Oregon Health & Science University
OHSU Knight Cancer Institute
IRB Protocol #: 7943

TITLE: A Randomized, Double-Blind Phase II, Study of Gemcitabine Alone or in Combination with Pazopanib for Refractory Soft Tissue Sarcoma

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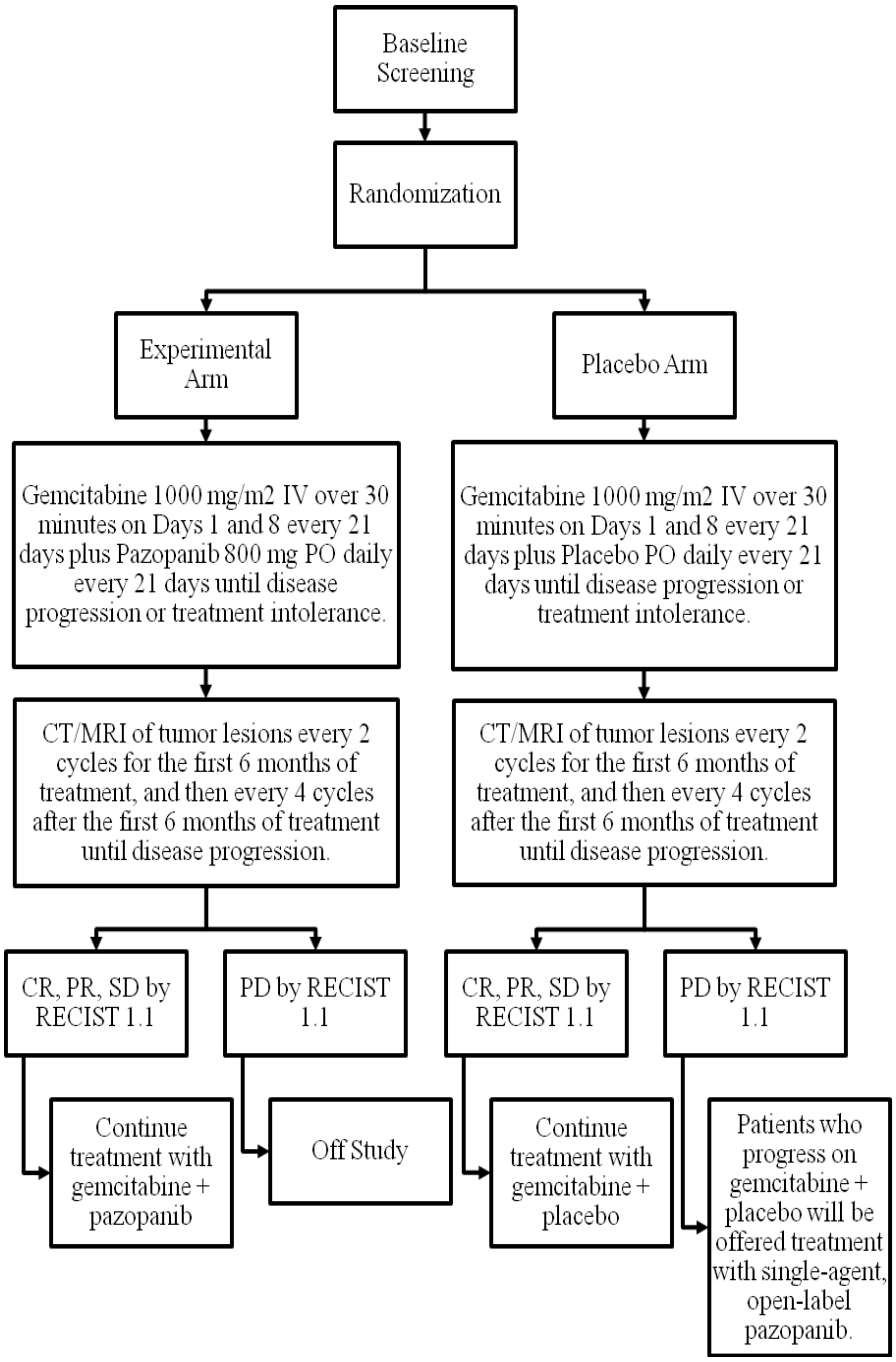
Final Protocol Date: *10/12/2011*
Protocol Revision Dates: *3/26/2013*
08/20/2017

SCHEMA


Baseline Screening
Randomization
Experimental Arm
Placebo Arm
Gemcitabine 1000 mg/m2 IV over 30 minutes on Days 1 and 8 every 21 days plus Pazopanib 800 mg PO daily every 21 days until disease progression or treatment intolerance.
Gemcitabine 1000 mg/m2 IV over 30 minutes on Days 1 and 8 every 21 days plus Placebo PO daily every 21 days until disease progression or treatment intolerance.
CT/MRI of tumor lesions every 2 cycles for the first 6 months of treatment, and then every 4 cycles after the first 6 months of treatment until disease progression.
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CR, PR, SD by RECIST 1.1
PD by RECIST 1.1
CR, PR, SD by RECIST 1.1
PD by RECIST 1.1
Continue treatment with gemcitabine + pazopanib
Off Study
Continue treatment with gemcitabine + placebo
Patients who progress on gemcitabine + placebo will be offered treatment with single-agent, open-label pazopanib.

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1. OBJECTIVES

1.1. Primary Objective

1.1.1. To investigate whether treatment with gemcitabine plus pazopanib improves the median progression-free survival (PFS) of patients with metastatic soft tissue sarcoma when compared to gemcitabine plus placebo.

1.2. Secondary Objectives

1.2.1. To assess overall response in this population to gemcitabine plus pazopanib compared to gemcitabine plus placebo.
1.2.2. To assess overall survival (OS) in this population to gemcitabine plus pazopanib compared to gemcitabine plus placebo.
1.2.3. To investigate differences in treatment response in different histologic subgroups (liposarcoma vs. all other eligible soft tissue sarcoma subtypes).
1.2.4. To evaluate the safety and tolerability of the combination of gemcitabine plus pazopanib.
1.2.5 To assess the progression-free survival and overall response in patients treated with single agent pazopanib following administration of gemcitabine in the cross-over portion of this study.
1.2.6 To collect specimens for an exploratory analysis of potential biomarkers that predict response in patients receiving combination therapy with gemcitabine plus pazopanib.

2. BACKGROUND

2.1 Soft Tissue Sarcomas

Soft tissue sarcomas are a rare and heterogeneous group of malignant tumors of mesenchymal origin that comprise approximately 1% of all adult malignancies and 12% of pediatric cancers[1,2]. This group includes more than 50 different histologic subtypes of soft tissue sarcoma[1]. Surgery with or without radiotherapy is the cornerstone of therapy for patients with early stage localized soft tissue sarcomas. However, many of these patients develop advanced disease for which the prognosis is poor[3].

Chemotherapy is used for the treatment of advanced and/or metastatic soft tissue sarcomas, but few cytotoxic drugs have demonstrated activity in this disease. Doxorubicin and ifosfamide remain the most active agents for treating these tumors, with overall response rates of less than 25%[4] and survival benefit never having been demonstrated in randomized trials.

2.2 Angiogenesis and VEGF

Angiogenesis, the process of new blood vessel formation, plays an important role in the development of malignancy as well as the growth and progression of metastatic lesions. The molecular pathways involved in angiogenesis have been targeted for anti-tumor therapy. Numerous growth factors and cytokines are involved in the angiogenic process. Among these factors, vascular endothelial growth factor (VEGF) has a predominant role as a central mediator of tumor-related angiogenesis, and its expression has been shown to be an adverse prognostic factor for a number of solid tumors[5-7].

The VEGF family consists of several glycoproteins including VEGF-A, -B,-C, -D, -E, and placental

growth factor[8]. Cellular signaling is initiated when members of the VEGF family bind to cell surface receptors including VEGFR-1 (Flt-1), VEGFR-2 (KDR or Flk-1), and VEGFR-3 (Flt-4). Given the key role of VEGF and its family of receptors in regulating angiogenesis, inhibitors of both VEGF and its receptors are actively being developed as anti-cancer therapies.

2.3 VEGF and Soft Tissue Sarcoma

Overexpression of PDGFR, VEGF, and VEGFR have been seen in soft tissue sarcomas[9-11], but it is not clear whether VEGF and VEGFR expression correlate with clinical outcome[12,13]. Certain histologic subtypes of soft tissue sarcoma are more likely to express PDGFR, VEGF, and VEGFR including angiosarcomas and solitary fibrous tumors (previously termed hemangiopericytomas)[10,14-16].

Several VEGF inhibitors have been studied in patients with refractory soft tissue sarcoma including bevacizumab, sunitinib, sorafenib, and pazopanib. A Phase II study of doxorubicin and bevacizumab showed a response rate of only 12% but 65% of patients had stable disease through 4 cycles of treatment[17]. Two Phase II studies have been performed using the VEGF tyrosine kinase inhibitor (TKI), sunitinib. The study by George, et al demonstrated durable disease control in patients with DSRCT and solitary fibrous tumor[18]. Another study of sunitinib in patients with refractory soft tissue sarcoma by Mahmood, et al showed a progression-free rate of >40% in patients with liposarcoma and leiomyosarcoma[19]. Two Phase II studies have also been performed using another VEGF TKI, sorafenib. A study by Maki, et al showed a response rate of 14% in patients with angiosarcoma and minimal activity in other soft tissue sarcomas with a median progression-free survival (PFS) in all subtypes of 3.2 months[20]. Another study using sorafenib by von Mehren, et al showed an overall median PFS of 3 months but a median PFS of 5 months in patients with vascular sarcoma subtypes[21]. Studies of the VEGF TKI, pazopanib are discussed in section 2.5.

2.4 Pazopanib

2.4.1 Introduction

Pazopanib is an orally-bioavailable, ATP-competitive tyrosine kinase inhibitor of VEGFR (-1, -2, and -3), PDGFR (-α and -β), and c-Kit[22]. Pazopanib has been approved by the FDA for treatment of renal cell carcinoma and soft tissue sarcoma. In nonclinical experiments, pazopanib has demonstrated encouraging potency and selectivity for VEGF receptors: for example, pazopanib demonstrated significant inhibition of VEGF-induced VEGFR-2 phosphorylation in human umbilical vein endothelial cells and was 3- to 400-fold selective for VEGF receptors 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 (e.g., the Matrigel plug assay, the cornea micropocket, and the laser-induced choroidal neovascularization models). Further physico-chemical characteristics of pazopanib as well as more detailed results of nonclinical studies are described in the Investigator Brochure (IB)[23].

2.4.2 Summary of Pharmacokinetic and Pharmacodynamic Data

Results of pharmacokinetic and pharmacodynamic analyses demonstrate that pazopanib is absorbed after oral administration; a plateau is reached in steady-state systemic exposure at a dose of 800 mg daily; a maximum tolerated dose has not been reached at pazopanib doses up to 2000 mg daily; and doses of pazopanib that maintain plasma pazopanib concentrations above 15 μg/mL - 20 μg/mL (i.e., 800 mg daily and 300 mg twice daily [BID]) are associated with pharmacodynamic and clinical

effects[23].

2.4.3 **Drug-Drug Interactions**

In vitro data indicate that pazopanib is a potential inhibitor for CYP2C9, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Pregnane X receptor transient transfection assay suggested some potential for human CYP3A4 induction at high concentrations. Due to the early phase of development, human experience with pazopanib is limited and definitive information on the metabolism and drug interaction profile of pazopanib is not available. However, coadministration of pazopanib and medications which are substrates for the CYP450 enzymes and which have the potential to cause serious and/or life-threatening adverse events is PROHIBITED[23].

2.4.4 **Summary of Adverse Events (AEs) and Serious Adverse Events (SAEs)**

The most common AEs reported to date include diarrhea, fatigue, nausea, hypertension, hair color changes (hair depigmentation), anorexia, vomiting, dysgeusia, headache, abdominal pain, rash, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) increase, constipation, cough, and arthralgia. Most of these events were Grade 1 or 2 using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 3.0. The most frequent Grade 3 or 4 events were hypertension, fatigue, diarrhea, and AST and ALT increases. Less common AEs of note include hand-foot syndrome, mucositis/stomatitis, proteinuria, venous thrombotic events, and bleeding. Intestinal perforations and arterial thromboses were uncommon. The most common SAEs occurring in patients enrolled in pazopanib studies regardless of treatment assignment include vomiting, diarrhea, abdominal pain, hypertension / hypertensive crisis, dyspnea, pleural effusion, pyrexia, anemia, dehydration, and pulmonary embolism[23].

2.4.5 **Summary of Laboratory Abnormalities**

Treatment-emergent laboratory abnormalities are available for two Phase II studies (VEG20002 and VEG102616). A review of the data from these 2 studies suggest that laboratory abnormalities of all grades occurring commonly in patients receiving pazopanib include AST and ALT elevations, hyperbilirubinemia, alkaline phosphatasemia, amylase and lipase elevations, elevations in creatinine, hyponatremia, hyperkalemia, lymphopenia, leukopenia, thrombocytopenia, neutropenia and anemia, hyperglycemia, and increased thyroid-stimulating hormone (TSH). Concomitant elevations in transaminases and bilirubin have been rare; for example, in Study VEG102616 they were observed in 2 (<1%) patients. Elevations in amylase and lipase have been primarily Grade 1 or 2. Most have been asymptomatic; clinical signs and symptoms of pancreatitis have been uncommon. Hyponatremia and hyperkalemia have not been reported concomitantly in the same patients in a manner that would suggest adrenal insufficiency[23].

