **Strong inducers of CYP3A4**, such as rifampin, may decrease pazopanib concentrations, **are prohibited**. (See **Section 7.2**)
- Medications which have narrow therapeutic windows and are substrates of CYP3A4, CYP2D6, or CYP2C8 should be avoided and, if necessary, administered with caution. (See **Section 7.2**)

A list of medications that are specifically prohibited or those that should be used with caution during this trial of pazopanib can be found in **Section 7.2**. Comprehensive lists of agents that could affect pazopanib through the cytochrome P450 system can be found in **Appendix D**.

Pazopanib, 800 mg once daily, has no effect on CYP2C9, CYP1A2, or CYP2C19 *in vivo* but does *in vitro*. Therefore, therapeutic doses of warfarin, a substrate of CYP2C9, and omeprazole, a substrate of CYP2C19 are permitted. Caffeine, a substrate of CYP1A2, is also permitted.

5.2.l Certain medications that are associated with a risk for QTc prolongation and/or Torsades de Pointes, although not prohibited, should be avoided or replaced with medications that do not carry these risks, if possible. Comprehensive lists of agents that that are associated with a risk for QTc prolongation and/or Torsades de Pointes can be found in **Appendix E**.

5.2.m Subjects who require heparin other than low-molecular weight heparin

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5.2.n Subjects with any condition that may impair the ability to swallow or absorb oral medications/investigational product including:

- any lesion, whether induced by tumor, radiation or other conditions, which makes it difficult to swallow capsules or pills
- prior surgical procedures affecting absorption including, but not limited to major resection of stomach or small bowel
- active peptic ulcer disease, not on a proton pump inhibitor
- malabsorption syndrome

5.2.o Subjects with any condition that may increase the risk of gastrointestinal bleeding or gastrointestinal perforation, including

- active peptic ulcer disease, not on a proton pump inhibitor
- known intraluminal metastatic lesions
- inflammatory bowel disease (*e.g.*, ulcerative colitis, Crohn's disease) or
- other gastrointestinal conditions which increase the risk of perforation
- history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 28 days prior to beginning study treatment

5.2.p Subjects with any of the following cardiovascular conditions within the past 6 months

- cerebrovascular accident (CVA) or transient ischemic attack (TIA)
- cardiac arrhythmia
- admission for unstable angina
- cardiac angioplasty or stenting
- coronary artery bypass graft surgery
- pulmonary embolism, untreated deep venous thrombosis (DVT) or DVT which has been treated with therapeutic anticoagulation for less than 6 weeks
- arterial thrombosis
- symptomatic peripheral vascular disease.
- Class III or IV heart failure as defined by the NYHA functional classification system. A subject who has a history of Class II heart failure and is asymptomatic on treatment may be considered eligible.

5.2.q History of hemoptysis in excess of 2.5 mL (1/2 teaspoon) within 8 weeks prior to first dose of study drug

5.2.r History of serious or non-healing wound, ulcer, or bone fracture.

5.2.s HIV-positive subjects on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with pazopanib.

5.2.t Subjects with severe hepatic impairment

- Bilirubin >3 ✕ ULN, regardless of any level of ALT

6.0 SUBJECT REGISTRATION AND RANDOMIZATION

All subjects will be registered by the coordinating center (University of Washington) and entered into the Protocol Accrual Tracking System (PATS). Information regarding the PATS system is available at http://www.cancerconsortium.org/rto/protocol_office/pats/. A complete, signed study consent and HIPAA consent are required for registration. An Investigator must review and sign the eligibility list for patients enrolled on the trial.

This is a double-blinded study. Patients will be randomized 2:1 to receive pazopanib versus placebo by the SCCA Investigator Drug Supply (IDS) Pharmacy according to a computer program from randomization.com. Physicians, research study staff, and patients will be blinded from the time of enrollment until the time of the patient's surgery, when unblinding will occur.

7.0 TREATMENT PLAN

TREATMENT	PAZOPANIB RUN-IN [A]	CYCLES 1 AND 2[B]	CYCLES 3 AND 4[C]	PRE-OP RT [D]	SURGERY [E]	CYCLES 5 AND 6[B]	POST-OP RT[F]
DOXORUBICIN		75 MG/M2 CIVI OVER 3 DAYS, EACH CYCLE WEEKS 3-8	75 MG/M2 CIVI OVER 3 DAYS, EACH CYCLE WEEKS 9-14	WEEKS 16-21	2-4 WEEKS AFTER COMPLE-TION OF PRE-OPERATIVE THERAPY	75 MG/M2 CIVI OVER 3 DAYS, EACH CYCLE 2-4 WEEKS AFTER SURGERY	2-4 WEEKS AFTER COMPLETION OF CHEMO-THERAPY
IFOSFAMIDE		2 GM/M2 IV, DAYS 1-5, EACH CYCLE WEEKS 3-8 (6-DAY WASHOUT AFTER PAZOPAN-IB	2 GM/M2 IV, DAYS 1-5, EACH CYCLE WEEKS 9-14			2 GM/M2 IV, DAYS 1-5, EACH CYCLE 2-4 WEEKS AFTER SURGERY	

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TREATMENT	PAZOPANIB RUN-IN A	CYCLES 1 AND 2B	CYCLES 3 AND 4C	PRE-OP RT D	SURGERY E	CYCLES 5 AND 6B	POST-OP RTF
MESNA[I]		AFTER EACH DOSE OF IFOS	AFTER EACH DOSE OF IFOS			AFTER EACH DOSE OF IFOS	
PAZOPANIB OR PLACEBO	800 MG PO DAILY, WEEKS 1-2						
PAZOPANIB MAINTEN-ANCE[G]							1 WEEK AFTER COMPLETION OF CHEMO/RT (DURATION 52 WEEKS)

A Pazopanib versus placebo run-in 14 days

B Chemotherapy cycles every 21 days. Cycle 1 may not commence until a 6 day washout period of pazopanib has occurred.

C Cycles 3 and 4 will only be given if there is a response to chemotherapy identified on imaging after cycles 1 and 2.

D Pre-operative radiation administration, when given, will consist of external beam 50 Gy in 25 fractions of 2 Gy/fraction over 5 weeks. If the target volume encompasses sensitive structures such as bowel or lung, the dose can be reduced to 45 Gy in 25 fractions of 1.8 Gy without protocol violation.

E Surgery should be planned for 2-4 weeks after completion of pre-operative therapy. Any planned post surgical adjuvant chemotherapy should be initiated only after adequate wound healing has been achieved. Patients who require a delay of greater than 10 weeks from the initial surgery due to inadequate wound healing will be removed from further protocol therapy.

F Post-operative radiation administration, when given, will consist of external beam 50 Gy in 25 fractions of 2 Gy/fraction over 5 weeks, followed by 10 Gy boost (in 5 fractions) to a reduced, or boost, volume. For contaminated or close margins, the boost dose will be 10 - 16 Gy; for microscopically positive margins, 16 - 20 Gy, and for grossly positive margins, 20 – 26 Gy.

For patients who received pre-operative radiation, but have positive surgical margins, 16 – 20 Gy (2Gy x 8 - 10 fractions) will be given by external beam following any planned adjuvant chemotherapy.

G Pazopanib may be resumed 1 week after completion of post-operative therapy (chemotherapy +/- radiation) for those randomized to the treatment who had a response by imaging, to be continued for 1 year. Unblinding occurs during the first post-op visit after surgery.

H PEG-Filgrastim should be administered approximately 24-48 hours after completing chemotherapy. 10 days of filgrastim may be substituted.

I Mesna will be given at 400 mg/m^2. Post IFOS doses will be at 4 hours and 8 hours (+/- standard clinical dosing windows)

7.1 Agent Administration

7.1.1 Pazopanib Administration

Subjects will be randomized to receive either pazopanib 800 mg orally daily or placebo for 14 days as a Run-in period, prior to beginning neoadjuvant chemotherapy with doxorubicin and ifosfamide. Doses of pazopanib/placebo will be taken fasting (at least 1 hour prior and/or 2 hours after).

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Subjects deemed to be responders to pazopanib preoperative therapy (defined in **Section 11.3**), will have the option to receive one year of therapy with pazopanib 800 mg orally daily following completion of surgery and post-operative adjuvant treatments.

Treatment Regimen

Treatment will be administered on an outpatient basis. Subjects receive pazopanib versus placebo at a dose of 800 mg/day (four 200-mg tablets or two 400 mg tablets; dose modification will be accomplished by combining 200-mg tablets as necessary). Subjects are instructed to swallow tablets once a day (preferably in the morning) on an empty stomach, either 1 hour before or 2 hours after food with about 1 cup (240 mL) water. Tablets should be swallowed whole; they must not be chewed, broken, or crushed. Treatment continues until one of the criteria in **Section 7.3** applies.

For the subjects who will have intensive pharmacokinetic analyses performed during pazopanib maintenance, subjects should wait to take the pazopanib on-site (observed dose by study personnel). Subjects should either wait to eat on-site (1 hour after pazopanib dosing) or make sure to eat at least 2 hours before the planned time of pazopanib dosing for that day.

Subjects will be provided with a Medication Diary for pazopanib, instructed in its use, and asked to bring the diary with them to each appointment. A new copy of the Medication Diary will be given to subjects whose dose is reduced due to AEs. Prior to the scheduled study visit, subjects will be reminded to document the exact time of pazopanib dosing the day before blood is drawn for measurement of trough concentrations. Subjects will also be reminded not to take their morning pazopanib dose until after the blood draw for trough concentrations has been completed.

All prescription and over-the-counter medications as well as alternative medicines that have been taken within 4 weeks prior to the first dose of pazopanib must be fully documented in the Case Report Form (CRF; indication, dose information and dates of administration). The Investigator or a designee must be informed as soon as possible about any new medication taken from the time of screening until the end the study; these new medications will be fully documented in the CRF (indication, dose information, and dates of administration).

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

Precautions/Warnings

Certain drugs which induce or inhibit cytochrome P450 enzymes are prohibited. **Medical personnel must refer to the list of prohibited agents in Section 7.4 prior to administering treatment.**

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Certain drugs which are listed as "use with caution" should be avoided if possible, but if necessary, subjects who receive these medications should be closely monitored for AEs. **Medical personnel must refer to the list of "use with caution" agents in Section 7.4_ prior to administering treatment.**

Hypertension is an important AE associated with pazopanib. Frequent **blood pressure (BP) monitoring is important** in subjects receiving pazopanib versus placebo starting on day 8 and continuing until the subject is off study. Experience to date suggests that increases in BP may occur following dosing with pazopanib for a number of weeks and that these increases may occur relatively quickly. **Section 7.7** includes specific guidelines on the management of treatment-emergent hypertension. Recommendations for hypertension monitoring and management are presented in **Appendix F**.

QTc prolongation and Torsades de Pointes is a rare but serious adverse event associated with pazopanib. Therefore, the following is required:

- **Intensive QTc monitoring. A baseline ECG is required prior to study registration, and subjects with QTc≥480 msec are excluded**. Repeat **ECG** must be performed during the week 2. After surgery, for those subjects continuing on maintenance pazopanib, if the QTc interval at 4 weeks is ≥500 msec, the ECG should be repeated within 7 days and, if the QTc interval remains ≥500 msec, the subject should be removed from the study. Additionally, if the QTc interval is increased by 60 msec or more from baseline but the QTc interval remains at <500 msec, an ECG should be repeated within 7 days. If the repeat ECG again shows a ≥60 msec increase in the QTc interval from baseline, consideration should be given to removing the subject from the study or increasing monitoring, after discussion with the Principal Investigator.

- **Subjects must be questioned about family history of prolonged QTc, personal history of prolonged QTc, relevant cardiac disease, and concomitant medications which are associated with a high risk of causing QTc prolongation prior to study registration**.

- **Concomitant treatment with drugs that are associated with a high risk of causing QTc prolongation should be changed to similar agents that do not pose such a risk, if possible, prior to a subject receiving the first dose of pazopanib.** A comprehensive list of agents that are associated with a risk of prolonging the QTc interval is provided in **Appendix E.**

- **Potassium, calcium, phosphate, and magnesium levels must be obtained before administration of the first dose of pazopanib and frequently thereafter (as described in the Study Calendar, Appendix A).**

- **Abnormalities that occur after enrollment in potassium, calcium, phosphate, and magnesium levels should be managed as follows:** Pazopanib should be held and an ECG must be performed for hypokalemia or hyperkalemia ≥grade 2; hypocalcemia or hypercalcemia ≥grade 3; hypophosphatemia ≥grade 3; hypomagnesemia or hypermagnesemia ≥grade 3. Grading is according to CTCAE v4. These laboratory values should be corrected as soon as possible in a manner consistent with good medical judgment. Pazopanib may be re-administered when hypokalemia or hyperkalemia is grade 1 or within institutional limits; hypocalcemia or hypercalcemia is ≤grade 2, hypophosphatemia is ≤grade 2; and hypomagnesemia or hypermagnesemia is ≤grade 2. Even though pazopanib administration is allowed at these lower grades, every effort should be made to correct the abnormal lab values to normal if possible.

  If an ECG, obtained because of these lab values, reveals an increase in the QTc to >500 msec or an increase in the QTc by at least 60 msec from baseline, the ECG should be repeated before re-administration of pazopanib. If the QTc interval, on the repeat ECG, is still ≥500 msec, the subject should be removed from the study. If the QTc, on the repeat ECG, remains increased in the QTc by at least 60 msec from baseline but is less than 500 msec, consideration should be given to removing the subject from the study.

Renal function (creatinine and urinary protein) should be frequently monitored as suggested by the pathologic changes noted in animal studies and evidence from studies of other antiangiogenic agents. Specific guidelines for management of proteinuria and elevated creatinine are presented in **Section 7.7.**

Hepatic Function monitoring include ALT, AST, GGT, alkaline phosphotase and total bilirubin at the following visits:

- at screening;
- before initiation of pazopanib treatment;
- end of week 2;
- prior to Day 1 of each cycle;
- at post-treatment visit;
- final visit;
- 30-day follow-up

Periodic monitoring should continue monthly if pazopanib monotherapy is continued. Pazopanib is not recommended for subjects with severe hepatic impairment (defined as >3✕ULN, regardless of any level of ALT).

7.1.2 Chemotherapy Administration

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Pre-operative chemotherapy will consist of doxorubicin and ifosfamide administered on an inpatient basis. Subjects may also receive 2 to 4 cycles of post-operative chemotherapy, (up to 6 cycles total of neoadjuvant plus adjuvant chemotherapy).

Doxorubicin: 75 mg/m^2 by continuous IV infusion days 1 through 3 of each cycle.

Ifosfamide: 2.0 g/m^2 over 4 hours IV, days 1 through 5 of each cycle.

Mesna: 400 mg/m^2 IV pre, 4 hours post, and 8 hours post each dose of ifosfamide.

Hydration: D5W with 100 meq/L sodium acetate, 20 meq/L potassium acetate, 4 meq/L magnesium sulfate continuous IV infusion at a rate of 83 mL/hour, begun approximately 2 hours prior to chemotherapy and discontinued after completion of chemotherapy and Mesna.

Cycle 1 of chemotherapy may only commence after a minimum 6-day washout period of pazopanib.

7.2 Radiation Therapy

Radiation treatment (XRT) will be administered using standard of care delivery and quality assurance techniques, using mega-voltage photons. Electrons may be used if dosimetrically appropriate, but no other particle therapy such as neutrons or protons may be used. Brachytherapy and IORT may be used for boost volumes to sites of residual disease, when appropriate. Simulation must be CT-based, using contrast if possible, and appropriate immobilization devices. Target delineation for preoperative XRT must include the GTV, CTV, PTV and organs at risk, with identified dose constraints, and for postoperative XRT, delineation must include the pre-operative GTV, CTV (i.e., surgical bed), PTV and organs at risk, also with identified dose constraints. Treatment planning must generate dosimetry with no more than plus or minus 5% heterogeneity, while sparing an adequate strip of circumferential tissue to allow ongoing lymphatic drainage, and utilizing external beam delivery techniques, such as IMRT and 3-D conformal approaches when necessary, to achieve this aim. The use of bolus is at the discretion of the radiation oncologist, but is rarely indicated in the preoperative setting.

For preoperative XRT, the prescribed dose to the PTV should be 50 Gy in 25 fractions of 2 Gy/fraction over 5 weeks. If the target volume encompasses sensitive structures such as bowel or lung, the dose can be reduced to 45 Gy in 25 fractions of 1.8 Gy without protocol violation.

For postoperative XRT, the prescribed dose to the PTV should be 50 Gy in 25 fractions of 2 Gy/fraction over 5 weeks, followed by 10 Gy boost (in 5 fractions) to a reduced volume. For contaminated or close margins, the boost dose will be 10 - 16 Gy; for microscopically positive margins, 16 - 20 Gy, and for grossly positive margins, 20– 26 Gy.

Verification must include initial and weekly isocenter imaging checks with image guidance with cone beam CT as appropriate to the technique, as well as weekly on-treatment patient review visits. Diode checks and physics review must be completed as standard procedure.

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Maintenance pazopanib for those who respond to therapy during the Run-in period, may not commence until one week following completion of radiation.

7.3 Surgery

The goal of surgical treatment is to resect the tumor with negative margins. All lesions of the trunk and extremities will be treated with conservative resection (minimal wide excision) after pre-operative therapy. Surgical resection should remove as wide a margin of tissue around the tumor as possible without compromising function. If postoperative pathology evaluation reveals positive soft-tissue margins other than bone, nerve, or large blood vessels, this margin should be re-resected if possible. If bone, major blood vessel or nerve is microscopically positive additional radiation should be given as noted in the protocol. Resectability will depend upon the judgment of the operating surgeon. For the extremities, limb salvage procedure is standard of care if achievable. For other anatomic areas, it must be the judgment of the operating surgeon that he/she may reasonably expect to obtain negative margins. Extremity patients who are not resectable without amputation may be amputated, and should complete chemotherapy per protocol.

7.4 Concomitant Medication and Supportive Care Guidelines

7.4.1 Potential Drug Interactions

Pazopanib is primarily metabolized by the human CYP3A4 isoenzyme. Potent CYP3A4 inhibitors and inducers **are prohibited on the trial.**

Medications prohibited during pazopanib therapy that strongly inhibit CYP3A4 include (but are not limited to):

- Antibiotics: clarithromycin, telithromycin, troleandomycin, erythromycin
- HIV: protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir)
- Antifungals: itraconzaole, ketoconazole, voriconazole
- Antidepressants: nefazodone
- Antiarrythmics: ditiazem, felodipine, nicardipine, quinidine, verapamil

Medications prohibited during pazopanib therapy that strongly induce CYP3A4 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, troglitazone, canertinib, erlotinib, lapatinib

Pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6. Drugs that have narrow therapeutic windows and are substrates for these enzymes **should be administered with**

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extreme caution. Because of pazopanib's long half-life, caution should continue to be exercised for at least 14 days after the last dose of pazopanib when administering these medications.

Medications to use with caution that are substrates for these enzymes *and* have narrow therapeutic windows 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, simvastatin, bevacizumab, topotecan, short-acting antacids and PPIs.

Pazopanib can prolong the QTc interval. Drugs that are generally accepted to have a risk of causing Torsades de Pointes (**see Appendix E**) should be discontinued or replaced with drugs that do not carry this risk, if at all possible. Subjects who receive potential QTc-prolonging medications (**see Appendix E**) should be monitored closely.

Pazopanib may increase bleeding. Subjects, receiving pazopanib and anticoagulation, should be monitored for bleeding.

Pazopanib may cause decreased glucose. Subjects, receiving pazopanib and hypoglycemia agents, should be monitored for hypoglycemia.

7.4.2 Supportive Care

Anti-Emetics

Routine use of anti-emetics is recommended for subjects due to the highly emetogenic nature of the chemotherapy regimen. Selection of anti-emetics is based on the institution's standard and is at the Investigator's discretion.

Prophylactic Antibiotics

Prophylactic antibiotics for prevention of neutropenic fever may be used at the discretion of the Investigator. Use of prophylactic antibiotics must be recorded in the case report forms.

Growth Factors

Administration of growth factor is required after all chemotherapy cycles:

PEG-filgrastim 6 mg administered as a subcutaneous injection starting 24-48 hours after completion of chemotherapy (may substitute filgrastim 5 mcg/kg/day (rounded to nearest vial

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size) administered as a subcutaneous injection starting 24-48 hours after completion of chemotherapy for 10 days, or until white blood count has recovered after nadir (ANC > 10,000)

Transfusion of Blood Products
Depending on the particular setting, red blood cell and platelet transfusions may be appropriate, at the Investigator's discretion and with the subject's consent.

7.5 Duration of Therapy

Treatment should continue until the end of protocol therapy, defined as the completion of all adjuvant treatments following surgical resection of the primary tumor, or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse events(s),
- Greater than 3-week delay in therapy due to adverse event
- The subject or legal representative requests to withdraw from the study, or
- Changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the Investigator.

7.6 Duration of Follow-Up

When a subject discontinues the study, a Final Visit will be conducted. All subjects will have one Follow-up Visit approximately 30 days after the Final Visit. This Follow-up Visit does not need to be performed for subjects who have had a Final Visit conducted ≥ 30 days after discontinuation of maintenance pazopanib therapy.

Study visits and evaluations will be performed in clinic at Screening and within approximately 72 hours prior to hospital admission for each chemotherapy cycle (neoadjuvant as well as adjuvant). Assessments will include interval history, physical examination, blood counts and chemistries. Radiological assessments including FDG-PET CT, MRI of the primary tumor, and diagnostic CT chest will be performed prior to the 14 day Run-in period of pazopanib versus placebo. After the Run-in period, and prior to commencement of preoperative chemotherapy, subjects will undergo repeat FDG-PET CT and MRI of the primary tumor. After 2 cycles of chemotherapy, FDG-PET CT and MRI of the primary tumor will be repeated. (**Refer to Section 4.3 and Appendix A**). Study procedures may be performed up to approximately 72 hours before or after the scheduled visit date.

Subjects will be evaluated daily during radiation therapy. Following surgery, subjects who remain on pazopanib monotherapy will have study visits and evaluations monthly for the one year duration of therapy, and follow-up visits will be every 3 months for those not on pazopanib. CT of the chest without contrast will be performed every 3 months for the first

year following surgery and MRI (or CT) of the primary site of the tumor will be performed every 6 months.
Following the Final Visit and/or 30-day Follow-up Visit, follow-up will proceed as described in the study calendar (Appendix A) until recurrence or progression. Patients experiencing recurrence or progression will be contacted every 4 months for overall survival, unless the patient has withdrawn consent for the study has ended.

7.7 Dosing Delays/Dose Modifications

Recommendations for pazopanib dose interruptions/modifications in case of specific treatment-emergent AEs are provided in the following sections.

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 subject should be monitored for approximately 10 to 14 days at each dose level. If toxicity does not abate during this monitoring time, the IP 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).

General: Pazopanib dosing will be modified for adverse events according to the following sections. Reference the following Dose Level table:

Dose Level	Pazopanib
-2*	400 mg daily
-1	600 mg daily
1	800 mg daily

*Patients will be removed from protocol treatment if dose reduction below this level is indicated.

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

Recommendations for pazopanib (investigational product, IP) dose interruptions/modifications in case of specific treatment-emergent AEs are provided in Table 1.