2.5 **Pazopanib and Soft Tissue Sarcoma**

A Phase II single arm EORTC study of pazopanib in relapsed and refractory STS was performed[24]. This study was stratified by histology (liposarcoma vs leiomyosarcoma vs synovial sarcoma vs other soft tissue sarcoma subtypes). The drug was well tolerated. Amongst 142 patients, grade 3-4 neutropenia, and thrombocytopenia were seen in 6 and 2 pts, respectively. Grade 3-4 bilirubin, AST, ALT, and creatinine elevations in 9, 6, 6, and 5 pts, respectively. The main other toxicities (all grades; grade 3-4) were fatigue (36.6%; 7.7%), hypertension (40.1%; 7.7%), nausea (35.9%, 0.7%), diarrhea (28.9%; 3.5%), and hypopigmentation (35.2%, 0%). The majority of other reported adverse events (all grades;

grade 3-4) were fatigue (70.4%; 14.1%), hypertension (43.7%; 7.7%), nausea (44.4, 1.4), diarrhea (30.3%; 3.5%), and hypopigmentation (36.6%, 0%).

Pazopanib 800 mg once daily showed encouraging efficacy in patients with advanced or metastatic soft tissue sarcoma in the EORTC Phase II study. The progression-free rate at 12 weeks was 18 of 41 patients (44%) for leiomyosarcoma; 18 of 37 patients (49%) for synovial sarcoma; 5 of 19 patients (26%) for liposarcoma, and 16 of 41 patients (39%) for other types of sarcoma. Progression-free survival was 91 days for leiomyosarcoma, 161 days for synovial sarcoma, 80 days for liposarcoma, and 91 days for other types of sarcoma.[24].

A subsequent Phase III study of pazopanib vs. placebo in refractory soft tissue sarcomas excluding liposarcoma reported a median progression-free survival of 4.6 months for pazopanib compared with 1.6 months for placebo (HR 0.31, 95% CI 0.24-0.40; $p<0.0001$) . This study led to FDA approval of pazopanib for the treatment of patients with advanced soft tissue sarcoma who have received prior chemotherapy. Because liposarcoma was excluded from this trial, the FDA indication includes a limitation of use stating that the efficacy of pazopanib for the treatment of adipocytic soft tissue sarcoma has not been demonstrated [25].

2.6 Gemcitabine and Soft Tissue Sarcoma

Single agent gemcitabine has been assessed in a number of Phase II trials in the second line setting in patients with refractory STS and is well tolerated. A study by Hartmann, et al in 2006 using gemcitabine 1000 mg/m^2 over 30 min on days 1, 8, and 15 every 4 weeks showed moderate efficacy with a progression-free rate at 3 and 6 months of 46.7% and 13.3% respectively[26]. The median progression-free survival was 3 months. Patel, et al found a median time to progression of 3 months in patients treated with single agent gemcitabine[27]. A study of gemcitabine in patients with refractory uterine leiomyosarcoma by Look, et al showed an overall response rate of 20.5%[28]. Ferraresi, et al investigated fixed dose-rate gemcitabine (10 mg/m^2/min over 100 min) in patients with refractory STS and found a median time to progression of 3.1 months[29]. Fixed-dose rate gemcitabine infusion has not been shown to be superior to standard administration.

The combination of gemcitabine and docetaxel is a frequently used regimen, especially in the treatment of leiomyosarcoma, the histology in which the highest response rates have been reported. A Bayesian design, randomized Phase II trial of gemcitabine vs. gemcitabine plus docetaxel suggested a survival benefit of the combination[30]. This trial randomized patients receiving 1st to 4th line therapy. The median progression-free survival in this study was 6.2 months for gemcitabine-docetaxel and 3.0 months for gemcitabine alone. The median overall survival was 17.9 months for gemcitabine-docetaxel and 11.5 months for gemcitabine. The French TaxoGem trial randomized patients to receive gemcitabine or gemcitabine and docetaxel as second line therapy for metastatic leiomyosarcoma. A pooled analysis of the Bayesian Phase II trial and the French trial have recently been presented[31]. Primary data from 121 patients with leiomyosarcoma were analyzed. For the subgroup of patients with uterine leiomyosarcoma, the response rate was 18% for those treated with gemcitabine and 23% for the combination, and progression-free survival was 4.9 and 6 months respectively. For patients with extra uterine leiomyosarcoma, the response rate was 13% for those treated with gemcitabine and 10% for those treated with the combination, and progression-free survival was 5.5 and 7 months respectively. There was no significant difference in response or progression-free survival between the gemcitabine and gemcitabine and docetaxel arms. Patients treated with gemcitabine had moderate toxicity, whereas 17% of cycles were complicated by grade 3/ 4 thrombocytopenia in patients treated with the combination.

2.7 Combination of Gemcitabine and Pazopanib

To our knowledge, there is no published preclinical data regarding potential synergy of the combination of gemcitabine and pazopanib. However, there is preclinical data reporting synergy of pazopanib with other cytotoxic chemotherapies including the combination of pazopanib with docetaxel in docetaxel-resistant bladder cancer cells[32]. There is another study reporting increased effect of the combination of pazopanib with metronomic topotecan therapy in preclinical ovarian cancer models compared to either agent alone[33]. Clinically, a survival benefit has been seen with the combination of other antiangiogenic therapies in combination with cytotoxic chemotherapy in lung cancer and colon cancer with the addition of bevacizumab to standard cytotoxic chemotherapy regimens. Several mechanisms have been proposed that may account for the additive or synergistic activity of antiangiogenic agents and cytotoxic chemotherapy, including the possibility that anti-VEGF therapy may transiently normalize leaky tumor vasculature, which could facilitate more effective drug delivery to the tumor[34].

A Phase I, open-label, study of the safety, tolerability, and pharmacokinetics of pazopanib in combination with gemcitabine for advanced solid tumors was conducted from April 2008 through March 2010[35]. This study used a standard cohort 3 + 3 design (dose level 0 – pazopanib 400 mg PO daily and gemcitabine 1000 mg/m^2 by 30 minute infusion on days 1 and 8 of a 21 day treatment cycle; dose level 1 – pazopanib 800 mg PO daily and gemcitabine 1000 mg/m^2 by 30 minute infusion on days 1 and 8 of a 21 day treatment cycle; and dose level 2 – pazopanib 800 mg PO daily and gemcitabine 1250 mg/m^2 by 30 minute infusion on days 1 and 8 of a 21 day treatment cycle).

There were 6 patients treated at dose level 0, 3 patients at dose level 1, and dose level 2 was expanded with a total of 13 patients treated at that dose level. One death occurred in a subject assigned to dose level 0, which was considered by the investigator to be related to study treatment. The subject withdrew from the study due to pneumonia and died 5 days after the last dose of study treatment. Two dose-limiting toxicities (DLTs) were reported in 2 subjects during cycle 1: Grade 4 thrombocytopenia (dose level 0) and grade 3 fatigue (dose level 2). Although dose level 2 was expanded, upon analysis of tolerability based on dose intensity, it was determined that dose level 1 (pazopanib 800 mg PO daily and gemcitabine 1000 mg/m^2 by 30 minute infusion on days 1 and 8 of a 21 day treatment cycle) would be carried forward to Phase II studies (internal GSK communication).

One PR was reported in a patient with melanoma and stable disease was observed in 14 subjects with various tumor types including cholangiocarcinoma, melanoma, and colorectal cancer.

2.8 **Study Rationale**

Gemcitabine is an agent with activity in soft tissue sarcomas. The combination of gemcitabine and docetaxel is a frequently used regimen, especially in the treatment of leiomyosarcoma, the histology in which the highest response rates have been reported. A Bayesian design, randomized Phase II trial of gemcitabine vs. gemcitabine plus docetaxel suggested a survival benefit of the combination[30]. However, the combination of gemcitabine with docetaxel is a relatively poorly-tolerated regimen associated with significant fatigue with 40% of patients discontinuing treatment due to non-hematologic toxicity within 6 months of therapy, despite dose reductions. Furthermore, the additional benefit of docetaxel to gemcitabine is without clear rationale, as single-agent taxanes have minimal benefit in the treatment of most soft tissue sarcomas.

There is a need for development of new treatments for soft tissue sarcomas, which has been difficult given the biologic heterogeneity of this group of tumors. Recently, interesting data have emerged regarding the potential role of VEGF-directed therapies for soft tissue sarcomas. The VEGF tyrosine

kinase inhibitor pazopanib has shown some activity in the second line setting[24], and a placebo controlled Phase III trial of pazopanib in refractory soft tissue sarcomas has recently reported an increase in median progression-free survival of 13 weeks[25]. **We hypothesize that the combination of gemcitabine plus pazopanib will result in improved PFS compared to single agent therapy with gemcitabine.**

3. PATIENT SELECTION

3.1 Eligibility Criteria

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

3.1.2 Age ≥ 18 years

3.1.3 Histologically confirmed diagnosis of metastatic or unresectable soft tissue sarcoma, excluding gastrointestinal stromal tumors, Kaposi's sarcoma, Ewing's family of tumors, and embroynal or alveolar rhabdomyosarcoma

3.1.4 Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 (See Appendix A for description)

3.1.5 Measurable disease per RECIST 1.1

3.1.6 Patients must have received at least one, but not more than three, systemic regimens for treatment of metastatic soft tissue sarcoma. Patients must have had a prior anthracycline in the neoadjuvant, adjuvant or metastatic setting unless medically inappropriate for the patient.

3.1.7 Neoadjuvant or adjuvant therapy will not count towards prior treatment for metastatic disease, unless the patient relapsed within 2 years of completing such therapy.

3.1.8 Adequate organ system function as defined in Table 1

Table 1: Definitions for Adequate Organ Function

System	Laboratory Values
Hematology	
Absolute neutrophil count (ANC)	≥1.5 X 10^9/L
Hemoglobin[a]	≥8 g/dL
Platelets	≥100 X 10^9/L
Prothrombin time (PT) or international normalized ratio (INR)[b]	≤1.2 X ULN
Activated partial thromboplastin time (aPTT)	≤1.2 X ULN
Hepatic	
Total bilirubin	≤1.5 X ULN
Alanine amino transferase (ALT) and Aspartate aminotransferase (AST)[c]	≤2.5 X ULN
Renal	
Serum creatinine	≤1.5 mg/dL (133 µmol/L)
Or, if >1.5 mg/dL: Calculated creatinine clearance (Cl_{CR}) (Appendix B)	≥30 mL/min
Urine Protein to Creatinine Ratio (UPC; Appendix C)[d]	<1
Or 24-hour urine protein	<1 g

a. Subjects may not have had a transfusion within 7 days of screening assessment.

b. Subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation.

c. Concomitant elevations in bilirubin and AST/ALT above 1.0 x ULN (upper limit of normal) are not permitted.

d. If UPC ≥1, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value <1 g to be eligible. Use of urine dipstick for renal function assessment is not acceptable.

3.1.9 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), including any female who has had:
  - A hysterectomy
  - A bilateral oophorectomy (ovariectomy)
  - A bilateral tubal ligation
  - Is post-menopausal

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

Subjects using HRT must have experienced total cessation of menses for >= 1 year and be

greater than 45 years of age OR have had documented evidence of menopause based on FSH and estradiol concentrations prior to initiation of HRT.

- Childbearing potential, including any female who has had a negative serum pregnancy test within 7 days prior to the first dose of study treatment, preferably as close to the first dose as possible, and agrees to use adequate contraception. Defined as follows:
    - Complete abstinence from sexual intercourse for 14 days before exposure to investigational product, through the dosing period, and for at least 21 days after the last dose of investigational product
    - Oral contraceptive, either combined or progestogen alone
    - Injectable progestogen
    - Implants of levonorgestrel
    - Estrogenic vaginal ring
    - Percutaneous contraceptive patches
    - Intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year
    - Male partner sterilization (vasectomy with documentation of azoospermia) prior to the **female subject's entry** into the study, and this male is the sole partner for that subject
    - Double barrier method: condom and an occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/film/cream/suppository)

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

3.2. **Exclusion Criteria**

3.2.1 Prior malignancy

Note: Subjects who have had another malignancy and have been disease-free for >3 years, or subjects with a history of completely resected non-melanomatous skin carcinoma, successfully treated in situ carcinoma, or successfully treated superficial bladder cancer are eligible.

3.2.2 History or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis, except for individuals who have previously-treated CNS metastases, are asymptomatic, and have had no requirement for steroids or anti-seizure medication for 6 months prior to first dose of study drug. Screening with CNS imaging studies (computed tomography [CT] or magnetic resonance imaging [MRI]) is required only if clinically indicated or if the subject has a history of CNS metastases.