Table 1 Dose Modification Algorithms for Potential Treatment-Related Adverse Events

AE Terms & Descriptions	Dose Modification Algorithms

AE Terms & Descriptions	Dose Modification Algorithms
Hypertension	
(A). Asymptomatic and persistent SBP of ≥140 and <170 mmHg, or DBP ≥90 and <110 mmHg, or a clinically significant increase in DBP of 20 mmHg (but still below 110 mmHg).	Step 1. Continue investigational product (IP) 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 IP, as clinically indicated. 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. Step 4. Once BP is well-controlled, restart IP dose-reduced by 200 mg if IP was interrupted.
(C). Symptomatic hypertension or recurring SBP ≥170 mmHg, or DBP ≥110 mmHg, despite modification of antihypertensive medication(s)	Step 1. Interrupt IP 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 IP dose-reduced by 200 mg.
(D). Refractory hypertension unresponsive to above interventions.	Discontinue IP and continue follow-up per protocol.
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. **Refer to Section 7.1.1 for ECG monitoring**	
QTc ≥ 480 < 500 msec	Continue IP; monitor as clinically indicated.
QTc ≥ 500 msec	Discontinue IP 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 IP. Step 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 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 contact the Novartis Study Physician to discuss whether further treatment with pazopanib is appropriate.

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	For other Grade I hemorrhage/bleeding events, continue pazopanib at the current dose; monitor as clinically indicated.
Grade 2	Step 1. If pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue IP and continue follow-up per protocol. Otherwise, interrupt IP until the AE resolved to ≤ Grade 1. Step 2. Restart IP; consider reducing dose and monitor as clinically indicated.
Grade 3 or 4, or Recurrent ≥ Grade 2 event after dose interruption/reduction.	Discontinue IP and continue with follow-up per protocol.
Venous Thrombosis (DVT, PE)	
Grade 2	Continue IP at the current dose; monitor as clinically indicated
Grade 3	Step 1. Interrupt IP. Step 2. Initiate and monitor anticoagulation as clinically indicated. Step 3. Resume IP at 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 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 IP dosing (eg, re-initiating, escalating/de-escalating, or discontinuing IP), 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 IP and continue follow-up per protocol.
Arterial Thrombosis/Ischemia	
Any Grade	Discontinue IP and continue follow-up per protocol.
Thrombocytopenia: Investigate and document underlying cause	
Grade 1 or 2	Continue IP with current dose; monitor as clinically indicated.
Grade 3 or 4	Step 1. Interrupt IP until toxicity resolves to ≤ Grade 2. Step 2. Restart IP dose-reduced by 200 mg and monitor as clinically indicated. If no recovery to ≤ Grade 2 or recurrent Grade 3 or 4 thrombocytopenia, discontinue IP 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	

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Grade 1 Minimal skin changes or dermatitis without pain (erythema, oedema, hyperkeratosis)	1. Continue IP at present dose
Grade 2 Skin changes with pain; limiting instrumental activities of daily living (ADLs) (peeling, blisters, oedema, bleed, hyperkeratosis)	1. Hold IP 2. Treat as clinically appropriate 3. Upon resolution to Level 1 or better restart IP with a dose reduction to 400 mg 4. If recurrent consider a further dose reduction to 200mg or discontinuation
Grade 3 Severe skin changes with pain and limiting self care ADLs	1. Discontinue IP
Other Clinically Significant Adverse Events[b]	
Grade 1	Continue IP; monitor as clinically indicated.
Grade 2 or 3, if clinically significant	Step 1. Interrupt IP until toxicity resolves to ≤ Grade 1. Step 2. Restart IP dose-reduced by 200 mg and monitor as clinically indicated.
Grade 4	Discontinue IP 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)
Abbreviations: BP, blood pressure; IP, investigational product.

7.7.2 Dose Interruptions/Modifications for Hepatoxicity

AST, ALT and/or Bilirubin	
Isolated AST/ALT elevations between 3X ULN and 8X ULN	Reduce pazopanib dose to 200 mg QD, and monitor weekly until AST/ALT returns to ≤ 2.5 or baseline
AST/ALT >8 X ULN	Hold pazopanib until AST/ALT returns to ≤ 2.5 X ULN or baseline. If the potential benefit of reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then consider reintroducing pazopanib at a reduced dose of 400 mg once daily and measure serum liver tests weekly for 8 weeks only after discussion with the PI. If AST/ALT elevations >3 X ULN recur, then pazopanib should be permanently discontinued.
AST/ALT >3 X ULN and concurrent bilirubin elevations >2 X ULN	Permanently discontinue pazopanib.
Mild indirect hyperbilirubinemia, known or suspected Gilbert's syndrome, and elevation in AST/ALT >3 X ULN	Continue pazopanib, but monitor weekly until AST/ALT returns from >3 X ULN to grade 1 (NCI CTCAE) or baseline.

Severe hepatic impairment, defined as bilirubin >3 X ULN, regardless of any level ALT	Permanently discontinue pazopanib.

7.7.3 Chemotherapy Dose Modifications

A treatment cycle may not begin unless the patient's absolute neutrophil count (ANC) is ≥1500/μL and platelet count is ≥100,000/μL (without transfusion).

Patients who experience Grade 3 or 4 hematologic or non-hematologic toxicity that is attributable to chemotherapy and not to the underlying disease should have chemotherapy held until the toxicity resolves to ≤ Grade 1**.** Dose modifications for doxorubicin and ifosfamide-related toxicity will be based on the Investigator's discretion.

Patients who are delayed greater than 3 weeks due to non-resolution of such toxicity will be taken off study.

7.8 Criteria for Evaluability and Removal/Withdrawal from Treatment

Criteria for evaluability of the Trial

- **Patients must have received a total of at least 80% of the intended dose of doxorubicin, ifosfamide, and pazopanib to be evaluable for the trial. If less than this amount is received, the patient may remain on the study, but will not be evaluated for primary endpoints.**

Criteria for stopping therapy:

- Substantial non-compliance with the requirements of the study.
- Any adverse event which, in the Investigator's opinion, requires termination of the study medication.
- Disease progression, unless at the discretion of the Investigator (in collaboration with Novartis) continued treatment with study drug is appropriate.
- The patient would benefit from additional radiation therapy beyond that specified in the protocol.
- Request by the patient or a legal representative/relative to stop the treatment.
- The patient presents with a beta-HCG test consistent with pregnancy. Pregnancy will be reported along the same timelines as a serious adverse event.
- The patient uses illicit drugs or other substances that may, in the opinion of the
- Investigator, have a reasonable chance of contributing to toxicity or otherwise interfering with results.
- The development of a second malignancy that requires treatment, which would interfere with this study.
- The patient is lost to follow-up.
- Interruption in administration of pazopanib or chemotherapy for greater than 3-week delay.
- Development of an intercurrent illness or situation which would, in the judgment of the Investigator, affect assessments of clinical status and study endpoints to a significant degree.

Criteria for study withdrawal:

- Study closure.
- Patient decision to withdraw from both study therapy and follow-up.

The Investigator will make every reasonable effort to keep each patient in the study unless it is in the patient's best interest to discontinue participation. If a patient is removed from the study or declines further participation, all End of Treatment evaluations should be performed if the patient is willing and able to be assessed. A description of the reason(s) for withdrawal from the study will be recorded on the case report form (CRF). The Investigator should also ensure that all patients are followed up for survival and recurrence after the Final Visit.

Relevant visit data should be entered on the CRF and any unused study medication will be accounted for and returned for all patients participating in the study, even for a brief period of time. Patients who discontinue following entry will have relevant information completed and recorded on the CRF. All patients who discontinue because of adverse events or clinically significant laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome will be recorded. If any patient should die during the trial or within 30 days of stopping study treatment, the Investigator will inform the IRB and the Novartis representative. The cause of death should be recorded in detail, within 24 hours, on a serious adverse event (SAE) form and reported to the IRB and Novartis.

Subjects who are withdrawn from the study prior to surgery will be replaced and randomized to treatment with pazopanib versus placebo according to the 2:1 design.

8.0 GUIDELINES FOR ADVERSE EVENT REPORTING

8.1 Adverse Event Reporting/ Institutional Policy

In accordance with institutional policy, all adverse events which in the opinion of the Principal Investigator are unexpected **and** related or possibly related to the research **and** serious or suggest that the research places research participants or others at greater risk of physical or psychological harm than was previously known or recognized be reported to the IRB within 10 calendar days of learning of the problem.

Definitions:

Adverse Event: - Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, medical treatment or procedure and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, medical treatment or procedure whether or not considered related to the medicinal product.

Life-threatening Adverse Event: – Any adverse event that places the patient or subject, in view of the Investigator, at immediate risk of death from the reaction.

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Unexpected Adverse Event: – An adverse event is "unexpected" when its nature (specificity), severity, or frequency are not consistent with (a) the known or foreseeable risk of adverse events associated with the research procedures described in the Protocol-related documents, such as the IRB-approved research protocol, informed consent document and other relevant sources of information such as product labeling and package inserts; and are also not consistent with (b) the characteristics of the subject population being studied including the expected natural progression of any underlying disease, disorder or condition any predisposing risk factor profile for the adverse event.

Serious Adverse Event (SAE): – Any adverse event occurring that results in any of the following outcomes:

- death;
- a life-threatening adverse event (real risk of dying);
- inpatient hospitalization or prolongation of existing hospitalization (for reasons other than planned chemotherapy or post-surgical care)
- a persistent or significant disability/incapacity;
- a congenital anomaly;
- requires intervention to prevent permanent impairment of damage.

Attribution: - The following are definitions for determining whether an adverse event is related to a medical product, treatment or procedure:

An adverse event is "**related or possibly related to the research procedures"** if in the opinion of the Principal Investigator, it was more likely than not caused by the research procedures.

Adverse events that are **solely** caused by an underlying disease, disorder or condition of the subject or by other circumstances unrelated to either the research or any underlying disease, disorder or condition of the subject are **not "related or possibly related."**

If there is any question whether or not an adverse event is related or possibly related, the adverse event should be reported.

The Cancer Consortium Expedited Reporting Form should be completed for all adverse events that meet the expedited reporting requirements. The AE form should be faxed to the IRO at (206) 667-6831. All available information should be submitted.

It is the responsibility of the Principal Investigator and/or a designated staff member to notify Novartis, NIH, and the FDA of adverse events that meet expedited reporting (such as Serious Adverse Events) as required in the protocol.

Also considered serious for the purposes of this study:

- ALT >3.0 x ULN with concomitant elevation in bilirubin (defined as total bilirubin <2.0 x ULN or direct bilirubin 35%) or with hypersensitivity symptoms (e.g., fever, rash) – bilirubin fractionation should be performed in testing available.
- ALT >8.0 x ULN without bilirubin elevation (defined as total bilirubin <2.0 x ULN or direct bilirubin 35%) and without hypersensitivity symptoms (e.g., fever, rash) – bilirubin

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fractionation should be performed if testing available.

Serious Adverse Events

For Open Label Portion of Study:
All SAEs arising during the study in subjects exposed to pazopanib will be reported to Novartis using copies of the original Case Report Form pages and within 24 hours of first becoming aware of the event, regardless of causality assessments.

For Blinded Portion of Study:
Study conduct procedures will be ensured and in place to allow for the expedited reporting of relevant SAEs to the appropriate regulatory authorities, IEC(s) or IRB(s) as required, during the course of the study.

SAEs will be sent to Novartis as they arise in subjects exposed to pazobanib using copies of the original Case Report Form pages and within 24 hours of first becoming aware of the event, regardless of causality assessments.

Pregnancy Reports
Reports of pregnancy information on any female subjects who becomes pregnant while participating in the study and following exposure to the study product will be sent to Novartis using copies of the original Case Report Form pages and within two weeks of the pregnancy (including premature termination of the pregnancy).

Information on the status of the mother and child will be reported to the coordinating center. Generally, follow-up will be requested by Novartis no longer than 8 weeks following the estimated delivery date.