3.2.3 Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding including, but not limited to:

- Active peptic ulcer disease
- Known intraluminal metastatic lesion/s with risk of bleeding

- Inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease), or other gastrointestinal conditions with increased risk of perforation
- History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment

3.2.4 Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including, but not limited to:
- Malabsorption syndrome
- Major resection of the stomach or small bowel

3.2.5 Presence of uncontrolled infection

3.2.6 Corrected QT interval (QTc) > 480 msecs using Bazett's formula

3.2.7 History of any one or more of the following cardiovascular conditions within the past 6 months:
- Cardiac angioplasty or stenting
- Myocardial infarction
- Unstable angina
- Coronary artery bypass graft surgery
- Symptomatic peripheral vascular disease

3.2.8 Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA) (See Appendix D for description)

3.2.9 Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg]

Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. Following antihypertensive medication initiation or adjustment, blood pressure (BP) must be re-assessed three times at approximately 2-minute intervals. At least 24 hours must have elapsed between anti-hypertensive medication initiation or adjustment and BP measurement. These three values should be averaged to obtain the mean diastolic blood pressure and the mean systolic blood pressure. The mean SBP / DBP ratio must be <140/90 mmHg.

3.2.10 History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.

Note: Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible.

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

3.2.12 Evidence of active bleeding or bleeding diathesis

3.2.13 Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels that increase the risk of pulmonary hemorrhage

3.2.14 Hemoptysis in excess of 2.5 mL (or one half teaspoon) within 8 weeks of first dose of study drug

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

3.2.16 Unable or unwilling to discontinue use of prohibited medications listed in Section 5.1.4.6 for at least 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of study drug and for the duration of the study. Administration of any non-oncologic investigational drug within 30 days or 5 half lives whichever is longer prior to receiving the first dose of study treatment.

3.2.17 Treatment with any of the following anti-cancer therapies:

- Radiation therapy, surgery or tumor embolization within 14 days prior to the first dose of pazopanib OR
- Chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days (or 28 days in the case of monoclonal antibody therapy) prior to the first dose of PazopanibAny prior treatment with pazopanib
- Prior treatment with a VEGF or VEGFR-targeting agents other than pazopanib (eg. sorafenib, sunitinib, and bevacizumab) in the metastatic setting. Prior use of such agents in the neoadjuvant or adjuvant setting is permitted.
- Any prior treatment with gemcitabine for metastatic disease. Prior use of gemcitabine in the neoadjuvant or adjuvant setting is permitted.

3.2.18 Any ongoing toxicity from prior anti-cancer therapy that is > Grade 1 and/or that is progressing in severity, except alopecia

4. TREATMENT PLAN

4.1. Agent Administration

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Patients will be randomized to either the experimental arm or the placebo arm prior to starting treatment (See Section 8.2 for details regarding randomization.)

Study drug (pazopanib/placebo) should be taken orally without food at least one hour before or two hours after a meal.

The time of day for administration of study drug should be relatively constant.

If a patient misses a dose of study drug, the patient should take the dose as soon as possible, but not less than 12 hours before the next dose is due.

If the next dose is due in less than 12 hours, the patient should skip the missed dose and take the next dose as scheduled.

A diary will be kept by all subjects indicating that the study drug was taken as per protocol.

4.1.1 **Experimental Arm**

- Gemcitabine 1000 mg/m2 IV over 30 minutes on Days 1 and 8 every 21 days
- Pazopanib 800 mg (4x200mg) PO daily

4.1.2 **Placebo Arm**

- Gemcitabine 1000 mg/m2 IV over 30 minutes on Days 1 and 8 every 21 days
- Placebo 4 tablets PO daily

Placebo tablets matching the 200 mg pazopanib tablets will be used for the study.

Patients who progress on gemcitabine + placebo will be offered cross-over treatment with single-agent, open-label pazopanib.

4.1.3 **Cross-over treatment eligibility criteria**

Subjects who discontinue treatment on the placebo arm of the randomized portion of the protocol due to disease progression are eligible for treatment with open-label pazopanib alone (800 mg PO daily). Subjects who develop disease progression on the Experimental arm (pazopanib arm) will NOT be eligible for treatment with open-label pazopanib alone.

Subjects have 4 weeks after documented disease progression on the randomized portion of the protocol to begin treatment with open-label pazopanib. If more than 4 weeks elapse, subjects will not be eligible for cross-over treatment with pazopanib.

The subject must meet the following eligibility criteria to be eligible for the cross-over portion of the protocol:

- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 (See Appendix A for description)
- Adequate contraceptive method for subjects with reproductive potential (See section 3.1.9 for details)
- Must have adequate organ function:

Table 1: Definitions for Adequate Organ Function

System	Laboratory Values
Hematology	
Absolute neutrophil count (ANC)	≥1.5 X 10^9/L
Hemoglobin[a]	≥8 g/dL
Platelets	≥100 X 10^9/L
Prothrombin time (PT) or international normalized ratio (INR)[b]	≤1.2 X ULN
Activated partial thromboplastin time (aPTT)	≤1.2 X ULN
Hepatic	
Total bilirubin	≤1.5 X ULN
Alanine amino transferase (ALT) and Aspartate aminotransferase (AST)[c]	≤2.5 X ULN
Renal	
Serum creatinine	≤1.5 mg/dL (133 μmol/L)
Or, if >1.5 mg/dL: Calculated creatinine clearance (Cl_{CR}) (Appendix B)	≥30 mL/min
Urine Protein to Creatinine Ratio (UPC; Appendix C)[d]	<1
Or 24-hour urine protein	<1 g

a. Subjects may not have had a transfusion within 7 days of screening assessment.

b. Subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation.

c. Concomitant elevations in bilirubin and AST/ALT above 1.0 x ULN (upper limit of normal) are not permitted.

d. If UPC ≥1, then a 24-hour urine protein must be assessed. Subjects must have a 24-hour urine protein value <1 g to be eligible. Use of urine dipstick for renal function assessment is not acceptable.

- No uncontrolled infection
- Corrected QT interval (QTc) ≤ 480 msecs using Bazett's formula
- Adequately controlled hypertension (see section 3.2.9 for details)
- No prior major surgery or trauma within 28 days prior to first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major)
- No radiation therapy or tumor embolization within 14 days prior to the first dose of pazopanib
- No evidence of active bleeding or bleeding diathesis
- No known endobronchial lesions and/or lesions infiltrating major pulmonary vessels
- No hemoptysis in excess of 2.5 mL (or one half teaspoon) within 8 weeks of first dose of study drug
- No history of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months. Subjects

with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible.

- No history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days prior to beginning study treatment
- No known intraluminal metastatic lesion/s with risk of bleeding
- No history or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis, except for individuals who have previously-treated CNS metastases, are asymptomatic, and have had no requirement for steroids or anti-seizure medication for 6 months prior to first dose of study drug.
- No history of any one or more of the following cardiovascular conditions within the past 6 months:
  - Cardiac angioplasty or stenting
  - Myocardial infarction
  - Unstable angina
  - Coronary artery bypass graft surgery
  - Symptomatic peripheral vascular disease
- No class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA) (See Appendix D for description)
- Must be able and willing to discontinue use of prohibited medications listed in Section 5.1.4.6 for at least 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of study drug and for the duration of the study.

4.1.4 **Procedure for entering the cross-over portion of the study**

As described in Section 8.2.2, subjects may be unblinded after progression if the investigator and subject want to proceed with open-label pazopanib. In order to do this, documentation of progression and documentation of the investigator's intent to treat the patient with open label pazopanib if the patient is found to be on the placebo arm will be provided to the coordinating center. Once progression has been confirmed by the coordinating center, the blind will be broken by the OHSU Research Pharmacy and if subject was on the placebo arm of the randomized portion of the trial, the patient may proceed with screening for the open-label pazopanib study arm. Once an eligibility checklist documenting the subject's eligibility for open-label pazopanib treatment has been submitted and approved by the coordinating center, open label pazopanib can be dispensed for the subject per the study schedule. The patient must start taking open label pazopanib within 4 weeks of documentation of progression on the randomized portion of the protocol.

4.1.5 **Cross-over treatment**

Treatment on the cross-over portion of the study is with pazopanib 800 mg PO daily. A cycle will be considered 21 days. No chemotherapy, radiation therapy or investigational agents are permitted. Dose modifications and management of toxicity is the same as for the pazopanib/placebo portion of the randomized part of the study (see Section 5.1).

Treatment on the cross-over portion of the study should continue until:

- Unacceptable toxicity, as per section 5.1
- Disease progression using the disease burden at the time of cross-over as baseline (per RECIST 1.1)

4.1.6 **Schedule of events for cross-over treatment**

Please see section 8.10.

4.2 Supportive Care Guidelines

4.2.1 General guidelines

Appropriate anti-emetics per institutional standard and at the investigator's discretion should be used prior to gemcitabine administration.

Normal saline IV piggyback may be run with gemcitabine to decrease vein discomfort.

Use of erythroid growth factors to support hemoglobin levels are permitted, at the discretion of the investigator.

Use of myeloid growth factors for neutropenia are permitted, at the discretion of the investigator.

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.

4.2.2 Supportive care guidelines for diarrhea, nausea, and vomiting associated with the study drug (pazopanib or placebo)

4.2.2.1 *Diarrhea*

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

Standardized and universal guidelines have been developed by an American Society of Clinical Oncology panel for treating chemotherapy-induced diarrhea[36].

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

The NCI CTCAE Version 4.0 criteria for defining diarrhea are provided in Table 2 below:

Table 2. NCI CTCAE Version 4.0 criteria for diarrhea.

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

Uncomplicated diarrhea is considered mild to moderate and is defined as CTCAE Grade 1 to 2 with no complicating signs or symptoms.

Complicated diarrhea is severe and defined as CTCAE Grade 3 or 4 or Grade 1 or 2 with one or more of the following signs or symptoms: severe cramping, ≥Grade 2 nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, obvious bleeding, dehydration.

Management Guidelines

Uncomplicated diarrhea of CTCAE Grade 1 or 2:

- Hydration: have subject drink 8 to 10 large glasses (approximately 2 liters) of clear non-caffeinated liquids a day (e.g., broth or electrolyte-containing sports drinks).
- If Grade 2 diarrhea, consider holding study drug. Consider dose reduction for recurrent toxicity (see section 5.1.1).
- Dietary modifications: have subject stop all lactose-containing products and eat frequent, small meals
- Pharmacologic intervention using loperamide:
    - Begin loperamide at initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool. The recommended maximum daily dose of loperamide is 16 mg/day.
    - Continuation of loperamide is suggested until diarrhea-free for 12 hours.
    - If mild to moderate diarrhea persists for more than 24 hours, administer loperamide 2 mg every 2 hours and pursue evaluation for other treatable causes.
    - If mild to moderate diarrhea persists after 48 hours total treatment with loperamide, discontinue study drug(s) and consider initiation of second-line agents (lomotil, octreotide).

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

- Subject must call study site physician immediately in response to any event of severe diarrhea with or without complications as listed above.
- Hospitalization may be required for subjects most at risk for life-threatening complications.
  - Hold study drug and refer to dose modification guidelines in section 5.1.1.
- If loperamide has not been initiated, begin loperamide usage immediately at an initial dose of 4 mg followed by 2 mg every 2 hours or after every unformed stool. The recommended maximum daily dose of loperamide is 16 mg/day.
- If no improvement in severity after 24-hours of maximal loperamide dosing, subject must be medically evaluated:
- For dehydration, use intravenous fluids as appropriate.
- Antibiotic therapy should be considered in patients, who present with signs and symptoms of bacterial diarrhea such as fever, bloody diarrhea, and presence of fecal leukocytes. Investigators should have a low threshold to start such treatment in patients with Grade 3 or Grade 4 neutropenia.
- Before initiation of antimicrobial therapy, stool cultures should be obtained. When bacterial etiology for diarrhea is suspected, study-treatment and anti-motility agents (loperamide or others) should be held.
- Intervention should be continued until diarrhea free for 24 hours.

Alternative Pharmacologic Intervention for Uncomplicated and Complicated Diarrhea

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

4.2.2.2 *Nausea and Vomiting*

Every attempt should be made to control nausea and vomiting in subjects who have emesis and are unable to retain the study drug.

As necessary, symptomatic subjects should be treated with anti-nausea/anti-emetic therapy per institutional standards.

If a subject vomits after taking study drug, the subject should be instructed not to take a replacement dose on that same day. The subject should resume taking study drug at the next scheduled dose on the following day. If vomiting persists, then the subject should contact their physician.

4.3. Duration of Therapy

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

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse events(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5. DOSING DELAYS/DOSE MODIFICATIONS

5.1. Study Drug (Pazopanib/Placebo)

5.1.1 Dose Modification for Potential Treatment-Related Adverse Events

Dose modification algorithms for specific toxicities (hypertension, proteinuria, hemorrhage, thrombosis, thrombocytopenia, neutropenia, palmar-plantar erythrodysesthesia, QTc interval prolongation, and liver dysfunction) are detailed below in Tables 3 and 4. For all other Grade 3 or 4 non-hematologic toxicities (except alopecia, nausea, or vomiting) that are at least in part *attributable* to the study drug, the dose should be held until the toxicity resolves to ≤ Grade 1. Treatment should then be resumed at a reduction of one dose level. For recurrent grade 3 or 4 toxicity, the study drug should again be held until the toxicity resolves to ≤ Grade 1 and then reintroduced at another dose level reduction. Up to 3 dose reductions are allowed, after which patient will be removed from protocol treatment if the grade 3-4 toxicity recurs. If the toxicity has abated with reduction of the dose and dose re-escalation is considered safe by the investigator, the study drug dose can then be increased step-wise back to the pre-event dose (in 200 mg increments, after monitoring for 14 days at each dose level to ensure that toxicity did not recur or worsen). Patients who require a reduction of dose below Dose Level -3 will be removed from study treatment.