8.2 Study-Specific Adverse Event Capture

8.2.1 Duration and Grade of Adverse Event Capture

All grade 3 and 4 adverse events occurring after the subject has taken the first dose of study drug until the end of study will be recorded in the subject's case record form.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the Investigator, should be reported as an adverse event. Each grade 3 or 4 event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

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8.2.2 Adverse Event Grading

Toxicities will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (the most current version available. The scale in its entirety can be found at:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

9.0 DATA AND SAFETY MONITORING PLAN

9.1 Data Monitoring

Data and safety monitoring for the study will be performed by the Clinical Research Support Office of the Fred Hutchinson/University of Washington Cancer Consortium (the "Consortium"). The purpose of the monitoring is to verify the accuracy of the study data, assess compliance with the protocol and with Good Clinical Practice (GCP) regulations, and assure the timely and complete reporting of safety (adverse event) data. To facilitate the monitoring, medical records for subjects enrolled by the University of Washington/Seattle Cancer Care Alliance (the coordinating center) and Oregon Health & Science University will be reviewed by the Clinical Research Support Office. The records will be made available for monitoring by study staff.

Monitoring for this study will be scheduled in accordance with the Cancer Consortium Data and Safety Monitoring Plan. The intervals and scope are detailed in the monitoring plan.

9.2 Safety Monitoring

Investigators will conduct continuous review of data and patient safety. Bi-monthly review meetings will include Principal Investigators and study coordinators. Other study staff may be included per the PI's discretion. A summary of the following will be presented at each meeting:

- Total subject accrual
- Significant toxicities experienced by enrolled subjects
- Dose modifications and responses

The Principal Investigators and co-Investigators will provide study oversight and will review adverse events for trends that indicate a change in the known risks to the study participant. The Principal Investigator will meet with these individuals on a regular basis to review recently acquired data, and adverse events. If it is the opinion of any investigator that the risks or benefits to a patient warrant suspension or termination of study activity, the recommendation must be submitted in writing to the Principal Investigator for safety committee review. The safety committee will include John Thompson, MD, and Bojana Askovich, Ph.D in addition to the Principal Investigators and primary study staff. Suspension or termination of study activities may also be initiated based on the bi-monthly review.

9.3 Auditing

All trials conducted or coordinated by UW/SCCA are subject to audit. Internal audit reports will be reviewed at bi-monthly meetings.

9.4 Quality Assurance Review (QAR)

All trials conducted or coordinated by UW/SCCA are subject to quality assurance review (QAR). Quality assurance review reports will be reviewed at bi-monthly meetings.

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10.0 STUDY AGENT INFORMATION

10.1 Pazopanib (GW786034) (NSC 737754)

Other Names: Pazopanib HCl, GW786034B (the suffix B denotes the monohydrochloride salt), Votrient.

Classification: VEGFR tyrosine kinase inhibitor

Mechanism of Action: Pazopanib is a highly potent inhibitor of vascular endothelial growth factor (VEGF) receptor tyrosine kinases (VEGFR1, VEGFR2, and VEGFR3). Vascular endothelial growth factor receptor inhibition may block VEGF driven angiogenesis and, as a consequence, constrain tumor growth.

Molecular Formula: $C_{21}H_{23}N_7O_2S$-HCl

M.W.: 474.

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

Approximate Solubility: The monohydrochloride salt is very slightly soluble in 0.1 M HCl (0.65 mg/mL), and is practically insoluble in pH 7.0 phosphate buffer (0.00005 mg/mL), and in pH 11 piperidine buffer (0.0002 mg/mL).

How Supplied: GW786034 monohydrochloride is supplied as a series of aqueous film-coated tablets containing 100 mg, 200 mg, 400 mg, and 500 mg of the free base:

- 100 mg, round, white to off white, packaged in bottles containing 100 tablets each
- 200 mg, oval-shaped, white, packaged in bottles containing 34 tablets each
- 400 mg, oval-shaped, white, packaged in bottles containing 68 tablets each
- 500 mg, capsule shaped, white to off white, packaged in bottles containing 68 tablets each

Tablet excipients in all tablet sizes include microcrystalline

cellulose, povidone, sodium starch glycolate, and magnesium stearate. The film-coat consists of titanium dioxide, hypromellose, polyethylene glycol, and polysorbate 80.

Storage: The intact bottles should be stored at controlled room temperature.

Stability: Stability studies are ongoing.

Route of Administration: Oral pazopanib should be taken on an empty stomach either 1 hour before or 2 hours after meals. The tablets should be swallowed whole and cannot be crushed or broken.

Method of Administration: Subjects should fast for 2 hours before and 1 hour after each pazopanib dose.

Availability: Pazopanib is a commercial product provided to the SCCA for the study by Novartis.

Expected Adverse Events:

The CTEP Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with pazopanib. A subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only.

Version 2.2, March 18, 2010[1]

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 4 Term) [n= 1019]			**EXPECTED AEs FOR ADEERS REPORTING Agent Specific Adverse Event List (ASAEL)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	***Expected***
CARDIAC DISORDERS			
Chest pain			***Angina***
Bradycardia			***Bradycardia***
QT-prolongation			
	Cardiac dysfunction		
		Left ventricular systolic dysfunction	
		Myocardial infarction	
ENDOCRINE DISORDERS			

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	Hypothyroidism		
		Liver Failure	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain***
	Constipation		
	Flatulence		
Diarrhea			***Diarrhea***
		Gastrointestinal fistula[2]	***Gastrointestinal fistula[2]***
		Gastrointestinal hemorrhage[3]	
		Gastrointestinal perforation[4]	***Gastrointestinal perforation[4]***
Nausea			***Nausea***
Vomiting			***Vomiting***
Dyspepsia			
		Pancreatitis	***Pancreatitis***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue***
Chills/Rigors			
		Vital organ hemorrhages	
		Infection	

INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased***
	Blood bilirubin increased		***Blood bilirubin increased***
	Gamma-glutamyl transpeptidase increased		***GGT Increased***
		Electrocardiogram QTc interval prolonged (accompanied by Torsades de pointes)	
	Lipase increased		
Lymphocyte count decreased			***Leukopenia***
	Neutrophil count decreased		***Neutropenia***
Platelet count decreased			***Thrombocytopenia***
	Serum amylase increased		
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia***
	Dehydration		***Dehydration***
Hyperglycemia			***Hyperglycemia***
	Hypermagnesemia		

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Hypoglycemia			***Hypoglycemia***
	Hypomagnesemia		
	Hypophosphatemia		***Hypophosphatemia***
Weight Loss			
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Arthralgia			***Arthralgia***
Myalgia			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Tumor pain		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness***
Dysgeusia			
	Extrapyramidal disorder		
	Headache		***Headache***
		Stroke	***Aneurysm***
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
Hematuria			
Proteinuria			***Proteinuria***
		Urinary fistula	***Urinary fistula***
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
		Female genital tract fistula	***Female genital tract fistula***
		Uterine fistula	***Uterine fistula***
		Vaginal fistula	***Vaginal fistula***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Cough			
Dyspnea			
	Respiratory hemorrhage[5]		***Respiratory hemorrhage[5]***
Oral stomatitis			***Mouth sores***
Dysphonia			***Hoarseness***
	Pneumothorax		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia***
Edema in face, hands, ankles, feet and/or eyelids			
Desquamation			
Hemoptysis			
Blurred vision			***Ametropia***
	Palmar-plantar erythrodysesthesia syndrome		
Rash maculo-papular			***Rash maculo-papular***
Skin hypopigmentation			***Skin hypopigmentation***
VASCULAR DISORDERS			

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Hypertension			***Hypertension***
	Thromboembolic event (venous)[6]		
		Thrombotic microangiopathy (including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome)	
		Vital organ hemorrhage	
		Vascular disorders – other (arterial thromboembolic event)[6]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV.

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

[3]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

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

[5]Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[6]These events can result in life-threatening pulmonary, cardiac, cerebral, and other complications.

10.2 **Ifosfamide** (Isophosphamide, Iphosphamide, Z4942, Ifex®) NSC #109724 (122004)

Source and Pharmacology: Ifosfamide is a structural analogue of cyclophosphamide. Ifosfamide requires hepatic microsomal activation (P-450 3A isoenzymes) for the production of the reactive 4-hydroxyoxazaphorine intermediate which serves as a carrier molecule for the ultimate intracellular liberation of acrolein and phosphoramide mustard which is an active bifunctional alkylating species. Acrolein is thought to be the cause of the hemorrhagic cystitis as seen with cyclophosphamide. Ifosfamide demonstrates dose-dependent pharmacokinetics whereby the terminal half-life ranges from 7 to 16 hours at doses of 1.6-2.4g/m² to 3.8-5 g/m², respectively. At 1.6-2.4g/m²/d, 12 to 18% of the dose was excreted as unchanged drug in the urine, whereas at a 5g/m² single-dose, 61% was excreted in the urine as the parent drug. Evidence also exists to suggest that ifosfamide metabolism is inducible, with more rapid clearance occurring in the second and later doses when a course of therapy is given as fractionated doses over 3 to 5 days. There is more chloroethyl side chain oxidation of ifosfamide (up to 50%) than of cyclophosphamide (<10%), and the degree of such metabolism is more variable than with cyclophosphamide. Oxidation of the chloroethyl groups produces chloroacetaldehyde, which is thought to be responsible for the neurotoxicity and renal toxicity that have been seen with ifosfamide therapy.

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Formulation and Stability: Available in 1 g and 3 g single dose vials of lyophilized white powder without preservatives. Reconstitute with sterile water for injection or bacteriostatic water for injection, 20ml for the 1gm vial or with 60mL for the 3gm vial to produce a final concentration of 50mg/ml ifosfamide. Although the reconstituted product is stable for 7 days at room temperature and up to 6 weeks under refrigeration, the manufacturer recommends refrigeration and use within 24 hours to reduce the possibility of microbial contamination. Store unreconstituted vials at room temperature 20°-25°C (68°-77° F). Protect from temperatures above 30°C (86° F). Ifosfamide may liquefy at temperatures > 35°C.

Guidelines for Administration: Solutions of ifosfamide may be diluted further to concentrations of 0.6 to 20 mg/ml in dextrose or saline containing solutions. Such admixtures, when stored in large volume parenteral glass bottles, Viaflex bags or PAB bags, are physically and chemically stable for 1 week at 30°C (86°F) or 6 weeks at 5°C (41°F). The manufacturer recommends refrigeration and use within 24 hours to reduce the possibility of microbial contamination.

Supplier: Commercially available from various manufacturers.

Pregnancy: Women should avoid becoming pregnant while on therapy. Breastfeeding should be discontinued during therapy.

Expected adverse events:

Central nervous system: Somnolence, confusion, hallucinations in 12% and coma (rare) have occurred and are usually reversible; usually occur with higher doses or in patients with reduced renal function; depressive psychoses, polyneuropathy. **Note:** CNS depression can be reversed with methylene blue (50 mg intravenously) and methylene blue is recommended for prophylaxis for subsequent doses if the patient has CNS manifestations with the first dose.

Dermatologic: Alopecia occurs in 50% to 83% of patients 2-4 weeks after initiation of therapy; may be as high as 100% in combination therapy. Phlebitis, dermatitis, nail ridging, skin hyperpigmentation, impaired wound healing.

Gastrointestinal: Nausea and vomiting in 58% of patients is dose and schedule related (more common with higher doses and after bolus regimens); nausea and vomiting can persist up to 3 days after therapy; also anorexia, diarrhea, constipation, transient increase in LFTs and stomatitis noted.

Genitourinary: Hemorrhagic cystitis has been frequently associated with the use of ifosfamide; a urinalysis prior to each dose should be obtained; **ifosfamide should never be administered without a uroprotective agent (MESNA)**; hematuria has been reported in 6% to 92% of patients; renal toxicity occurs in 6% of patients and is manifested as an increase in BUN or serum creatinine and is most likely related to tubular damage; renal toxicity, including ARF, may occur more frequently with high-dose ifosfamide; metabolic acidosis may occur in up to 31% of patients.