Dose Level	Study Drug Dose
0	800 mg PO daily
-1	600 mg PO daily
-2	400 mg PO daily
-3	200 mg PO daily

Table 3. Dose Modification Algorithms for Specific Study Drug-Related Adverse Events

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 the study drug 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 the study drug, as clinically indicated. Step 2. Adjust current or initiate new antihypertensive medication. Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Step 4. Once BP is well-controlled, restart the study drug dose-reduced by one dose level if the study drug was interrupted.
(C). Symptomatic hypertension or recurring SBP ≥170 mmHg, or DBP ≥110 mmHg, despite modification of antihypertensive medication(s)	Step 1. Interrupt the study drug. 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 the study drug dose-reduced by one dose level.
(D). Refractory hypertension unresponsive to above interventions.	Discontinue the study drug and continue follow-up per protocol.
Proteinuria	
UPC <3	Continue the study drug at the current dose; monitor as clinically indicated
UPC ≥3 or 24-h urine protein ≥3g	Step 1. Interrupt the study drug. Step 2. Weekly UPC or 24-hr urine protein monitoring until UPC is <3 or 24-hr urine protein is <3 grams. Then restart the study drug dose-reduced by one dose level.

AE Terms & Descriptions	Dose Modification Algorithms
	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 study drug dose can no longer be reduced, discontinue the study drug and continue follow-up per protocol.
Hemorrhage /Bleeding: Investigate and document underlying etiology of the bleeding	
Grade 1	For hemoptysis, interrupt the study drug and consider whether further treatment with the study drug is appropriate. For other Grade 1 hemorrhage/bleeding events, continue the study drug at the current dose; monitor as clinically indicated.
Grade 2	Step 1. If pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue the study drug and continue follow-up per protocol. Otherwise, interrupt the study drug until the AE resolved to ≤ Grade 1. Step 2. Restart the study drug; consider reducing dose and monitor as clinically indicated.
Grade 3 or 4, or Recurrent ≥ Grade 2 event after dose interruption/reduction.	Discontinue the study drug and continue with follow-up per protocol.
Venous Thrombosis (DVT, PE)	
Grade 2	Continue the study drug at the current dose; monitor as clinically indicated
Grade 3	Step 1. Interrupt the study drug. Step 2. Initiate and monitor anticoagulation as clinically indicated. Step 3. Resume the study drug at reduced dose only if all of the following criteria are met: • The subject must have been treated with anticoagulant at the desired level of anticoagulation for at least one week. • No Grade 3 or 4 or clinically significant Grade 2, hemorrhagic events have occurred while on anticoagulation treatment. Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment. When

AE Terms & Descriptions	Dose Modification Algorithms
	treating with warfarin, international normalized ratio (INR) should be monitored within three to five days after any change in the study drug dosing (eg, re initiating, escalating/de-escalating, or discontinuing the study drug), 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 the study drug and continue follow-up per protocol.
Arterial Thrombosis/Ischemia	
Any Grade	Discontinue the study drug and continue follow-up per protocol.
Thrombocytopenia/Neutropenia - Study drug dosing will be modified only for persistent grade 3-4 thrombocytopenia or neutropenia despite gemcitabine modification.	
Grade 1 or 2	Continue the study drug with current dose; monitor as clinically indicated.
Grade 3 or 4	Step 1. Interrupt the study drug until toxicity resolves to ≤ Grade 2. Step 2. Restart the study drug dose-reduced by one dose level and monitor as clinically indicated. If no recovery to ≤ Grade 2 or recurrent Grade 3 or 4 thrombocytopenia despite maximum dose reduction of gemcitabine, discontinue the study drug and follow-up per protocol
Anemia: No specific dose reduction rules are indicated for anemia unless due to hemorrhage or bleeding as noted above.	
Palmar-plantar Erythrodysesthesia Syndrome	
Grade 1 Minimal skin changes or dermatitis without pain (erythema, edema, hyperkeratosis)	1. Continue the study drug at present dose
Grade 2 Skin changes with pain; limiting instrumental activities of daily living (ADLs) (peeling, blisters, edema, bleed, hyperkeratosis)	1. Hold the study drug 2. Treat as clinically appropriate 3. Upon resolution to Grade 1 or better restart the study drug with a dose reduction to 400 mg (dose level -2) 4. If recurrent consider a further dose reduction to 200mg (dose level -3) or discontinuation
Grade 3 Severe skin changes with pain and limiting self care ADLs	1. Discontinue the study drug
Prolongation of QTc Interval: If the QTc is prolonged, the ECG should be manually read to ensure	

AE Terms & Descriptions	Dose Modification Algorithms
accuracy of the reading. The values below refer to manually-read ECGs.	
QTc ≥ 480 < 500 msec	Continue the study drug; monitor as clinically indicated.
QTc ≥500 msec	Discontinue the study drug 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.

5.1.2 **Dose Modifications and Management of Liver Toxicity**

Recommendations for study drug dose interruptions/modifications in case of liver-related treatment-emergent AEs are provided in Table 4. As a general rule, since many subjects are taking multiple concurrent medications, it is critical to (a) do a thorough evaluation of the subject's concurrent medications, and (b) identify and discontinue those with known hepatotoxicity and replace with a non-hepatotoxic equivalent for the same indication if necessary. Liver dysfunction must be fully evaluated even if clinical signs and symptoms indicate progression of liver tumor lesions. Imaging studies must be obtained to document potential progression of malignancy.

Table 4. Dose Modification Algorithms for Liver Dysfunction

Event	Dose Modification Algorithms
(A). ALT of ≤ 3.0 x ULN	Continue the study drug at current dose with full panel LFTs[a] monitored as per protocol.
(B). ALT >3.0 x ULN to ≤8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[b] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	**Liver Event Monitoring Criteria:** (1) Continue the study drug at current dose levels. (2) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1.
(C). ALT >8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[b] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	**1st occurrence – Liver Event Interruption Criteria:** (1) Interrupt the study drug until toxicity resolves to ≤Grade 1 or baseline. Report the event to Novartis as an SAE **within 24 hours** of learning of its occurrence (refer to section 10.7.7 for details regarding SAE reporting). Make every reasonable attempt to have subjects return to the clinic within 24 to 72 hours for repeat liver chemistries and liver event follow up assessments. (2) Liver imaging and other laboratory investigations should be considered as clinically appropriate. (3) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1. (4) Re-treatment may be considered if ALL following criteria are met: - ALT/AST reduced to Grade 1 - Total bilirubin <1.5 x ULN or direct bilirubin ≤35% - No hypersensitivity signs or symptoms - Subject is benefiting from therapy. If criteria are met, reintroduce pazopanib at a -2 dose level (400 mg once daily) and measure serum LFTs weekly for 8 weeks. **Recurrence – Liver Event Stopping Criteria:** Following reintroduction of pazopanib, if ALT/AST elevations >3 X ULN recur, then pazopanib should be permanently discontinued. Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1.

Table 4. Dose Modification Algorithms for Liver Dysfunction

Event	Dose Modification Algorithms
(D). ALT >3.0 x ULN **with** concomitant elevation in bilirubin[b] (defined as total bilirubin ≥2.0 x ULN; with direct bilirubin >35%) or **with** hypersensitivity symptoms (e.g., fever, rash).	**Liver Event Stopping Criteria:** (1) Discontinue the study drug permanently immediately, report the event to Novartis as an SAE **within 24 hours** of learning of its occurrence (refer to section 10.7.7 for details regarding SAE reporting). Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries and liver event follow up assessments. (2) Consider consulting a gastroenterologist / hepatologist. Consider performing the following assessments to identify potential co-factors: - Eosinophil count - Viral serology for hepatitis A, B, C and E, cytomegalovirus, Epstein-Barr virus (IgM antibody, heterophile antibody, or monospot testing) - Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies. - Serum creatinine phosphokinase for possible muscle injury caused LFT elevation - Liver imaging - Consider toxicological blood screen for possible contributing chemical/medical entities (3) Monitor subject closely for clinical signs and symptoms; record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form. Perform full panel LFTs[a] weekly or more frequently if clinically indicated until LFTs are reduced to Grade 1.
For isolated total bilirubin[b] elevation without concurrent ALT increases (defined as ALT <3 X ULN).	(1) Isolated hyperbilirubinemia (i.e., in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. The study drug inhibits UGT1A1 and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury. (2) If bilirubin is >1.5 x ULN in the absence of ALT elevation, fractionation of bilirubin elevation should be performed. If bilirubin is >35% direct (conjugated), further evaluation for underlying cause of cholestasis should be performed.

a. Full panel LFTs include: AST, ALT, alkaline phosphatase, and total bilirubin. Coagulation tests should be performed as clinically indicated.
b. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin >1.5 x ULN, then the event should be promptly reported as an SAE.

Abbreviations: ALT alanine aminotransferase; AST aspartate aminotransferase; LFT liver function tests; PK pharmacokinetics; SAE serious adverse event; ULN upper limit of normal

5.1.3 **Treatment of Study Drug (Pazopanib/Placebo) Overdose**

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

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

Following an overdose, additional monitoring of the subject for AEs/SAEs and laboratory abnormalities should be considered. A plasma sample for pharmacokinetic analysis for pazopanib may be requested by the Novartis Study Physician on a case-by-case basis. This plasma sample should be collected as soon as possible, but within 7 days from the date of the last dose of study drug.

Information regarding the quantity of the excess dose, as well as the duration of overdosing, should be documented in the CRF.

5.1.4 **Concomitant Medications**

5.1.4.1 *Concomitant Medications and Non-Drug Therapies*

If future changes are made to the list of permitted/prohibited medications, formal documentation will be provided by Novartis and stored in the study file. Any such changes will be communicated to the investigative sites in the form of a letter.

5.1.4.2 *Permitted medications*

All subjects will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the 4 weeks prior to Screening. The investigator must be informed as soon as possible about any new medication(s) taken from the time of Screening until the completion of the post-treatment follow-up visit.

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

Patients should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, analgesics, erythropoietin, or bisphosphonates, when appropriate. Anti-emetics (such as prochlorperazine, lorazepam, ondansetron or other 5-HT antagonists) may be administered prophylactically in the event of nausea. Anti-diarrheals, such as loperamide, may be administered as needed in the event of diarrhea. Although acetaminophen at doses of ≤2 g/day is permitted, it should be used with caution in subjects with impaired liver function.

5.1.4.3 *Use with caution*

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

Specific recommendations regarding hypoglycemic therapy including insulin:
Results from drug-drug interaction studies conducted in subjects with cancer suggest that there will be no clinically relevant pharmacokinetic interaction between pazopanib and hypoglycemic agents. Transient decreases in serum glucose (mainly Grade 1 and 2, rarely Grade 3) have been observed in clinical studies with pazopanib. In addition, decreases in blood sugar have been recently reported in subjects treated with another small molecule tyrosine kinase inhibitor, sunitinib[37]. Such changes may require an adjustment in the dose of hypoglycemic and/or insulin therapy. Subjects should be advised to report symptoms of hypoglycemia (e.g., confusion, visual disturbances, palpitations, sweating). Serum glucose should be tested during treatment with pazopanib as outlined in the protocol and as clinically indicated.

5.1.4.4 *The Effects of Pazopanib on Other Drugs*

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

- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine (potential increased risk for developing ergot toxicity that includes severe vasospasm leading to peripheral as well as cerebral ischemia)
- Neuroleptics: pimozide (potential increased risk for QT interval prolongation, ventricular arrhythmia, and sudden death)
- Antiarrhythmics: bepridil, flecainide, lidocaine, mexiletine, amiodarone, quinidine, propafenone (potential increased risk for QT interval prolongation and Torsade de Pointes)

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

5.1.4.5 *The Effects of Other Drugs on Pazopanib*

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

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

CYP3A4 inducers may decrease plasma Pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal enzyme induction potential is recommended.

Drugs that induce CYP3A4 and may decrease Pazopanib plasma concentrations include (but are not limited to):

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

5.1.4.6 *Prohibited medications*

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

Medications that inhibit CYP3A4 may result in increased plasma Pazopanib concentrations; therefore, co-administration of strong CYP3A4 inhibitors is **PROHIBITED** beginning **14** days prior to the first dose of study drug until discontinuation from the study.

Strong CYP3A4 inhibitors include (but are not limited to):

- Antibiotics: clarithromycin, telithromycin, troleandomycin
- HIV: protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir)
- Antifungals: itraconzaole, ketoconazole, voriconazole, fluconazole
- Antidepressants: nefazodone

5.2. **Gemcitabine**

Dose modifications for gemcitabine-related toxicity will be based on the following dose level schema. All patients will start treatment at dose level 0. Patients who require a reduction of dose below Dose Level –2 will be removed from study treatment.