Endocrine & metabolic: SIADH

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Hematologic: Myelosuppression: Leukopenia is mild to moderate, thrombocytopenia and anemia are rare. However, myelosuppression can be severe when used with other chemotherapeutic agents or with high-dose therapy; be cautious with patients with compromised bone marrow reserve

Respiratory: Nasal stuffiness, pulmonary fibrosis

Cardiovascular: Cardiotoxicity

Miscellaneous: Immunosuppression, sterility, possible secondary malignancy, allergic reactions

10.3 Doxorubicin (Adriamycin®) NSC #123127 (042006)

Source and Pharmacology: An anthracycline antibiotic isolated from cultures of Streptomyces peucetius. The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytocidal activity. Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases and dehydrogenases generate highly reactive species including the hydroxyl free radical OH•. Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both. Doxorubicin serum decay pattern is multiphasic. The initial distributive t½ is approximately 5 minutes suggesting rapid tissue uptake of doxorubicin. The terminal t½ of 20 to 48 hours reflects a slow elimination from tissues. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 ml/min/kg and is predominately by metabolism and biliary excretion. The P450 Cytochromes which appear to be involved with doxorubicin metabolism are CYP2D6 and CYP3A4. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Binding of doxorubicin and its major metabolite, doxorubicinol to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin.

Formulation and Stability: Doxorubicin is available as red-orange lyophilized powder for injection in 10mg, 20mg, 50mg, 150mg vials and a preservative free 2mg/ml solution in 10mg, 20mg, 50mg, 75mg, 200mg vials. Aqueous Solution: Store refrigerated 2° to 8°C, (36° to 46°F). Protect from light. Retain in carton until contents are used. Powder for injection: Store unreconstituted vial at room temperature 15° to 30°C (59° to 86°F). Retain in carton until contents are used. Reconstitute with preservative free normal saline to a final concentration of 2mg/ml. After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature under normal room light and 15 days under refrigeration 2° to 8°C (36° to 46°F). Protect from exposure to sunlight.

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Guidelines for Administration: Administer by IV push; by IV side arm into a running infusion; or doxorubicin may be further diluted in saline or dextrose containing solutions and administered by infusion. Protect final preparation from light. Avoid extravasation.

Supplier: Commercially available from various manufacturers.

Pregnancy: Women should avoid becoming pregnant while on therapy. Breastfeeding should be discontinued during therapy.

Expected adverse events:

Hematologic: Hematologic side effects have been reported in 60% to 80% of patients and they may be profound (depending entirely on dose). While myelosuppression can affect all cell lines, leukopenia is most common, appearing in 60% to 75% of all treated patients. Absolute white blood cell counts of less than 1,000/mm3 are not uncommon after recommended therapeutic doses. Severe thrombocytopenia and anemia may also occur.

Gastrointestinal: Gastrointestinal side effects have included acute nausea and vomiting in 20% to 85% of patients. Stomatitis has been reported in up to 80% of patients, and is dose and schedule-related. Ulceration of the esophagus and the colon (particularly the cecum) have also been reported. Anorexia and diarrhea have been reported in approximately 15% of patients. Rare cases of tongue hyperpigmentation have also been associated with the use of doxorubicin.

Dermatologic: Alopecia, flushes, skin and nail hyperpigmentation, oncholysis (nail loss), photosensitivity, hypersensitivity to irradiated skin.

Extravasation: Infiltration can cause severe inflammation, tissue necrosis, and ulceration. If the drug is infiltrated, consult institutional policy, apply ice to area, and elevate the limb. May require debridement.

Hypersensitivity: Hypersensitivity reactions have occasionally been reported, and may include fever, chills, urticaria, angioneurotic edema or anaphylaxis. Local IV site "flares" can be confused with extravasation, but are probably due to allergy to this drug. Flare reactions were reported in 3% to 18% of patients, but are now rare since the vehicle in which doxorubicin is carried has changed. Flare reactions are characterized by erythema, appear proximally along the affected vein, and typically resolve within 45 minutes. Pain, burning and adverse sequelae are infrequent or absent. Extravasation, on the other hand, appears at the injection site and resolves slowly over days to weeks. As opposed to flare reactions, pain, burning, and edema are common, and adverse sequelae are variable and may be serious. Allergic reactions have also been reported after the intravesical administration of doxorubicin.

Renal: Renal insufficiency has been associated with doxorubicin-induced hyperuricemia (secondary to cell lysis). Animal data suggest that doxorubicin may cause glomerular basement membrane injury via production of reactive oxygen species. Renal side effects have included rare cases of new or worsened renal insufficiency. A single case of rapidly progressive glomerulonephritis without evidence of a secondary cause or immunologic mechanism has been reported.

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Ocular: Ocular side effects have included rare cases of conjunctivitis, periorbital edema, lacrimation, blepharospasm, keratitis, and decreased visual acuity.

Genitourinary: Genitourinary side effects including rare cases of bladder contracture have been reported.

Musculoskeletal: Musculoskeletal side effects have been extremely rare. In one case, administration of doxorubicin was associated with a clinically significant flare of ankylosing spondylitis.

Cardiac: Anthracycline-induced cardiac toxicity may be manifested by early or late events. Early cardiac toxicity consists mainly of sinus tachycardia and/or ECG abnormalities such as non-specific ST-T wave changes, but tachyarrhythmias, bradycardia, as well as atrioventricular and bundle-branch block have also been reported. Although rhythm disturbances are common after acute administration they are rarely of clinical importance. Early effects of anthracyclines also include extremely rare cases of pericarditis-myocarditis (which can affect patients with no prior history of cardiac disease and which carries a high mortality rate of about 20%), and left ventricular dysfunction (which may lead to clinically significant heart failure in patients with limited cardiac reserve). Isolated cases of symptomatic supraventricular tachycardia, heart block, and ventricular arrhythmias (some sudden and fatal) have also been reported. Cardiovascular side effects have included congestive heart failure due to the development of left ventricular (LV) systolic dysfunction in 1% to 2% of patients. Retrospective data have shown that the incidence of clinical heart failure in patients with preexisting LV systolic dysfunction (ejection fraction [LVEF] < 50%), who experienced a decline of 10% or more in absolute LVEF, and who received at least 450 mg/m2 cumulative dose, is approximately 16%. (Data have shown right ventricular septal wall motion may also be affected and that LV diastolic dysfunction may precede the development of doxorubicin-induced LV systolic dysfunction.).

Secondary Leukemia: The occurrence of secondary acute myelogenous leukemia has been reported in patients treated with anthracyclines.

Other: Radiation pneumonitis or esophagitis may be more likely with the combination of doxorubicin and XRT than with XRT alone. Prior cardiac or mediastinal XRT appears to portend a higher risk of doxorubicin-induced cardiomyopathy. Other side effects of doxorubicin have included the predisposition of patients who have previously received radiation therapy (XRT) to demonstrate the so-called "recall" phenomenon

10.4 **Mesna** (sodium 2-mercaptoethane sulfonate,UCB 3983, Mesnex®) NSC #113891 (012006)

Source and Pharmacology: Mesna was developed as a prophylactic agent to reduce the risk of hemorrhagic cystitis induced by ifosfamide. Mesna is rapidly oxidized to its major metabolite, mesna disulfide (dimesna). Mesna disulfide remains in the intravascular compartment and is rapidly eliminated by the kidneys. In the kidney, the mesna disulfide is reduced to the free thiol compound, mesna, which reacts chemically with the urotoxic ifosfamide metabolites (acrolein and 4-hydroxy-ifosfamide) resulting in their detoxification. The first step in the detoxification process is the binding of mesna to 4-hydroxyifosfamide forming a nonurotoxic 4-

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sulfoethylthioifosfamide. Mesna also binds to the double bonds of acrolein and to other urotoxic metabolites. In multiple human xenograft or rodent tumor model studies, mesna in combination with ifosfamide (at dose ratios of up to 20-fold as single or multiple courses) failed to demonstrate interference with antitumor efficacy. After an 800mg dose the half lives for Mesna and DiMesna are 0.36 hours and 1.17 hours, respectively. Approximately 32% and 33% of the administered dose was eliminated in the urine in 24 hours as mesna and dimesna, respectively. The majority of the dose recovered was eliminated within 4 hours. Mesna tablets have an oral bioavailability of 45-79% and a urinary bioavailability which ranged from 45-79% of intravenously administered mesna. The oral bioavailability is unaffected by food. When compared to intravenously administered mesna, the intravenous plus oral dosing regimen increases systemic exposures (150%) and provides more sustained excretion of mesna in the urine over a 24-hour period.

Unknown Frequency and Timing: **Fetal toxicities and teratogenic effects of mesna have not been noted in animals fed 10 times the recommended human doses. There are however no adequate and well controlled studies in pregnant women. It is not known if mesna or dimesna is excreted into human milk.

Guidelines for Administration: For IV administration, dilute to 20 mg/mL with dextrose or saline containing solutions. Mesna may be mixed with ifosfamide or cyclophosphamide. After dilution for administration, mesna is physically and chemically stable for 24 hours at 25ºC (77ºF). Carefully expel air in syringes prepacked for use to avoid oxidation to dimesna. Mesna may cause false positive test for urinary ketones.

Supplier: Commercially available from various manufacturers.

Pregnancy: Women should avoid becoming pregnant while on therapy. Breastfeeding should be discontinued during therapy.

Expected adverse events:

Cardiovascular: Hypotension

Central nervous system: Malaise, headache

Gastrointestinal: Diarrhea, nausea, vomiting, bad taste in mouth, soft stools

Neuromuscular & skeletal: Limb pain

Dermatologic: Skin rash, itching

10.5 Pegfilgrastim (pegylated filgrastim, PEG filgrastim, SD/01, Neulasta®) (072006)

Source and Pharmacology: Pegfilgrastim is the pegylated form of recombinant methionyl human G-CSF (filgrastim). Pegfilgrastim is produced by covalently binding a 20-kilodalton (kD) monomethoxypolyethylene glycol molecule to the N-terminal methionyl residue of filgrastim. The molecular weight of pegfilgrastim is 39 kD. G-CSF is a lineage specific colony-stimulating factor which regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with

respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens). After subcutaneous injection the elimination half-life of pegfilgrastim ranges from 15 to 80 hours and the time to peak concentration ranges from 24 to 72 hours. Serum levels are sustained in most patients during the neutropenic period postchemotherapy, and begin to decline after the start of neutrophil recovery, consistent with neutrophil-dependent elimination.

Formulation and Stability: Supplied as a preservative-free solution containing 6 mg (0.6ml) of pegfilgrastim (10mg/ml) in a single-dose syringe with 27 g, ½ inch needle with an UltraSafe® Needle Guard. Store refrigerated at 2-8º C (36-46ºF) and in the carton to protect from light. Prior to injection, pegfilgrastim may be allowed to reach room temperature protected from light for a maximum of 48 hours. Avoid freezing.

Guidelines for Administration: Pegfilgrastim should not be administered in the period between 2 weeks before and 24 hours after chemotherapy. Do not shake.

Supplier: Commercially available from various manufacturers

Pregnancy: Women should avoid becoming pregnant while on therapy. Breastfeeding should be discontinued during therapy.

Expected Adverse Events:
Bone pain was the most frequent adverse event attributable to pegfilgrastim in clinical trials. Hypoxia was observed in one patient. Toxicities associated with the parent compound, filgrastim include:

Central nervous system: Neutropenic fever, fever.

Dermatologic: Alopecia.

Gastrointestinal: Nausea, vomiting, diarrhea, mucositis, splenomegaly (this occurs more commonly in patients with cyclic neutropenia/congenital agranulocytosis who received S.C. injections for a prolonged (>14 days) period of time; ~33% of these patients experience subclinical splenomegaly; ~3% of these patients experience clinical splenomegaly).

Neuromuscular & skeletal: Medullary bone pain (24% incidence--this occurs most commonly in lower back pain, posterior iliac crest, and sternum and is controlled with non-narcotic analgesics), weakness.

Cardiovascular: Chest pain, fluid retention, transient supraventricular arrhythmia, pericarditis.

Central nervous system: Headache.

Dermatologic: Skin rash.

Gastrointestinal: Anorexia, stomatitis, constipation.

Hematologic: Leukocytosis.

Local: Pain at injection site, thrombophlebitis.

Respiratory: Dyspnea, cough, sore throat.

Miscellaneous: Anaphylactic reaction.