Dose Level	Gemcitabine Dose (mg/m^2 days 1 and 8)
0	1000
-1	750
-2	500

5.2.1 **Hematologic Toxicity**

5.2.1.1 **ANC and Platelets**

Day 1: A treatment cycle may not begin unless the patient's absolute neutrophil count (ANC) is 1500/L and platelet count is 100,000/L (without transfusion).

Day 8:
If ANC is 1000 to 1499/L or platelet count is 75,000 to 99,000/L (without transfusion), reduce by one dose level for day 8 of current cycle only. If the patient is already at dose level -2, further dose reduction for D8 is at investigators discretion. If ANC is <1000/L or platelet count is <75,000/L, hold day 8 gemcitabine dose of current cycle; if treatment parameters are met by day 15, gemcitabine may be administered and the next cycle should begin 2 weeks later. If the patient does not meet treatment parameters by day 15, gemcitabine should be held until the next cycle.

5.2.1.2 **Neutropenic fever or grade 4 neutropenia for >5 days:**

Reduce by one dose level for next and all subsequent cycles

5.2.1.3 **Grade 3-4 thrombocytopenia with clinically significant bleeding or grade 4 thrombocytopenia lasting >5 days:**

Reduce by one dose level for next and all subsequent cycles

5.2.1.4 **Anemia:**

Supportive care at physician's discretion

5.2.2 **Non-hematologic Toxicity**

Patients who experience Grade 3 or 4 toxicity (except alopecia, nausea, or vomiting) that is attributable to gemcitabine and not to the underlying disease or exclusively to the study drug (pazopanib/placebo) should have chemotherapy held until the toxicity resolves to ≤ Grade 1. Treatment should then be resumed at a reduction of one dose level for the next and all subsequent cycles. Patients who are delayed greater than 3 weeks due to non-resolution of such toxicity will be removed from study treatment. In the case of grade 3 or 4 hypertension or proteinuria, study drug

should be dose reduced first. Gemcitabine will only be modified for grade 3 or 4 hypertension or proteinuria that is persistent despite study drug dose modification.

6. AGENT FORMULATION AND PROCUREMENT

6.1. Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of the study agent.

6.2. Pazopanib (Votrient)

Availability: Pazopanib is supplied to investigators by Novartis.

Product description: Pazopanib hydrochloride is a white to slightly yellow solid. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media. 200 mg tablets of pazopanib are modified capsule-shaped, gray, film-coated with GS JT debossed on one side in bottles of 120 tablets. Each 200 mg tablet of pazopanib contains 216.7 mg of pazopanib hydrochloride, equivalent to 200 mg of pazopanib free base.

The inactive ingredients of pazopanib are: *Tablet Core:* Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate. *Coating:* Gray film-coat: Hypromellose, iron oxide black, macrogol/polyethylene glycol 400 (PEG 400), polysorbate 80, titanium dioxide.

Solution preparation: Not applicable

Storage requirements: Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F).

Stability*:* The current shelf life is 36 months.

Route of administration: Orally once daily without food (at least 1 hour before or 2 hours after a meal. Do not crush tablets due to the potential for increased rate of absorption which may affect systemic exposure. If a dose is missed, it should not be taken if it is less than 12 hours until the next dose.

Expected adverse events:

Table 5. Adverse Reactions Occurring in ≥10% of Patients who Received Pazopanib

	Pazopanib (N = 290)			Placebo (N = 145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
Adverse Reactions	**%**	**%**	**%**	**%**	**%**	**%**
Diarrhea	52	3	<1	9	<1	0
Hypertension	40	4	0	10	<1	0
Hair color changes	38	<1	0	3	0	0
Nausea	26	<1	0	9	0	0
Anorexia	22	2	0	10	<1	0
Vomiting	21	2	<1	8	2	0
Fatigue	19	2	0	8	1	1
Asthenia	14	3	0	8	0	0
Abdominal pain	11	2	0	1	0	0
Headache	10	0	0	5	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Table 6. Selected Laboratory Abnormalities Occurring in >10% of Patients who Received Pazopanib and More Commonly (≥5%) in Patients who Received Pazopanib Versus Placebo

Parameters	Pazopanib (N = 290)			Placebo (N = 145)		
	All Grades[a]	Grade 3	Grade 4	All Grades[a]	Grade 3	Grade 4
	%	**%**	**%**	**%**	**%**	**%**
Hematologic						
Leukopenia	37	0	0	6	0	0
Neutropenia	34	1	<1	6	0	0
Thrombocytopenia	32	<1	<1	5	0	<1
Lymphocytopenia	31	4	<1	24	1	0
Chemistry						
ALT increased	53	10	2	22	1	0
AST increased	53	7	<1	19	<1	0
Glucose increased	41	<1	0	33	1	0
Total bilirubin increased	36	3	<1	10	1	<1
Phosphorus decreased	34	4	0	11	0	0
Sodium decreased	31	4	1	24	4	0
Magnesium decreased	26	<1	1	14	0	0
Glucose decreased	17	0	<1	3	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Other adverse reactions observed more commonly in patients treated with pazopanib than placebo and that occurred in <10% (any grade) were alopecia (8% versus <1%), chest pain (5% versus 1%), dysgeusia (altered taste) (8% versus <1%), dyspepsia (5% versus <1%), facial edema (1% versus 0%), palmar-plantar erythrodysesthesia (hand-foot syndrome) (6% versus <1%), proteinuria (9% versus 0%), rash (8% versus 3%), skin depigmentation (3% versus 0%), and weight decreased (9% versus 3%).

Hepatic Toxicity — In a controlled clinical study with pazopanib for the treatment of RCC, ALT >3 X ULN was reported in 18% and 3% of the pazopanib and placebo groups, respectively. ALT >10 X ULN was reported in 4% of patients who received pazopanib and in <1% of patients who received placebo. Concurrent elevation in ALT >3 X ULN and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >3 X ULN occurred in 5/290 (2%) of patients on pazopanib and 2/145 (1%) on placebo.

Hypertension — In a controlled clinical study with pazopanib for the treatment of RCC, 115/290 patients (40%) receiving pazopanib compared with 15/145 patients (10%) on placebo experienced hypertension. Grade 3 hypertension was reported in 13/290 patients (4%) receiving pazopanib compared with 1/145 patients (<1%) on placebo. The majority of cases of hypertension were manageable with anti-hypertensive agents or dose reductions with 2/290 patients (<1%) permanently discontinuing treatment with pazopanib because of hypertension. In the overall safety population for RCC (N = 586), one patient had hypertensive crisis on pazopanib.

QT Prolongation and Torsades de Pointes — In a controlled clinical study with pazopanib, QT prolongation (≥500 msec) was identified on routine electrocardiogram monitoring in 3/290 (1%) of patients treated with pazopanib compared with no patients on placebo. Torsades de pointes was reported in 2/586 (<1%) patients treated with pazopanib in the RCC studies.

Arterial Thrombotic Events — In a controlled clinical study with pazopanib, the incidences of arterial thrombotic events such as myocardial infarction/ischemia [5/290 (2%)], cerebral vascular accident [1/290 (<1%)], and transient ischemic attack [4/290 (1%)] were higher in patients treated with pazopanib compared to the placebo arm (0/145 for each event).

Hemorrhagic Events — In a controlled clinical study with pazopanib, 37/290 patients (13%) treated with pazopanib and 7/145 patients (5%) on placebo experienced at least 1 hemorrhagic event. The most common hemorrhagic events in the patients treated with pazopanib were hematuria (4%), epistaxis (2%), hemoptysis (2%), and rectal hemorrhage (1%). Nine (9/37) patients treated with pazopanib who had hemorrhagic events experienced serious events including pulmonary, gastrointestinal, and genitourinary hemorrhage. Four (4/290) (1%) patients treated with pazopanib died from hemorrhage compared with no (0/145) (0%) patients on placebo. In the overall safety population in RCC (N = 586), cerebral/intracranial hemorrhage was observed in 2/586 (<1%) patients treated with pazopanib.

Hypothyroidism — In a controlled clinical study with pazopanib, more patients had a shift from thyroid stimulating hormone (TSH) within the normal range at baseline to above the normal range at any post-baseline visit in pazopanib compared with the placebo arm (27% compared with 5%, respectively). Hypothyroidism was reported as an adverse reaction in 19 patients (7%) treated with pazopanib and no patients (0%) in the placebo arm.

Diarrhea — Diarrhea occurred frequently and was predominantly mild to moderate in severity. Patients should be advised how to manage mild diarrhea and to notify their healthcare provider if moderate to severe diarrhea occurs so appropriate management can be implemented to minimize its impact.

Proteinuria — In the controlled clinical study with pazopanib, proteinuria has been reported as an adverse reaction in 27 patients (9%) treated with pazopanib. In 2 patients, proteinuria led to discontinuation of treatment with pazopanib.

Lipase Elevations — In a single-arm clinical study, increases in lipase values were observed for 48/181 patients (27%). Elevations in lipase as an adverse reaction were reported for 10 patients (4%) and were Grade 3 for 6 patients and Grade 4 for 1 patient. In the studies of pazopanib in RCC studies, clinical pancreatitis was observed in 4/586 patients (<1%).

Cardiac Dysfunction — Pazopanib has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types, including RCC. In the overall safety population for RCC (N = 586), cardiac dysfunction was observed in 4/586 patients (<1%).

6.3. Gemcitabine (Gemzar)

Product description: Gemcitabine HCl is a white to off-white solid. It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents. The clinical formulation is supplied in a sterile form for intravenous use only. Vials of Gemzar contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment. This agent is commercially available.

Solution preparation: The recommended diluent for reconstitution of Gemzar is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for Gemzar upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided.

To reconstitute, add 5 mL of 0.9% Sodium Chloride Injection to the 200-mg vial or 25 mL of 0.9% Sodium Chloride Injection to the 1-g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200-mg vial or 1.3 mL for the 1-g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. Prior to administration the appropriate amount of drug must be diluted with 0.9% Sodium Chloride Injection. Final concentrations may be as low as 0.1 mg/mL.

Reconstituted Gemzar is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% Sodium Chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration prior to administration, whenever solution or container permit. If particulate matter or discoloration is found, do not administer.

When prepared as directed, Gemzar solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F). Discard unused portion. Solutions of reconstituted Gemzar should not be refrigerated, as crystallization may occur.

The compatibility of Gemzar with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

Route of administration: Intravenous infusion should be performed over 30 minutes. Prolongation of

the infusion time >60 minutes has been shown to increase toxicity.

Expected adverse events:

Hematologic — In studies in pancreatic cancer myelosuppression is the dose-limiting toxicity with Gemzar, but <1% of patients discontinued therapy for either anemia, leukopenia, or thrombocytopenia. Red blood cell transfusions were required by 19% of patients. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients should be monitored for myelosuppression during Gemzar therapy and dosage modified or suspended according to the degree of hematologic toxicity.

Gastrointestinal — Nausea and vomiting were commonly reported (69%) but were usually of mild to moderate severity. Severe nausea and vomiting (WHO Grade 3/4) occurred in <15% of patients. Diarrhea was reported by 19% of patients, and stomatitis by 11% of patients.

Hepatic — In clinical trials, Gemzar was associated with transient elevations of one or both serum transaminases in approximately 70% of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to Gemzar or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving Gemzar alone or in combination with other potentially hepatotoxic drugs.

Renal — In clinical trials, mild proteinuria and hematuria were commonly reported. Clinical findings consistent with the Hemolytic Uremic Syndrome (HUS) were reported in 6 of 2429 patients (0.25%) receiving Gemzar in clinical trials. Four patients developed HUS on Gemzar therapy, 2 immediately post therapy. The diagnosis of HUS should be considered if the patient develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of serum creatinine or BUN). Gemzar therapy should be discontinued immediately. Renal failure may not be reversible even with discontinuation of therapy and dialysis may be required.

Fever — The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that Gemzar may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.

Rash — Rash was reported in 30% of patients. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild to moderate severity involving the trunk and extremities. Pruritus was reported for 13% of patients.

Pulmonary — In clinical trials, dyspnea, unrelated to underlying disease, has been reported in association with Gemzar therapy. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of Gemzar. The etiology of these effects is unknown. If such effects develop, Gemzar should be discontinued. Early use of supportive care measures may help ameliorate these conditions.

Edema — Edema (13%), peripheral edema (20%), and generalized edema (<1%) were reported. Less than 1% of patients discontinued due to edema.

Flu-like Symptoms — "Flu syndrome" was reported for 19% of patients. Individual symptoms of fever, asthenia, anorexia, headache, cough, chills, and myalgia were commonly reported. Fever and asthenia

were also reported frequently as isolated symptoms. Insomnia, rhinitis, sweating, and malaise were reported infrequently. Less than 1% of patients discontinued due to flu-like symptoms.

Infection — Infections were reported for 16% of patients. Sepsis was rarely reported (<1%).

Alopecia — Hair loss, usually minimal, was reported by 15% of patients.

Neurotoxicity — There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias.

Extravasation — Injection-site related events were reported for 4% of patients. There were no reports of injection site necrosis. Gemzar is not a vesicant.

Allergic — Bronchospasm was reported for less than 2% of patients. Anaphylactoid reaction has been reported rarely. Gemzar should not be administered to patients with a known hypersensitivity to this drug.