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11.0 ASSESSMENT OF EFFICACY

Evaluability: In order for a patient to be evaluable, 80% of the intended dose of all three drugs must be delivered in the first 2 cycles of chemotherapy.

11.1 Pharmacodynamic Studies

The primary endpoint of the study is to evaluate the absolute values and changes in maximum standardized uptake values of tumors measured by FDG-PET pre- and post receipt of pazopanib versus placebo, and post receipt of 2 cycles of preoperative chemotherapy. This will be compared to tumor response by RECIST criteria.

FDG PET

PET imaging will be performed at baseline, after the 14 day Run-in Period with pazopanib versus placebo and after 2 cycles of neoadjuvant chemotherapy. Imaging studies will be performed on the SCCA GE discovery LS PET/CT imaging device operating in a two-dimensional high-sensitivity mode with 35 imaging planes per axial field of view of 15 cm (plane thickness 4.25 mm) and an in-plane resolution of 4 to 5 mm.

The UW/SCCA will follow FDG-PET protocol consensus recommendations[53] and PET Response Criteria in Solid Tumors (PERCIST), version 1.0.[54]

Key elements of PERCIST include performance of PET scans in a method consistent with the National Cancer Institute recommendations. Patients will fast for at least 4–6 h before undergoing scanning, and the measured serum glucose level (no correction) must be less than 200 mg/dL. The patients may be on oral hypoglycemics but not on insulin. A baseline PET scan will be obtained at 50–70 min after tracer injection. The follow-up scan should be obtained within 15 min (but always 50 min or later) of the baseline scan. All scans will be performed on the same PET scanner with the same injected dose +/- 20% of radioactivity. Appropriate attenuation correction along with evaluation for proper PET and CT registration of the quantitated areas will be performed. SUV will be corrected for lean body mass (SUL) and should not be corrected for serum glucose levels (glucose corrections have been variably useful, and errors in glucometer measurements are well known and may add errors). The SUL will be determined for up to 5 tumors (up to 2 per organ) with the most intense ^{18}F-FDG uptake. The SUV peak (this is a sphere with a diameter of approximately 1.2 cm—to produce a 1-cm^3-volume spheric ROI) centering around the hottest point in the tumor foci will be determined, and the image planes and coordinates will be noted (SUL peak). This SUL peak ROI will typically include the maximal SUL pixel (which should also be recorded) but is not necessarily centered on the maximal SUL pixel. Automated methods for searching for this peak region will be used. Tumor sizes will be noted and should be 2 cm or larger in diameter for accurate measurement, though smaller lesions of sufficient 18F-FDG uptake, including those not well seen anatomically, can be assessed. Each baseline (pretreatment) tumor SUL peak must be 1.5 x mean liver SUL + 2 SDs of mean SUL. If the liver is diseased, 2.0 x blood-pool 18F-FDG activity + 2 SDs in the mediastinum will be used as minimal metabolically measurable tumor activity.[54]

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Serial PET will measure the **SUV (SUV lean or SUL)** peak for up to 5 target lesions in order to assess FDG uptake pre-therapy, after a 14 day Run-in period of pazopanib versus placebo, and after 2 cycles of chemotherapy. Analysis of changes in SUV from baseline and after treatment with pazopanib versus placebo and then again after chemotherapy will test whether antiangiogenic therapy has anti-tumor efficacy as monotherapy and if so, what is its relative contribution to a decline in tumor metabolism compared to chemotherapy.

RECIST

The radiographic response of the primary tumor to preoperative therapy will be evaluated. For subjects with stage II (T2a) or III disease, the primary lesion will serve as the sole target lesion and will be recorded and measured at baseline. RECIST measurements will be performed on serial MRIs to evaluate the correlation with FDG-PET.

For patients with stage IV disease, target lesions will be chosen according to RECIST procedure. The longest diameter (LD) of the target lesions will be measured and reported as the baseline LD. The baseline LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease. This will be compared to changes in SUV on FDG PET. Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee.[55] Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 criteria.

11.2 Pharmacokinetic Studies

Trough level (22-24 hrs after pazopanib dosing): A blood sample will be drawn to assess the trough plasma pazopanib concentration during the 14 day Run-in period of pazopanib monotherapy (2 samples), after completion of adjuvant chemotherapy (2 samples), and every 3 months thereafter until completion of pazopanib maintenance therapy (4 samples). If all trough levels are drawn, a total of 8 samples are possible in a single subject. The trough levels will be compared for any differences over time and will be correlated with the change in SUV from FDG PET and with the change in RECIST measurements on MRIs.

In subjects consenting to the optional full intensive pharmacokinetic visit during Weeks 2-4 following surgery/adjuvant chemotherapy, blood will be obtained at the following timepoints: immediately before pazopanib dosing (within 5 minutes before giving pazopanib on the day of PK dosing) and 1, 2, 3, 4, 6, 8 hour timepoints (+/- 10 minutes) , and 24 hrs (range 22 to 24 hours) after dosing (a total of 8 samples/subject).
Pazopanib pharmacokinetic parameters of maximum observed plasma concentration (Cmax), the time to Cmax (peak time, Tmax), the area under the plasma concentration-time curve (AUC0-24hr), concentration at the end of the dosing interval (C_{tr}), oral clearance (CL/F), volume of distribution (Vd/F), and half-life ($t_{1/2}$) will be determined using noncompartmental methods. The correlation between trough concentrations and AUC will also be evaluated.

11.3 Efficacy Variables

11.3.1 FDG Criteria for Tumor Response

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Determination of SUV (SUV lean or SUL) of the primary tumor and metastases will be performed, for up up to 5 target lesions, and for non-target lesions. FDG changes of more than 25% from baseline cannot be attributed to the imprecision of the technique and are therefore regarded as true changes in tumor glucose metabolism.[54] FDG criteria for tumor response will be as per the PET Response Criteria in Solid Tumors (PERCIST) criteria.[54] PERCIST includes a specific percentage reduction in the SUV (SUV lean, or SUL) from baseline. Response to therapy is assessed as a continuous variable and expressed as percentage change in SUL peak (or sum of lesion SULs) between the pre- and post treatment scans. A complete metabolic response is defined as visual disappearance of all metabolically active tumor. A partial response is considered more than a 30% and a 0.8-unit decline in SUL peak between the most intense lesion before treatment and the most intense lesion after treatment, although not necessarily the same lesion. More than a 30% and 0.8-unit increase is SUL peak or new lesions is classified as progressive disease.

11.3.2 RECIST Criteria for Tumor Response

Response criteria will be assessed using RECIST (version 1.1).[55]

Evaluation of target lesions:

Complete Response (CR): Disappearance of all target lesions

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

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

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

Evaluation of best overall response:

The best overall response is the best response achieved prior to surgical resection of the target lesion.

Target Lesions	New Lesions	Overall Response
CR	No	CR
PR	No	PR
SD	No	SD
PD	Yes or No	PD
Any	Yes	PD

Note:
In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, this will be determined at the time of surgical resection.

11.3.3 Pathologic Response at Surgery

All specimens of primary tumor will be examined for pathologic response at the time of surgery. The study pathologist will estimate the amount of viable tumor, and report the percentage of necrosis. For purpose of analysis, tumors will be classified as either ≥95% necrosis or <95% necrosis.

11.3.4 Duration of Response/Stable Disease

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

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

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.

11.3.5 Definition of Disease Progression

Disease progression will be defined as:

- Radiologic progression of disease by FDG PET PERCIST 1.0 criteria
- Radiologic progression of disease by RECIST (version 1.1) criteria.

11.3.6 Time-to-Event Measures

Time to Local Recurrence- Defined as the duration of time from surgical resection of the primary tumor until local recurrence (amputated patients excluded).

Local Disease-Free Survival- Defined as the duration of time from surgical resection of the primary tumor until local recurrence or death, whichever occurs first.

Distant Disease-Free Survival - Defined as the duration of time from randomization until development of distant metastatic disease or death, whichever occurs first. Subjects with stage IV disease will be censored from this analysis.

Disease-Free Survival - Defined as the duration of time from surgical resection to local recurrence, distant metastatic disease, or death, whichever occurs first. Subjects with stage IV disease will be censored from this analysis.

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Progression-Free Survival - Defined as the duration of time from randomization to progressive disease (per RECIST), local recurrence, distant metastatic disease (exclusive of stage IV subjects), or death, whichever occurs first.

Overall Survival - Defined as the interval of time from randomization until death from any cause.

11.4 Determining Response to Pazopanib for Continuing on Maintenance

Subjects who have a partial response by either RECIST 1.1 criteria on CT or MRI, and/or PERCIST 1.0 criteria by FDG PET after the 14 day Run-in period on pazopanib will have the option to remain on pazopanib for one year of therapy following surgery and adjuvant chemotherapy/radiation.

12.0 DATA MANAGEMENT/CONFIDENTIALITY

The Investigator will ensure that data collected conform to all established guidelines. Each subject is assigned a unique patient number to assure subject confidentiality. Subjects will not be referred to by this number, by name, or by any other individual identifier in any publication or external presentation. The licensed medical records department, affiliated with the institution where the subject receives medical care, maintains all original inpatient and outpatient chart documents.

Subject research files including paper and electronic case report forms, diagnostic pathology reports, and lab tests will be stored in a secure location that protects confidential information.

13.0 CORRELATIVE STUDIES

Plasma will be collected for measurement of VEGF and soluble VEGFR2 (sVEGFR2) at baseline, after the 14 day Run-in period of pazopanib, after completion of neoadjuvant chemotherapy and every 3 months thereafter until completion of pazopanib maintenance therapy, when indicated.

Quantitative enzyme-linked immunosorbent assays (ELISA) for VEGF and sVEGFR2 will be performed on plasma and tumor extracts.

MicroRNAs have been shown to be promising blood and tissue-based markers for cancer detection.[56] An extension of this is that such markers may also be excellent candidates for measuring response to therapy. There are currently no validated biomarkers to predict response to antiangiogenic therapy. Consequently, the ability to test candidate microRNA biomarkers before, during and after neoadjuavnt systemic therapy offers an ideal setting to assess potential biomarkers. Blood samples will be collected for micro RNA at baseline, after the 14 day Run-in period of pazopanib, following neoadjuvant chemotherapy and every 3 months thereafter until completion of pazopanib maintenance therapy, when indicated.

Samples to be tested will be an additional 3 tablespoons of whole blood (23cc) at each time of clinical lab draw, collected as 10cc into EDTA tubes (plasma), 10cc into serum separator tubes, and 3cc into Tempus tubes (containing an RNA stabilizer).

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There may also be evaluation of other potential predictive and prognostic markers using analysis of protein, DNA and RNA from surgical tumor tissue.

14.0 STATISTICAL CONSIDERATIONS

14.1 Analysis plan

The primary objective is to compare FDG SUV (SUV lean, SUL) measures for patients receiving pazopanib and placebo. The primary endpoint is the percent change in SUV between baseline and the end of the 14-day Run-in period of pazopanib or placebo. The comparison will likely be conducted using a two-sided Wilcoxon rank sum test, often used as a nonparametric alternative to the two-sample t-test for studies with a small sample size. Additional endpoints will include SUV percentage change between baseline and the end of preoperative therapy, absolute post-treatment SUV (at 14 days and following preoperative chemotherapy), and absolute difference in SUV.

The analysis sample for the primary pharmacodynamic analysis is expected to exclude patients who have incomplete data due to missed PET scans or due to study withdrawal for toxicity. However, reasons for missing data will be examined, and multiple imputation will be considered if patients with incomplete data would be considered as part of the target population for future development of pazopanib in sarcoma. However, insofar as sarcoma is heterogeneous, the sample size is small, and covariates are limited – multiple imputation may not be applicable.

These pharmacodynamic response measures will be compared to tumor response by RECIST criteria, using graphical displays. Continuous measures of pharmacodynamic response (percentage change in SUL; response assessed using MRI) will also be compared to the trough plasma pazopanib, using graphical displays and correlation coefficients to investigate dose-response relationships related to patients' differing metabolism of pazopanib.