Cardiovascular — During clinical trials, 2% of patients discontinued therapy with Gemzar due to cardiovascular events such as myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension. Many of these patients had a prior history of cardiovascular disease**.**

7. CORRELATIVE/SPECIAL STUDIES

7.1. Angiogenic Biomarkers

Specimens will be collected for the following potential correlative studies.

7.1.1 Tumor Tissue

In an effort to explore tumor biomarkers that may correlate with response, archived formalin-fixed paraffin embedded tumor tissue will be collected for potential testing to examine expression levels of biomarkers (encoded in RNA or protein) in pathways relevant to angiogenesis (e.g. VEGF, PDGF) and related pathways. A tumor block of sufficient size must be sent to OHSU for testing. In the event a tumor block is not available, efforts will be made to obtain 20 slides of paraffin-embedded tissue.

Representative areas from each whole-mount paraffin block chosen as the best composite representation of tumor based on H&E morphology will be placed in standard-sized tissue cassettes. These will be re-embedded, sectioned at 4 μm, and mounted on poly-L-lysine–coated slides for immunohistochemistry. Sections of paraffin embedded tissue will be deparaffinized and rehydrated. After appropriate antigen retrieval methods, potential IHC staining with commercial antibodies including but not limited to VEGF-A, VEGF-R2, phospho-VEGF-R2, PDGFR, and phospho-PDGFR will be performed using an automated Dako immunostainer. Staining will be visualized by incubating the slides with 3,3'-diaminobenzidine solution, after which they will be rinsed, counterstained with hematoxylin, dehydrated in a Leica Autostainer XL, coverslipped, and reviewed by a single experienced pathologist who will score the percentage of positively staining cells.

7.1.2 Serum

Serum (10 mL blood sample) will be collected at baseline and at week 6. Serum samples will be collected for potential tumorigenic and angiogenic markers including but not limited to VEGF, VEGF-A, sVEGFR2, and bFGF at baseline to correlate with response, and to identify any changes in circulating markers levels in response to treatment. Blood samples (10 mL) will be drawn using venipuncture into a Vacutainer containing potassium EDTA and inverted gently several times to mix with anticoagulant. Within 10-15 minutes after collecting, blood samples will be centrifuged in a refrigerated (4C) centrifuge for 10 minutes to separate the plasma. If a refrigerated centrifuge is not available, the tubes should be chilled in an ice bath for 5-15 minutes and then placed in a standard centrifuge for 10 minutes to separate the plasma. The plasma will be transferred to polypropylene tubes and frozen at -70C or lower. The tubes will be labeled with the investigator's name, study number, and subject's study number, and time and date of the sample acquisition.

Quantitative enzyme-linked immunosorbent assays (ELISA) for angiogenic markers including but not limited to VEGF, VEGF-A, sVEGFR2, and bFGF may be performed on plasma using commercial kits. Manufacturers' protocols will be followed and samples are to be measured in duplicate.

7.2. Genetic mutation screen

Tumor specimens may be used to screen for genetic alterations in a number of genes. DNA will be extracted and purified from available tumor material. Mutations will be detected using multiplex PCR amplification of gene exons of interest, followed by primer extension reactions, and readout of primer extension products by mass spectrometry. Confirmation of mutations by mass spectrometry will be confirmed by sequencing.

8. STUDY PROCEDURES AND SCHEDULE OF EVENTS

8.1 Subject Registration

Written informed consent must be obtained before any study specific medical procedures are performed.

All patients must be registered through the Oregon Health & Science University Knight Cancer Center.

8.2. Randomization process

8.2.1 Method of blinding

The OHSU Knight Cancer Institute will serve as the data coordinating center for this multicenter study. The OHSU statistician will generate a list of randomization codes for each sarcoma subtype (liposarcoma vs. other sarcoma subtypes) for each study site. Each site pharmacy will have a list of randomization codes and the corresponding assignment to drug vs. placebo. The OHSU pharmacy will have a master list of the assigned randomization codes and corresponding drug assignments for all study sites.

When other coordinating sites have an eligible patient, they will contact the OHSU study coordinator who will review and approve patient eligibility. If eligible, the OHSU study site coordinator will assign the patient a unique ID# (randomization#) from the pre-generated list of randomization codes. The OHSU study site coordinator will then notify the OHSU research pharmacy and the study site pharmacy (if the patient is enrolled at another site) of the assigned

randomization code via a secure email. The unblinded research pharmacist will assign the patient to drug vs. placebo based on the corresponding drug assignment list. Double signature confirmation should be employed in the study specific enrollment record kept in the research pharmacy study binder.

The randomization procedure will use the Biostatistics Shared Resources (BSR) at Knight Cancer Institute (KCI), which will serve as the randomization center. The BSR center will be using Stata module called Ralloc to create a sequence of randomization assignment in blocks of varying sizes. The randomization sequence is stratified by both the sarcoma subtype (liposarcoma vs. other sarcoma subtypes) and the study site. The size and the order of the blocks are also randomized to lessen the chance of predicting future assignments.

8.2.2 **Unblinding procedure**

Treatment assignment will remain blinded throughout the Study Treatment Period. Upon documented disease progression, a request to unblind the treatment assignment may be made by the investigator as per section 4.1.4. Unblinding will be performed by the OHSU Research Pharmacy.

In the case of an emergency, when knowledge of the investigational product is essential for the clinical management or welfare of the patient, a patient's treatment assignment may be unblinded. The principal investigator should be contacted to authorize the unblinding after review of the circumstances. In the unlikely case that the principal investigator is not available, the OHSU Research Pharmacy is authorized to unblind the subject's treatment assignment upon provision of supporting documentation by the investigator or managing healthcare professional.

8.3. **Standard Laboratory Assessments**

Laboratory assessments should be performed as indicated in the Schedule and Events Tables (Sections 8.9 and 8.10). These assessments may be carried out within 3 days before the actual visit to allow flexibility in scheduling. Assessments may be performed more frequently if clinically indicated. Correction of electrolytes (most importantly, potassium, magnesium and calcium) to within normal ranges should take place prior to study entry and during study conduct as clinically indicated.

All laboratory tests with values that become abnormal and clinically significant while the subject is participating in the study or within 28 days after the last dose of study drug should be repeated until the values return to normal or baseline.

Table 7 shows the clinical laboratory assessments that should be reported.

Table 7. Clinical Laboratory Assessments

Clinical Chemistry	
Renal function	Urea, Creatinine[a]
Liver function test (LFT) Panel	Albumin, Alkaline phosphatase, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), and Bilirubin (total)[b]
Electrolytes and others	Calcium, Potassium, Sodium, and Glucose
Hematology	Hematocrit, Hemoglobin, White Blood Cell Count, Red Blood Cell Count, Neutrophils, and Platelets
Coagulation Tests	Activated partial thromboplastin (aPTT) and International Normalization Ratio (INR)[c]
Urinalysis for Proteinuria	UPC[d]
Thyroid Function Test	TSH and thyroxine (free T4)[e]

a) Estimated creatinine clearance should be calculated using the Cockcroft and Gault method (Appendix B). Alternatively, creatinine clearance can be measured directly by 24-hour urine collection.
b) A direct bilirubin level should be obtained if the total bilirubin level is greater than 1.5 X upper limit of normal (ULN). See Section 5.1.2 for stopping criteria and dose modification guidelines for treatment-emergent liver function abnormality.
c) Coagulation tests may also be performed in response to an AE/SAE of bleeding and as clinically indicated.
d) UPC should be evaluated as described in Appendix C or by 24-hour urine protein. If UPC ≥ 3 or if urine protein is ≥3g, then the dose modification table guidelines should be followed (Section 5.1.1).
e) Unscheduled thyroid function tests [TSH and thyroxine (free T_4)] should be performed if clinically indicated (e.g., if a subject develops signs and symptoms suggestive of hypothyroidism).

8.4. **Baseline Screening**

The following assessment will be completed prior to randomization:

- Medical history (information on prior lines of therapies given for soft tissue sarcoma are important)

- Physical examinations and demographics (age, gender, race, ethnicity, ECOG performance status, blood pressure, pulse rate and body weight)

- Blood pressure (BP): for patients presenting with hypertension, their BP must be adequately controlled to ≤140/90 mmHg prior to the first dose of study medication.

    - Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. Following antihypertensive medication initiation or adjustment, blood pressure (BP) must be re-assessed three times at approximately 2-minute intervals. At least 24 hours must have elapsed between anti-hypertensive medication initiation or adjustment and BP measurement. These three values should be averaged to obtain the mean diastolic blood pressure and the mean systolic blood pressure. The mean SBP / DBP ratio must be <140/90 mmHg in order for a subject to be eligible for the study.

- Adverse events

- Cancer signs and symptoms

- Complete blood counts (including hemoglobin, hematocrit, white blood cell count, red blood cell count, neutrophils, and platelets) and serum chemistry (including calcium, sodium, potassium, urea, creatinine, total bilirubin, alkaline phosphatase, AST, ALT, glucose and albumin), PT/INR, PTT

    - Note: In case of co-administration of pazopanib with the anticoagulant warfarin (or its derivatives): International normalized ratio (INR) should be monitored within three to five days after initiating, escalating/de-escalating or discontinuing pazopanib therapy, 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.

- Thyroid function: TSH and free T4

- UPC (Urine protein Creatinine ratio mg/dl, Appendix C) must be ≤1. If UPC > 1, urine protein excretion over 24h must be performed. Any patient with protein > 1 g over 24 hours would not be eligible.

- Pregnancy test (serum β-HCG) for women of childbearing potential. Serum or urine pregnancy testing is required within 7 days of enrollment.

- Cardiac function: 12-lead ECG and QTc measurement will be recorded.

- Disease assessment within 4 weeks prior to start of treatment:

    - Radiological assessment to include CT (with contrast) of chest, abdomen, pelvis (abdomen MRI with gadolinium and/or a non-contrast chest CT can be substituted for patients with renal insufficiency or if otherwise clinically indicated).

    - In case of suspicion of brain metastases perform CT or MRI brain (enhanced contrast).

The above assessments should be completed within the following timeframes:

Within 4 weeks of randomization:

- Medical history & Physical
- 12-lead ECG and QTc measurement
- Informed consent

Within 1 week of randomization:

Labs, including:

- CBC
- Chemistries
- LFTs
- Pregnancy test
- UPC
- TSH

- Free T4
- PT/INR
- aPTT

Prior to randomization and within 4 weeks of treatment start:

- CT (with contrast) of chest, abdomen, pelvis (abdomen MRI with gadolinium and/or non-contrast chest CT also acceptable with PI approval)

C1D1 of treatment must be within 7 days of randomization.

8.5. Study Visits

See section 8.9.

Toxicities and adverse experiences will be assessed at each visit using the NCI Common Toxicity Criteria for Adverse Events v4.0 (CTCAE, see appendix E).

8.6. Pathology Sample Submission

All pathology slides from the diagnostic biopsy must be submitted for central review at OHSU by a pathologist experienced in sarcoma.

8.7. Follow-up

After disease progression, the patient should be followed every 3 months for survival.

8.8. Early Termination

8.8.1 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
- Need for radiation therapy
- Request by the patient or a legal representative/relative to stop the treatment.
- The patient presents with a beta-HCG test consistent with pregnancy.
- 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 study drug's administration for greater than 3-weeks.
- 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.

If study treatment is stopped for any reason other than disease progression or patient death, every

effort should be made to continue to assess for disease progression according the study schedule until the patient progresses, starts a new therapy, or meets criteria for study withdrawal. The time of progressive disease will be recorded in the CRF.

8.8.2 **Criteria for study withdrawal:**

- Substantial non-compliance with the requirements of the study.
- Study closure
- Patient decision to withdraw from the study

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 OHSU 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 sponsor Drug Safety Unit.

8.9. **Schedule of Events for Randomized Portion of the Protocol**

	Screening[a]	Day 1 of each 21 day cycle (+/- 3 days)	Day 8 of each 21 day cycle (+/- 1 day)	End of Treatment
Informed Consent	X			
History/Progress Notes	X	X		X
Physical Exam	X	X		X
Vitals signs	X	X[b]	X	X
Performance Status	X	X		X
Treatment Toxicity		X		X
Chemistries[c]	X	X		X
LFTs[d]		X[d]	X[d]	
CBC[e]	X	X	X	X
Pregnancy test[f]	X	X		X
UPC	X	X		
Thyroid function test	X	X[g]		
Coagulation test	X[h]			
Correlative study labs	X	X[i]		
ECG with QTc measurement	X	X[j]		
Gemcitabine administration		X	X	
Study drug administration		X[k]	X[k]	
Disease assessment[l]	X	X		X
Submission of Pathology Slides	X			

[a]Screening History, physical exam, and performance status assessment may be substituted for cycle 1 day 1 if performed within 2 weeks. Laboratory exams (CBC, chemistries, LFTs, pregnancy test, UPC) may be substituted for cycle 1 day 1 if performed within 1 week. Cycle 1 Day 1 must occur within 7 days of randomization.

[b]Monitoring of BP only: A measurement of BP should be taken weekly during cycle 1, and then at the beginning of each cycle starting with cycle 2. BP can be assessed by any method (i.e., at home or by another physician) as long as the study physician is informed of the measurement, verifies any measurement that is not normal and takes appropriate action.