Descriptive displays of preliminary clinical endpoints (pathologic response, progression-free survival, overall survival) will compare response for the pazopanib and placebo groups, and will investigate the relationship between early pharmacodynamic response (by PET) and clinical endpoints. Response of high-risk soft tissue sarcoma to neoadjuvant chemoradiation therapy was estimated as 52% (38% no residual tumor, 14% >=95 pathologic necrosis) in a series of 496 patients.[9] A smaller series found only 13/46 (28%) with <10% viable tumor in surgical specimens following a variety of neoadjuvant regimens.[51] To direct planning of future studies, we will measure the rate of complete pathological response defined as greater than 95% necrosis in the surgical excision specimen. A 90% Wilson (score) binomial confidence interval will be computed for the rate of complete pathological response.

There are no stopping rules planned for toxicity, but safety will be monitored continuously. All subjects who are registered and receive at least one dose of study drug will be included in the safety analysis.

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All reported adverse events will be coded using the Cancer Therapy Evaluation Program (CTEP) Common Toxicity Criteria version 4.0. The number and percent of subjects reporting adverse events (all, severe or worse, serious and related) will be quantified. Listings will be provided for all on-study deaths and adverse events that lead to withdrawal from study. Narratives of all serious adverse events and deaths on-study will be provided.

Correlative study assays will be analyzed using descriptive statistics, generally comparing pazopanib and placebo groups. Correlation will also be evaluated between pazopanib trough concentrations and drug exposure over the dosing interval (area-under-the-concentration-curve, AUC) in subjects consenting to the full intensive pharmacokinetic visits.

14.2 Sample size justification

If the standard deviation for percent change in is 20% and the average change is 0% for placebo and a 30% decrease for pazopanib, there will be approximately 90% power to detect a difference between the placebo and pazopanib group in average percent change for n=21 and a 2:1 randomization.

14.3 Protocol Enrollment and Special Considerations

The ethnic and gender distribution chart below reflects estimates of race and gender of the population to be included in this study.

TARGETED / PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex / Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	0	0
Not Hispanic or Latino	10	11	21
Ethnic Category Total of All Subjects*	10	11	21
a) Racial Categories			
American Indian / Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	10	11	21
Racial Categories: Total of All Subjects*	10	11	21

15.0 RECORDS

15.1 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. The collaborating site

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will send signed consents and eligibility forms to the coordinating center with source documents demonstrating subject eligibility within 10 business days of enrollment.

Data entered in the CRF transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Current medical records must be available.

All data entered in to the CRF must be derived from source documents. CRF data will be submitted to the coordinating center by entry into REDCap™. Data entered into the CRF will be reviewed for accuracy against source documentation per section 9.0.

15.2 Access

The investigator and/or institution will permit study-related monitoring, audits, EC review and regulatory inspection, providing direct access to all related source data and documents. The study is monitored per section 9.0, which details the full scope and extent of monitoring and provides for immediate action in the event of the discovery of major violations. CRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the clinical study monitor, auditor and inspection by health authorities. The Clinical Research Associate (CRA) or auditor my review all CRFs and written informed consents. The accuracy of the data will be verified per section 9.0.

16.0 TERMINATION OF STUDY

The PI/IND sponsor may terminate the study at any time. The IRB and FDA also have the authority to terminate the study should it be deemed necessary.

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APPENDIX A: Study Activities and Treatment Calendar

	Screening	End of Week Two	Prior to Day 1 of each cycle	After 2 cycles of preop chemo	At time of surgery	Post-treatment follow-up every 4 weeks if receiving pazopanib, else every 3 months
Informed Consent	X					
History/Progress Notes	X	X	X			X
Physical Exam	X	X	X			X
Vitals signs	X	X	X			X
Performance Status	X	X	X			X
Treatment Toxicity		X	X			X
Pathology Review	X				X	
CBC, chemistries, Ca^{++}, phos, Mg^{+}, hepatic panel	X	X	X			X
UA	X		X			X
Pregnancy test	X					
INR	X					
ECG	X	X				X (every 3 months)
ECHO	X					
Tissue/blood for correlative studies	X	X		X	X	X (every 3 months)
FDG-PET	X	X		X		
MRI	X	X		X		
Plasma pazopanib trough level		X (2 visits)				X (every 3 months)
Full plasma pazopanib PK (optional)						X (once during Weeks 2-4)
CT-chest	X					X (every 3 months)

APPENDIX B

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.

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APPENDIX C

Additional Eligibility Criteria for Women

Criteria for women of non-childbearing potential (physiologically incapable of becoming pregnant):

- A hysterectomy or
- A bilateral oophorectomy (ovariectomy) or a bilateral tubal ligation or
- 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 <40 pg/mL (<140 pmol/L) *or*

  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

Criteria for women of childbearing potential, including any female who has had a negative serum pregnancy test within 2 weeks prior to the first dose of study treatment, preferably as close to the first dose as possible, and agrees to use adequate contraception. Acceptable methods of contraception are:

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)

APPENDIX D

Drugs Known to be Metabolized by Selected CYP450 Isoenzymes

CYP2C8/9

SUBSTRATES		INHIBITORS		INDUCERS	
Generic Name	**Trade Name**	**Generic Name**	**Trade Name**	**Generic Name**	**Trade Name**
Antibiotics: *e.g.*		Antifungals: *e.g.*		Sedatives: *e.g.*	
Rifampin	Rifadin	Fluconazole	Diflucan	Phenobarbiatl	Luminal
Sulfadiazine	--	Ketoconazole	Nizoral	Primidone	Mysoline
		Miconazole	Lotramin		
		Tioconazole	Monistat		
Misc. CV agents: *e.g.*		Antimalarials: *e.g.*		Anticonvulsants: *e.g.*	
Amiodarone	Cordarone	Pyrimethamine	Daraprim	Carbamazapine	Tegretol
Carvedilol	Coreg	Quinine	Legatrin	Phenobarbital	Luminal
				Phenytoin	Dilantin
Anti-asthmatics: *e.g.*		Anti-hyperlipidemics: *e.g.*		Antibiotics: *e.g.*	
Montelukast	Singulair	Fluvastatin	Lescol	Rifapentine	Priftin
Zafirlukast	Accolate	Gemfibrozil	Lopid	Rifampin	Rifadin
Antidepressants: *e.g.*		Antibiotics: *e.g.*			
Fluoxetine	Prozac	Isoniazid	INH, Nydrazid		
Sertraline	Zoloft	Sulfadiazine	--		
		Sulfamethoxazole	Bactrim, Septra		
		Trimethoprim	Primsol		
Anticonvulsants: *e.g.*		Analgesics: *e.g.*			
Fosphenytoin	Cerebyx	Flurbiprofen	Ansaid		
Phenytoin	Dilantin	Ibuprofen	Advil, Motrin		
		Indomethacin	Indocin		
		Mefenamic acid	Ponstel		
Anesthetics: *e.g.*		Anti-ulceratives: *e.g.*			
Ketamine	Ketalar	Omeprazole	Prilosec		
Propofol	Diprivan	Pantoprazole	Pantoloc		
Anti-diabetics: *e.g.*		Antihypertensives: *e.g.*			
Glimepiride	Amaryl	Irbesartan	Avapro		
Rosiglitazone	Avandia	Losartan	Cozaar		
		Nicardipine	Cardene		
Antihypertensives: *e.g.*					
Losartan	Cozaar				
Bosentan	Tracleer				
Paclitaxel	Taxol	Anti-diabetics: *e.g.*			
		Pioglitazone	Actos		
		Rosiglitazone	Avandia		
Alosetron	Lotronex	Amiodarone	Cordarone		
Torsemide	Demadex	Delavirdine	Rescriptor		
		Piroxicam	Feldene		
		Warfarin	Coumadin		
		Zafirlukast	Accolate		

When drugs classified as 'substrates' are co-administered with *(Study Agent)*, there is the potential for higher concentrations of the 'substrate'. When *(Study Agent)* is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of *(Study Agent)* is the potential outcome. The coadministration of 'inducers' would potentially lower plasma *(Study Agent)* concentrations.

Comprehensive list of drugs that may have potential interactions
CYP2C8/9

SUBSTRATES			
Alosetron	Losartan	Rifampin	Tolbutamide
Amiodarone	Mephenytoin	Rosiglitazone	Torsemide
Bosentan	Mestranol	Selegiline	Trimethoprim
Carvedilol	Montelukast	Sertraline	Voriconazole
Fluoxetine	Nateglinide	Sulfadiazine	Warfarin
Fosphenytoin	Paclitaxel	Sulfamethoxazole	Zafirlukast
Glimepiride	Phenytoin	Sulfinpyrazone	Zopiclone
Glipizide	Pioglitazone	Sulfisoxazole	
Ketamine	Propofol	Tamoxifen	

INHIBITORS			
Amiodarone	Felodipine	Modafinil	Sertraline
Amitryptiline	Fluconazole	Montelukast	Sildenafil
Amlodipine	Fluoxetine	Nateglinide	Simvastatin
Anastrozole	Fluphenazine	Nelfinavir	Sulconazole
Aprepitant	Flurbiprofen	Nicardipine	Sulfadiazine
Atazanavir	Fluvastatin	Nifedipine	Sulfamethoxazole
Azelastine	Fluvoxamine	Olanzapine	Sulfinpyrazone
Bortezomib	Gemfibrozil	Omeprazole	Sulfisoxazole
Candesartan	Ibuprofen	Ondansetron	Tamoxifen
Chloramphenicol	Imatinib	Orphenadrine	Teniposide
Cholecalciferol (Vitamin D_3)	Indinavir	Pantoprazole	Thioridazine
Cimetidine	Indomethacin	Paroxetine	Ticlopidine
Clopidogrel	Irbesartan	Pentamidine	Tioconazole
Clotrimazole	Isoniazid	Pioglitizone	Tolbutamide
Clozapine	Ketoconazole	Piroxicam	Tolcapone
Cyclosporine	Ketoprofen	Pravastatin	Tranylcypromine
Delavirdine	Lansoprazole	Progesterone	Tretinoin
Dexmedetomidine	Leflunomide	Propafenone	Triazolam
Diclofenac	Losartan	Propofol	Trimethoprim
Diltiazem	Lovastatin	Propoxyphene	Valdecoxib
Dimethyl sulfoxide	Mefenamic acid	Pyrimethamine	Valproic acid
Disulfiram	Meloxicam	Quinidine	Valsartan
Drospirenone	Methimazole	Quinine	Verapamil
Efavirenz	Methoxsalen	Ritonavir	Voriconazole
Entacapone	Metronidazole	Rosiglitazone	Warfarin
Eprosartan	Miconazole	Saquinavir	Zafirlukast
Etoposide	Midazolam	Selegiline	

INDUCERS			
Carbamazepine	Phenobarbital	Primidone	Rifapentine
Fosphenytoin	Phenytoin	Rifampin	Secobarbital

(Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 12TH ed. Hudson, OH; LexiComp Inc. 2004: 1619-1631.)

Selected Potential Cytochrome P450 (CYP) Drug Interactions

CYP3A4

SUBSTRATES		INHIBITORS		INDUCERS	
Generic Name	**Trade Name**	**Generic Name**	**Trade Name**	**Generic Name**	**Trade Name**
Anti-neoplastics: *e.g.*		Anti-arrhythmics: *e.g.*		Aminoglutethimide	Cytadren
Docetaxel	Taxotere	Amiodarone	Cordarone, Pacerone		
Gefitinib	Iressa	Diltiazem	Cardizem, Dilacor XR		
Irinotecan	Camptosar	Quinidine	Cardioquin		
Anti-virals: *e.g.*		Anti-virals: *e.g.*		Antibiotics: *e.g.*	
Amprenivir	Agenerase	Amprenavir	Agenerase	Rifabutin	Rifadin
Rifampin	Rifadin	Indinavir	Crixivan	Rifampin	Mycobutin
		Nelfinavir	Viracept		
		Ritonavir	Norvir		
Anxiolytics: *e.g.*		Cimetadine	Tagamet	Anticonvulsants: *e.g.*	
Diazepam	Valium			Carbamazapine	Tegretol
Sertraline	Zoloft			Phenytoin	Dilantin
				Pentobarbital	Nembutal
				Phenobarbital	Luminal
Cyclosporine	Sandimmune	Cyclosporine	Sandimmune	*Hypericum perforatum* (2)	St. John's Wort
Anti-infectives: *e.g.*		Antibiotics: *e.g.*			
Erythromycin	Erythrocin	Ciprofloxacin	Cipro, Ciloxan		
Tetracycline	Sumycin	Clarithromycin	Biaxin		
		Doxycycline	Adoxa, Periostat		
		Enoxacin	Penetrex		
		Isoniazid	Nydrazid, INH		
		Telithromycin	Ketek		
Steroids: *e.g.*		Imatinib	Gleevec		
Estrogens, conjugated	Premarin				
Estradiol	Climara				
Progesterone	Crinone				
Haloperidol	Haldol	Haloperidol	Haldol		
Cardiovascular agents: *e.g.*		Diclofenac	Cataflam, Voltaren		
Digitoxin	Crystodigin				
Quinidine	Cardioquin				
Anti-hypertensives: *e.g.*		Vasodilators: *e.g.*			
Nicardipine	Cardene	Nicardipine	Cardene		
Verapamil	Calan, Chronovera	Verapamil	Calan, Chronovera		
Anesthetics: *e.g.*		Anesthetics: *e.g.*			
Ketamine	Xylocaine	Lidocaine	Xylocaine		
Lidocaine	Diprivan	Propofol	Diprivan		
Nefazodone	Serzone	Anti-depressants: *e.g.*			
		Nefazodone	Serzone		
		Sertraline	Zoloft		
Cocaine		Anti-fungals: *e.g.*			
		Itraconazole	Sporanox		
		Ketoconazole	Nizoral		
		Miconazole	Lotrimin, Monistat		
Ketoconazole	Nizoral	Caffeine			
Sildenafil	Viagra	Grapefruit juice (1)			
Albuterol	Ventolin				
Carbamazapine	Tegretol				
Lovastatin	Mevacor				

When drugs classified as 'substrates' are co-administered with *(Study Agent)*, there is the potential for higher concentrations of the 'substrate'. When *(Study Agent)* is co-administered with compounds classified as 'inhibitors', increased plasma concentrations of *(Study Agent)* is the potential outcome. The coadministration of 'inducers' would potentially lower plasma *(Study Agent)* concentrations.

Comprehensive List of Drugs That May Have Potential Interactions

CYP3A4

SUBSTRATES			
Albuterol	Docetaxel	Ketoconazole	Quetiapine
Alfentanil	Doxepin	Lansoprazole	Quinidine
Alprazolam	Doxorubicin	Letrozole	Rabeprazole
Amlodipine	Doxycycline	Levomethadyl acetate hydrochloride	Repaglinide
Amprenavir	Efavirenz	Levonorgestrel	Rifabutin
Aprepitant	Eletriptan	Lidocaine	Rifampin
Aripiprazole	Enalapril	Losartan	Ritonavir
Atazanavir	Eplerenone	Lovastatin	Saquinavir
Atorvastatin	Ergoloid mesylates	Medroxyprogesterone	Sertraline
Benzphetamine	Ergonovine	Mefloquine	Sibutramine
Bisoprolol	Ergotamine	Mestranol	Sildenafil
Bortezomib	Erythromycin	Methadone	Simvastatin
Bosentan	Escitalopram	Methylergonovine	Sirolimus
Bromazepam	Esomeprazol	Methysergide	Sufentanil
Bromocriptine	Estradiol	Miconazole	Tacrolimus
Buprenorphine	Estrogens, conj., synthetic	Midazolam	Tamoxifen
Buspirone	Estrogens, conj., equine	Miglustat	Tamsulosin
Busulfan	Estrogens, conj., esterified	Mirtazapine	Telithromycin
Carbamazapine	Estrone	Modafinil	Teniposide
Cerivastatin	Estropipate	Montelukast	Terbinafine
Chlordiazepoxide	Ethinyl estradiol	Moricizine	Tetracycline
Chloroquine	Ethosuximide	Nateglinide	Theophylline
Chlorpheniramine	Etoposide	Nefazodone	Tiagabine
Cisapride	Felbamate	Nelfinavir	Ticlopidine
Citalopram	Felodipine	Nevirapine	Tolterodine
Clarithromycin	Fentanyl	Nicardipine	Toremifene
Clobazam	Flurazepam	Nifedipine	Trazodone
Clonazepam	Flutamide	Nimodipine	Triazolam
Clorazepate	Fosamprenavir	Nisoldipine	Trimethoprim
Cocaine	Fulvestrant	Nitrendipine	Trimipramine
Colchicine	Gefitinib	Norethindrone	Troleandomycin
Cyclophosphamide	Halofantrine	Norgestrel	Vardenafil
Cyclosporine	Haloperidol	Ondansetron	Venlafaxine
Dantrolene	Ifosfamide	Paclitaxel	Verapamil
Dapsone	Imatinib	Pergolide	Vinblastine
Delavirdine	Indinavir	Phencyclidine	Vincristine
Diazepam	Irinotecan	Pimozide	Vinorelbine
Digitoxin	Isosorbide dinitrate	Pioglitazone	Zolpidem
Dihydroergotamine	Isosorbide mononitrate	Primaquine	Zonisamide
Diltiazem	Isradipine	Progesterone	Zopiclone
Disopyramide	Itraconazole		
	Ketamine		

CYP3A4

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

INDUCERS			
Aminoglutethimide	Nevirapine	Phenytoin	Rifapentine
Carbamazapine	Oxcarbazepine	Primidone	
Fosphenytoin	Pentobarbital	Rifabutin	
St. John's wort	Phenobarbital	Rifampin	

(Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 12TH ed. Hudson, OH; LexiComp Inc. 2004: 1619-1631.)

(1) Malhorta *et al*. (2000). Clin Pharmacol Ther. 69:14-23

(2) Mathijssen *et al*. (2002). J Natl Cancer Inst. 94:1247-1249
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APPENDIX E
Drugs Associated with QTc Prolongation

The following table presents a list of drugs that prolong, may prolong or are unlikely to prolong the QTc. This list is frequently updated. For the most current list of medications, refer to the following website: *http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm*.

Drugs that are generally accepted to have a risk of causing Torsades de Pointes	*Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes*	*Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in subjects without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism).*
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Amiodarone /Cordarone®	Alfuzosin /Uroxatral®	Amitriptyline /Elavil®
Amiodarone /Pacerone®	Amantadine /Symmetrel®	Ciprofloxacin /Cipro®
Arsenic trioxide /Trisenox®	Atazanavir /Reyataz®	Citalopram /Celexa®
Astemizole /Hismanal®	Azithromycin /Zithromax®	Clomipramine /Anafranil®
Bepridil /Vascor®	Chloral hydrate /Noctec®	Desipramine /Pertofrane®
Chloroquine /Aralen®	Clozapine /Clozaril®	Diphenhydramine /Benadryl®
Chlorpromazine /Thorazine®	Dolasetron /Anzemet®	Diphenhydramine /Nytol®
Cisapride /Propulsid®	Dronedarone /Multaq®	Doxepin /Sinequan®
Clarithromycin /Biaxin®	Felbamate /Felbatrol®	Fluconazole /Diflucan®
Disopyramide /Norpace®	Flecainide /Tambocor®	Fluoxetine /Sarafem®
Dofetilide /Tikosyn®	Foscarnet /Foscavir®	Fluoxetine /Prozac®
Domperidone /Motilium®	Fosphenytoin /Cerebyx®	Galantamine /Reminyl®
Droperidol /Inapsine®	Gatifloxacin /Tequin®	Imipramine /Norfranil®
Erythromycin /Erythrocin®	Gemifloxacin /Factive®	Itraconazole /Sporanox®
Erythromycin /E.E.S.®	Granisetron /Kytril®	Ketoconazole /Nizoral®
Halofantrine /Halfan®	Indapamide /Lozol®	Mexiletine /Mexitil®
Haloperidol /Haldol®	Isradipine /Dynacirc®	Nortriptyline /Pamelor®
Ibutilide /Corvert®	Lapatinib /Tykerb®	Paroxetine /Paxil®
Levomethadyl /Orlaam®	Lapatinib /Tyverb®	Protriptyline /Vivactil®
Mesoridazine /Serentil®	Levofloxacin /Levaquin®	Sertraline /Zoloft®

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Drugs that are generally accepted to have a risk of causing Torsades de Pointes	*Drugs that in some reports have been associated with Torsades de Pointes and/or QTc prolongation but at this time lack substantial evidence for causing Torsades de Pointes*	*Drugs that, in some reports, have been weakly associated with Torsades de Pointes and/or QTc prolongation but that are unlikely to be a risk for Torsades de Pointes when used in usual recommended dosages and in subjects without other risk factors (e.g., concomitant QTc prolonging drugs, bradycardia, electrolyte disturbances, congenital long QTc syndrome, concomitant drugs that inhibit metabolism).*
Generic/Brand Name	**Generic/Brand Name**	**Generic/Brand Name**
Methadone /Dolophine®	Lithium /Lithobid®	Solifenacin /VESIcare®
Methadone /Methadose®	Lithium /Eskalith®	Trimethoprim-Sulfa /Sulfa®
Pentamidine /Pentam®	Moexipril/HCTZ /Uniretic®	Trimethoprim-Sulfa /Bactrim®
Pentamidine /NebuPent®	Moxifloxacin /Avelox®	Trimipramine /Surmontil®
Pimozide /Orap®	Nicardipine /Cardene®	
Probucol /Lorelco®	Nilotinib /Tasigna®	
Procainamide /Pronestyl®	Octreotide /Sandostatin®	
Procainamide /Procan®	Ofloxacin /Floxin®	
Quinidine /Cardioquin®	Ondansetron /Zofran®	
Quinidine /Quinaglute®	Oxytocin /Pitocin®	
Sotalol /Betapace®	Paliperidone /Invega®	
Sparfloxacin /Zagam®	Perflutren lipid microspheres /Definity®	
Terfenadine /Seldane®	Quetiapine /Seroquel®	
Thioridazine /Mellaril®	Ranolazine /Ranexa®	
	Risperidone /Risperdal®	
	Roxithromycin* /Rulide®	
	Sertindole /Serlect®	
	Sertindole /Serdolect®	
	Sunitinib /Sutent®	
	Tacrolimus /Prograf®	
	Tamoxifen /Nolvadex®	
	Telithromycin /Ketek®	
	Tizanidine /Zanaflex®	
	Vardenafil /Levitra®	
	Venlafaxine /Effexor®	
	Voriconazole /VFend®	
	Ziprasidone /Geodon®	

APPENDIX F

Blood Pressure – Recommendations for Data Collection/Recording and Event Management

Collection/Recording of Blood Pressure Information

1.0 General Guidelines

1.1 Frequency of monitoring. Blood pressure (BP) should be monitored at least every 2 weeks for the duration of treatment. More frequent monitoring should be considered on a study by study basis, particularly during the first two cycles of pazopanib therapy.

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

- Assessment date and time
- Pulse
- Systolic and diastolic BP (2 readings/assessment taken 5 minutes apart while subject sitting)

1.3 Risk factors for hypertension (assess and record data in baseline history/physical CRF)

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

2.0 Baseline data collection (at study entry)

2.1 All subjects

- Current BP
- Proteinuria, if present

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

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

3.0 Follow up BP data collection (during study)

3.1 All subjects (at each clinic visit)

- Current BP
- Proteinuria, if present

3.2 Subjects with treatment-emergent hypertension [defined as BP increase of >20 mmHg (diastolic) OR BP >150/100 (if previously within normal limits)] – record at time of hypertension diagnosis and at all subsequent clinic visits:

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

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3.3 Subjects with preexisting hypertension at study entry – record at each clinic visit

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

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