[c]Chemistries should include calcium, sodium, potassium, glucose, urea, and creatinine

[d]Monitoring of LFTs (total bilirubin, alkaline phosphatase, AST, ALT, and albumin): LFTs at day 8 cycle 1, then at day 1 for each subsequent cycle.

[e]CBC should include hemoglobin, hematocrit, white blood cell count, red blood cell count, neutrophils, and platelets

[f]Serum or urine pregnancy testing within 7 days of enrollment and with each cycle thereafter until study treatment end.

[g]Beginning with cycle 5, thyroid function tests (free T4 and TSH) are to be monitored every 4 cycles.

[h]Screening coagulation tests included PT/INR and PTT. If the patient is on warfarin, will repeat PT/INR 3-5 days after starting treatment and weekly thereafter until stable.

[i]Correlative study labs: At baseline and after 2 cycles.

[j]ECG: At baseline, cycle 2, and then every 3 cycles until end of treatment

[k]Study drug (pazopanib/placebo) administered daily (Days 1-21 of each 21 day cycle)

[l]Disease assessment recommendations: CT (with contrast) of chest, abdomen, pelvis (or abdomen and pelvis MRI with gadolinium and non-contrast chest CT) within 4 weeks of enrollment, then every 6 weeks (± 1 week) for the first 6 months of treatment, and then every 12 weeks (± 1 week) after the first 6 months of treatment until disease progression. If study treatment is stopped for any reason other than disease progression or patient death, disease assessment should continue according to the study schedule until progression, the patient starts a new therapy or otherwise meets criteria for study withdrawal.

8.10. **Schedule of Events for Cross-over Portion of the Protocol**

	Screening	Day 1 of each 21 day cycle (+/- 3 days)	End of Treatment
Documentation of cross-over eligibility	X		
History/Progress Notes		X	X
Physical Exam		X	X
Vitals signs		X[a]	X
Performance Status		X	X
Treatment Toxicity		X	X
CBC[b], chemistries[c], LFTs		X[d]	X
Pregnancy test[e]		X	X
UPC		X	
Thyroid function test		X[f]	
Coagulation test		X[g]	
ECG with QTc measurement		X[h]	
Scans for disease assessment[i]		X	X

[a]Monitoring of BP only: A measurement of BP should be taken weekly during cycle 1, and then at the beginning of each cycle starting with cycle 2. BP can be assessed by any method (i.e., at home or by another physician) as long as the study physician is informed of the measurement, verifies any measurement that is not normal and takes appropriate action.

[b]CBC should include hemoglobin, hematocrit, white blood cell count, red blood cell count, neutrophils, and platelets

[c]Chemistries should include calcium, sodium, potassium, glucose, urea, and creatinine

[d]Monitoring of LFTs (total bilirubin, alkaline phosphatase, AST, ALT, and albumin): Day 1 of each cycle and additionally between days 5 and 15 of cycles 2 and 3 only.

[e]Serum or urine pregnancy testing with each cycle until study treatment end.

[f] Beginning with cycle 5, thyroid function tests (free T4 and TSH) are to be monitored every 4 cycles. [g]If the patient is on warfarin, will repeat PT/INR 3-5 days after starting treatment and weekly thereafter until stable.

[h]ECG: At baseline, cycle 2, and then every 3 cycles until end of treatment

[i]Disease assessment recommendations: CT (with contrast) of chest, abdomen, pelvis (or abdomen and pelvis MRI with gadolinium and non-contrast chest CT) within 4 weeks of enrollment, then every 6 weeks (± 1 week) for the first 6 months of treatment, and then every 12 weeks (± 1 week) after the first 6 months of treatment until disease progression. If study treatment is stopped for any reason other than disease progression or patient death, disease assessment should continue according to the study schedule until progression, the patient starts a new therapy or otherwise meets criteria for study withdrawal.

9. MEASUREMENT OF EFFECT

For the purposes of this study, patients should be reevaluated for response every 6 weeks ±1 week for the first 6 months and every 12 weeks ±1 week thereafter. In addition to a baseline scan, confirmatory scans should also be obtained no sooner than 4 weeks following initial documentation of objective response.

9.1. Definitions

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 version 1.1[38]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

9.1.1 Measurable disease

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

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

9.1.2 Non-measurable disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

9.1.3 Target lesions

All measurable lesions up to a maximum of two lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

9.1.4 Non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements

of these lesions are not required but the presence or absence of each should be noted throughout follow-up.

9.2. Guidelines for Evaluation of Measurable Disease

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

Note: Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

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

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

Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US). When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

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

where known residual benign tumors can remain).

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

9.3. Response Criteria

9.3.1 Evaluation of target lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of the 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 diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
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

9.3.2 Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of "non-target" lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

9.3.3 **Evaluation of best overall response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Section 9.3.1).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

9.4. **Confirmatory Measurement/Duration of Response**

9.4.1 **Confirmation**

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 (see section 9.3.3).

9.4.2 **Duration of overall response**

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

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

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

9.4.3 **Duration of Stable Disease**

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

9.5. **Progression-Free Survival**

Progression free survival will be computed from the date of randomization to the first documented date of progression or the date of death, whatever the cause. If a patient's study treatment is unblinded for any reason prior to disease progression, progression free survival will be censored as of the date of unblinding for that patient. If a patient begins another treatment for sarcoma, progression free survival will be censored as of the date of starting the new treatment.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 **Protocol Review**

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute (CI) Clinical Research Review Committee (CRRC) and appropriate Institutional Review Board (IRB) prior to any patient being registered on this study.

10.2 **Informed Consent**

Written informed consent will be obtained from all patients, or the legally authorized representative of the patient, participating in this trial, as stated in the Informed Consent section of the case of Federal Regulations, Title 21, Part 50. If a patients signature cannot be obtained, and for all patients under the age of 18, the investigator must ensure that the informed consent is signed by the patients legally authorized representative. Documentation of the consent process and a copy of the signed consent shall be maintained in the patient's medical record.

10.3 **Changes to Protocol**

Any modification of this protocol must be documented in the form of a protocol revision or amendment signed by the principal investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the patient. In that event, the investigator must notify the CRRC and IRB in writing within 10 working days after the implementation. Investigators holding the IND must notify FDA of substantive changes to the protocol.

10.4 Maintenance of Records

If the investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution, another investigator, or to OHSU Knight Cancer Institute Clinical Research Management. Records must be maintained according to sponsor or FDA requirements.

10.5 OHSU IRB Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems (UP) and Adverse Events (AE) will be reported to IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site http://www.ohsu.edu/research/rda/irb/policies.shtml.

Fatal and life-threatening events must be reported to OHSU IRB within 7 calendar days after the PI learns of the event. If any of these require a change (as determined by the PI or the IRB) to the protocol or consent form, the PI will make those changes promptly and submit the revised documents to the OHSU IRB.

All other UP reports will be submitted to OHSU IRB no later than 15 calendar days of notification of the event. If the event requires changes as determined by the PI or the IRB) to the protocol or consent form, the PI will make the changes promptly and submit the revised documents to the IRB. UP and AE reports are submitted through OHSU e-IRB and will be reviewed by OHSU IRB.

10.6 Central Reporting of Adverse Events for Multicenter Studies

The SAE/UP reporting for multicenter investigator initiated clinical trials will follow the guidelines outlined in the OHSU Knight Cancer Institute Multi-Center Investigator Initiated Trials Coordinating Center Operations Manual.

A participating site must report an SAE to the to the institution's local IRB for action as required, as well as to the OHSU coordinating center study team by phone, fax, or email within 24 hours of learning of the event. In addition, they will forward UP data no later than 10 days of occurrence or notification of the events to OHSU for relation assessment and evaluation. The participating center will send the coordinating center materials regarding the SAE including a completed Medwatch form and any de-identified medical records supporting the incident. If medical records are not available, then the Medwatch form should be sent with intent to follow up in the future with the records.

SAE and UP reports and supporting documents will be faxed to:

Clinical Research Management
Attn: Phil Norr
Fax: 503-346-6868
OHSU Knight Cancer Institute
3030 SW Moody Ave, Ste 235, MDYKCT

Portland, OR 97201

The OHSU coordinating center study team will review and submit SAEs to the FDA, OHSU IRB, and any other required contacts as required by the Knight Data Safety Monitoring Plan. The principal investigator at the Coordinating Center is responsible for distributing IND and/or IDE Action Letters or

Safety Reports, as applicable, to participating institutions for review and submission to their institution's local IRB.

10.7 MedWatch Reporting

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E)
All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form). Instructions are available at www.fda.gov/medwatch. MedWatch reports can be submitted online at https://www.accessdata.fda.gov/scripts/medwatch/

When the serious adverse event is reported to the FDA, copies of the MedWatch 3500 form and supporting materials will be submitted to the OHSU IRB and the OHSU Drug Information Service. A copy of the MedWatch 3500 form and supporting materials will be kept on file in the study regulatory binder.

10.8 Adverse Events Reporting Guidelines

10.8.1 Definition of an adverse event

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

10.8.2 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Attribution of the AE:
- Definite – the AE is clearly related to the study treatment.
- Possible – the AE may be related to the study treatment.
- Unrelated – the AE is clearly NOT related to the study treatment.

10.8.3 Events meeting the definition of an adverse event (AE) include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline. Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE)

"Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

10.8.4 **Events that do not meet the definition of an AE include:**

- Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- B cell depletion and hypogammaglobulinemia due to ofatumumab treatment

10.8.5 **Definition of a serious adverse event (SAE)**

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

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

10.8.6 **Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs**

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline.

- All events meeting liver stopping criteria must be recorded as an SAE.

- However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

- B cell depletion, IgG below LLN, low CD19+ count, and hypogammaglobulinemia due to treatment with ofatumumab are not to be reported as AEs or SAEs.

- Infusion related AEs may lead to a prolonged infusion time. Overnight stay at the hospital due to slow infusion rate is not to be reported as a SAE.

10.8.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with investigational product or protocol design/procedures and the disease progression, then this must be reported as an SAE.

10.8.8 Time Period and Frequency of Detecting and SAEs

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E)

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

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

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

All events must be reported to Novartis within 24 hours of learning of its occurrence

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

All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. The end date of the first event must be provided.

SAEs, pregnancies, and liver function abnormalities meeting pre-defined criteria will be reported promptly to Novartis as described in the following table once the investigator determines that the event meets the protocol definition for that event.

Table 8. Reporting adverse events to the sponsor.

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	SAE data collection tool	24 hours	Updated SAE data collection tool
Pregnancy	24 hours	Pregnancy Notification Form	24 hours	Pregnancy Follow up Form
Liver chemistry abnormalities:				
ALT: >3.0 x ULN **with** concomitant elevation in bilirubin[a] (defined as total bilirubin ≥2.0 x ULN; with direct bilirubin >35%) **or with** hypersensitivity symptoms (e.g., fever, rash).	24 hours	SAE data collection tool. [b]Case Report Form (CRF) and liver imaging and/or biopsy if applicable	24 hours	Updated SAE data collection tool. [b]Updated CRF
ALT >8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[a] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	24 hours	SAE data collection tool. CRF[b]	24 hours	Updated SAE data collection tool. Updated CRF[b]

a. Bilirubin fractionation should be performed if testing is available. If testing is unavailable and a subject meets the criterion of total bilirubin >1.5 x ULN, then the event should be promptly reported as an SAE.
b. Liver event documents should be completed as soon as possible.

All serious adverse events must be reported by facsimile within 24 hours to Local Novartis Drug Safety and Epidemiology Safety Desk 1-877-778-9739

The SAE report should comprise a full written summary, detailing relevant aspects of the adverse events in question. Where applicable, information from relevant hospital case records and autopsy reports should be included. Follow-up information should be forwarded to Novartis within 24 hours.

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

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

Follow-up information is sent to the same fax number as the original SAE Report Form was sent, using a new fax cover sheet, stating that this is a follow-up to the previously reported SAE, and

giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the patient continued or withdrew from study participation.

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

10.8.9 **Pregnancy**

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

10.9 OHSU Knight Cancer Institute Data and Safety Monitoring Plan

In addition to complete study and pharmacy files, complete records must be maintained on each patient treated on this protocol. OHSU Knight Cancer Institute (CI), CRM shared resource is responsible for ensuring that all member investigators and affiliate investigators conduct clinical research studies in compliance with local IRB standards, FDA regulations and NIH policies. The Data and Safety Monitoring Committee (DSMC) is responsible for conducting Quality Assurance audits on CI approved protocols according to the Data and Safety Monitoring Plan policies and procedures http://ohsucancer.com/crm

Affiliate sites with their own DSMP will be responsible for forwarding the plan to OHSU CC upon study initiation, and must follow their DSMP by monitoring and auditing the trial at their site. Audit findings/letters should be sent to the CC as soon as possible following audit completion.

Locally initiated studies will be audited by an OHSU Knight CI DSMC audit team. Newly approved studies may be audited any time after enrollment. Each OHSU Knight CI approved treatment protocol will be audited on an annual basis.

10.10 Inclusion of Women, Minorities and Children

10.10.1 **Inclusion of Women and Minorities**

No OHSU Knight Cancer Institute study will focus on any particular gender, racial or ethnic subset. No subject will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied.

The projected gender, racial, and ethnic composition of the study will represent that of the state of Oregon.

Table 9: Population Demographics - Oregon (%)

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino			8.0
Not Hispanic or Latino			92.0
Ethnic Category: Total of all subjects*			100*
Racial Category			
American Indian or Alaskan Native			1.3
Asian			3.0
Black or African American			1.6
Native Hawaiian or other Pacific Islander			0.2
White			86.6
More than one race			3.1
Unknown/Other			4.2
Racial Category: Total of all subjects*			100*
TOTALS	50.4	49.6	100*

Source: Adapted from U.S. Census Bureau, 2000 *Totals may not equal 100 due to rounding.

Table 10: Projected Accrual for the Present Study

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	3-4	3-4	0	6-7
Not Hispanic or Latino	36-37	36-37	0	73-74
Unknown	0	0	0	0
Ethnic Category: Total of all subjects*	40	40	0	80*
Racial Category				
American Indian or Alaskan Native	0-1	0-1	0	1-2
Asian	1-2	1-2	0	2-3
Black or African American	0-1	0-1	0	1-2
Native Hawaiian or other Pacific Islander	0-1	0-1	0	0-1
White	34-35	34-35	0	69-70
More than one race	1-2	1-2	0	2-3
Unknown	1-2	1-2	0	3-4

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Racial Category: Total of all subjects*	40	40	0	80*

Source: Adapted from U.S. Census Bureau, 2000. *Totals must agree.

10.10.2 Inclusion of Children

In accordance with NIH guidelines on the inclusion of children as participants in research involving human subjects, children under the age of 18 years must be included in all human subjects research, conducted or supported by the NIH, unless there are clear and compelling reasons not to include them. Therefore, proposals for research involving human subjects must include a description of plans for the inclusion of children

This study will only include children adults. The safety of pazopanib in children is unknown and currently being investigated. Gemcitabine has been studied and been found to be safe in children. This protocol does not include children <18 years of age for the following reason: no dosing or adverse event data are currently available on the use of pazopanib in children, therefore, children <18 years of age are excluded from this study but will be eligible for future pediatric phase 2 combination trials.

10.11 DATA COLLECTION AND STORAGE

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Standard institutional practices will be followed as described in the OHSU's Information Security Directives to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures.
Loss of participant confidentiality is a risk of participation. Efforts will be made to keep study participant identities confidential except as required by law. Participants' samples will be identified by code only. Specifically, each consenting participant will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the trial. The coded identifier will also be used to identify any participant specific samples.

Basic accrual tracking information (subject demographics, consent type and date, visit information) will be captured in OHSU's electronic clinical information research system (eCRIS), hosted on OHSU servers and managed by OHSU's information technology group at their data center in downtown Portland, Oregon. Any additional printed documents containing participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location.

Study outcome data will be captured in electronic case report forms (eCRFs) using an electronic data capture (EDC) system on OHSU secure servers, which facilitates information being stored in a unified format and location. To further preserve confidentiality, PHI in the EDC system will be limited to just birth date and visit dates. The web-accessible EDC system is password protected and encrypted with role-based security, and administered by designated informatics staff within OHSU or Knight Cancer Institute. All users of the database are assigned a unique ID, username, and

password and must complete training appropriate to their role before they are authorized to enter, access, and store data in the database.

Data from correlative studies will be entered into the EDC system by study personnel at OHSU. All other electronic data extracts will be stored only on OHSU computers and restricted drives, limited only to study investigators and staff with authorization to access the data. Quality assurance will be conducted as outlined in Section 10.9

11.STATISTICAL CONSIDERATIONS

This is a double-blinded 1:1 randomized Phase II clinical trial that randomly assigns patients to either the gemcitabine plus pazopanib arm or the gemcitabine plus placebo arm. Randomization will be stratified by subtypes of sarcoma (liposarcoma vs. all other eligible soft tissue sarcoma subtypes) and the study sites. A total of 80 patients will be enrolled on the study. We expect 25% of the patients will have liposarcoma, while 75% of them will have other types of sarcoma such as pleomorphic sarcoma, leiomyosarcoma, synovial sarcoma, vascular sarcoma etc.

11.1 Study Endpoints and Objectives

11.1.1 Primary Endpoint and Primary Objective:

The primary endpoint for the study is progression-free survival (PFS), calculated as the time from randomization to the first documented progression or death whichever occurs first, or until time of last contact if no progression or death occurred.

The primary objective of the study is to evaluate the PFS of patients with metastatic soft tissue sarcoma treated with gemcitabine plus pazopanib, and compare that with the PFS of patients receiving gemcitabine plus placebo.

11.1.2 Secondary Endpoints and secondary objectives:

The secondary endpoints include:

Progression-free survival (PFS): (for a sub-group of patients treated with single agent pazopanib following administration of gemcitabine in the cross-over portion of this study)

The PFS for this sub-group of patients is defined somewhat differently from the PFS defined in the primary objective ---- it is calculated as the time from the crossover enrollment date to the next documented progression or death whichever occurs first.

Overall response and best overall response:

The response of patients is categorized into complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD) following RECIST version 1.1. Please see Section 9.3.1 and 9.3.2 for more details on the criteria to be used for response evaluation.

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence. Please see Section 9.3.3 for a detailed definition of best overall response.

Overall Survival (OS):

The overall survival is defined as the time from randomization to death due to any cause, or until last patient contact if the patient did not die, i.e., censored.

Adverse Events (AE) and Serious Adverse Events (SAE):

Adverse events of the study are defined using the Common Terminology Criteria for Adverse Events (CTCAE) v 4.0.

Serious adverse events are defined in great detail in Section 10.7.4.

The secondary objectives are:

- To assess overall response and best overall response in this population to gemcitabine plus pazopanib compared to gemcitabine plus placebo.
- To assess OS in this population to gemcitabine plus pazopanib compared to gemcitabine plus placebo. This will be an exploratory endpoint due to cross-over effects.
- To investigate differences in treatment response in different histologic subgroups (liposarcoma vs. all other eligible soft tissue sarcoma subtypes).
- To evaluate the safety and tolerability of the combination of gemcitabine plus pazopanib.
- To assess the progression-free survival and overall response in patients treated with single agent pazopanib following administration of gemcitabine in the cross-over portion of this study.

11.1.3 **Correlative/Exploratory Endpoint:**

Perform an exploratory analysis of potential biomarkers that predict response in patients receiving combination therapy with gemcitabine plus pazopanib.

11.2 Methods to assess study objectives

To address primary objective 1.1.1, the two treatment arms will be compared for PFS using a one-sided log-rank test stratified by the same factors used for the randomization. The study population for the efficacy analysis is the intent to treat (ITT) population of all randomized patients. Kaplan-Meier estimates and the survival curves for each treatment arm will be presented with the estimated hazard ratios and their associated confidence interval.

To address secondary objectives 1.2.1 and 1.2.3, the estimated odds ratio of treatment response will be reported with 95% confidence interval for the two histologic sarcoma subgroups (liposarcoma vs. all other eligible soft tissue sarcoma subtypes). Exact one-sided Cochran-Mantel-Haenszel (CMH) test will be used to determine whether the overall response differs for the subgroups in general. An overall odds ratio for overall response and best overall response will be reported with 95% confidence interval if the CMH test suggests the overall responses do not differ among sarcoma subgroups.

To address secondary objective 1.2.2, the two treatment arms will be compared for OS using a one-sided

log-rank test stratified by the same factors used for the randomization. The study population for the efficacy analysis is the intent to treat (ITT) population of all randomized patients. Kaplan-Meier estimates and the survival curves for each treatment arm will be presented with the estimated hazard ratios and their associated confidence interval.

To address secondary objective 1.2.4., toxicities will be descriptively tabulated. The study population for safety analysis will be comprised of all subjects who received at least one dose of assigned treatment, i.e., evaluable for toxicity. Frequency and severity of adverse events will be tabulated for each treatment arm based on the actual treatment the patient receives. Toxicity and adverse events will be summarized according to each major organ group and grade outlined in the CTCAE v4.0 criteria. In addition, the stopping rules for transaminase and bilirubin will inform the safety of the combination in terms of liver toxicity.

To address secondary objective 1.2.5., the patient population will be limited to the sub-group of patients who was originally randomized into the placebo group, had progression, and was then offered open-label treatment of pazopanib. Notice that because the baseline time point for the sub-group of patients is the start of open-label treatment of pazopanib, patients may not be followed-up long enough. Also, as the number of patients in this sub-group is limited, the statistical analysis is exploratory --- Kaplan-Meier estimate and the survival curve will be presented with the estimated hazard ratio and its associated 95% confidence interval.

To address secondary objective 1.2.6, a Wilcoxon test will be performed to test for biomarker level (continuous) with response (responder versus non-responder). Since these tests are exploratory, the results will not be considered definitive, but will be used to generate hypotheses to be validated in a future study.

All tests will be conducted at 0.05 significance level using SAS 9.3.

11.3 Safety Monitoring

The study population for safety analysis will be comprised of all subjects who received at least one dose of assigned treatment, i.e., evaluable for toxicity. Toxicity and adverse events will be summarized according to each major organ group and grade outlined in the CTCAE v4.0 criteria.

11.4 Sample Size and Power

The study will be powered to address the primary objective. The sample size is computed from a comparison of PFS between subjects randomized to gemcitabine placebo arm and subjects randomized to gemcitabine + pazopanib arm. The median PFS for the gemcitabine + placebo arm is estimated to be 3 months. With an overall one-sided alpha of 5%, a total of 73 patients (36 in the gemcitabine + placebo arm, and 37 in the gemcitabine + pazopanib arm) are required to achieve 80% power to detect a 2.5 month increase in median PFS (a hazard ratio of 0.55) between the two treatment arms. We expect to accrual 4-5 patients per month, and plan to accrue 80 patients to allow ~ 10% drop-out or loss to follow-up. The power analysis is conducted using PASS 2008 version 08.0.6 for log-rank test (Lakatos).

11.5 Interim Analysis and Stopping Rules

No interim analysis is planned for the study. However, the OHSU Knight Data Safety Monitoring Committee (DSMC) will monitor for safety as per the OHSU Knight Cancer Institute data and safety monitoring plan (see section 10.8).

APPENDIX A

Performance Status Criteria

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

APPENDIX B

Determination of Creatinine Clearance (Cl_{CR})

Estimation of creatinine clearance using Cockcroft and Gault method:

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

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

For SI units:

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

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

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

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

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

APPENDIX C

Urine Protein Creatinine Ratio (UPC)

Clinical meaning of UPC

There is a good correlation between the ratio of urine protein to creatinine concentrations (UPC) in a random urine sample and the amount of protein excreted in a 24-hour urine collection period. Thus, the UPC allows estimation of the 24-hour urine protein excretion from a random sample. The creatinine excretion is fairly constant throughout the day regardless of changes in urine flow rate:

Men excrete 20 mg to 25 mg of creatinine/kg of body weight/day
Women excrete 15 mg to 20 mg of creatinine/kg of body weight/day
Normal protein excretion is <100 mg to 150 mg/24 hours.
The UPC ratio is roughly equal to the 24 hour urine protein excretion in g/day

Calculating Urine Protein to Creatinine ratio (UPC)

UPC ratio = (Urine protein mg/dl) / (urine creatinine mg/dl) = numerically equivalent to gm protein excreted in urine over 24 hrs.

Example: Patient has a urine protein = 90 mg/dl and urine creatinine = 30 mg/dl.
UPC ratio= (90 mg/dl) / (30 mg/dl) = 3
Result UPC is 3 (correlates to roughly 3gm protein excretion in a 24 hour period)

Units for UPC ratio

Note: UPC is a calculated ratio. The guidelines in the protocol are based on having urine protein and urine creatinine measured in the same units (e.g., mg/dl). The SI units for urine protein and urine creatinine are not the same, so these must be converted to mg/dl before calculating the ratio.

For reference, the conversion factor for commonly used units for protein and creatinine is provided in the table below.

Starting units	**Conversion to mg/dl**
Protein (g/l)	Multiply by 100
Protein (mg/l)	Divide by 10
Creatinine (µmol/l)	Divide by 88.4
Creatinine (mmol/l)	Multiple by 11.3

Xin G, Wang M, Jian L, Xu F, Wang H. Protein-to-creatinine ratio in spot urine samples as a predictor of quantitation of proteinuria 2004. Clinica Chimica Acta 350:35-39.

APPENDIX D

New York Heart Association (NYHA) classification of heart failure

Class I Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.

Class II Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or angina pain.

Class III Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain.

Class IV Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

(The Criteria Committee of the New York Heart Association: Diseases of the Heart and Blood Vessels; Nomenclature and Criteria for Diagnosis, 6th ed Boston, Little, Brown 1964).

APPENDIX E

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Toxicities and adverse events will be assessed using the NCI Common Toxicity Criteria for Adverse Events v4.0 (CTCAE). Since CTEP has standardized the CTCAE, the NCI does not require the inclusion of the CTCAE within the protocol document. A copy can be downloaded from the CTEP home page http://ctep.cancer.gov/reporting/ctc.html

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