A Randomized, Open-label, Phase II, Multi-center Trial of Gemcitabine (G) with Pazopanib (P) or Gemcitabine (G) with Docetaxel (T) in Previously Treated Subjects with Advanced Soft Tissue Sarcoma.

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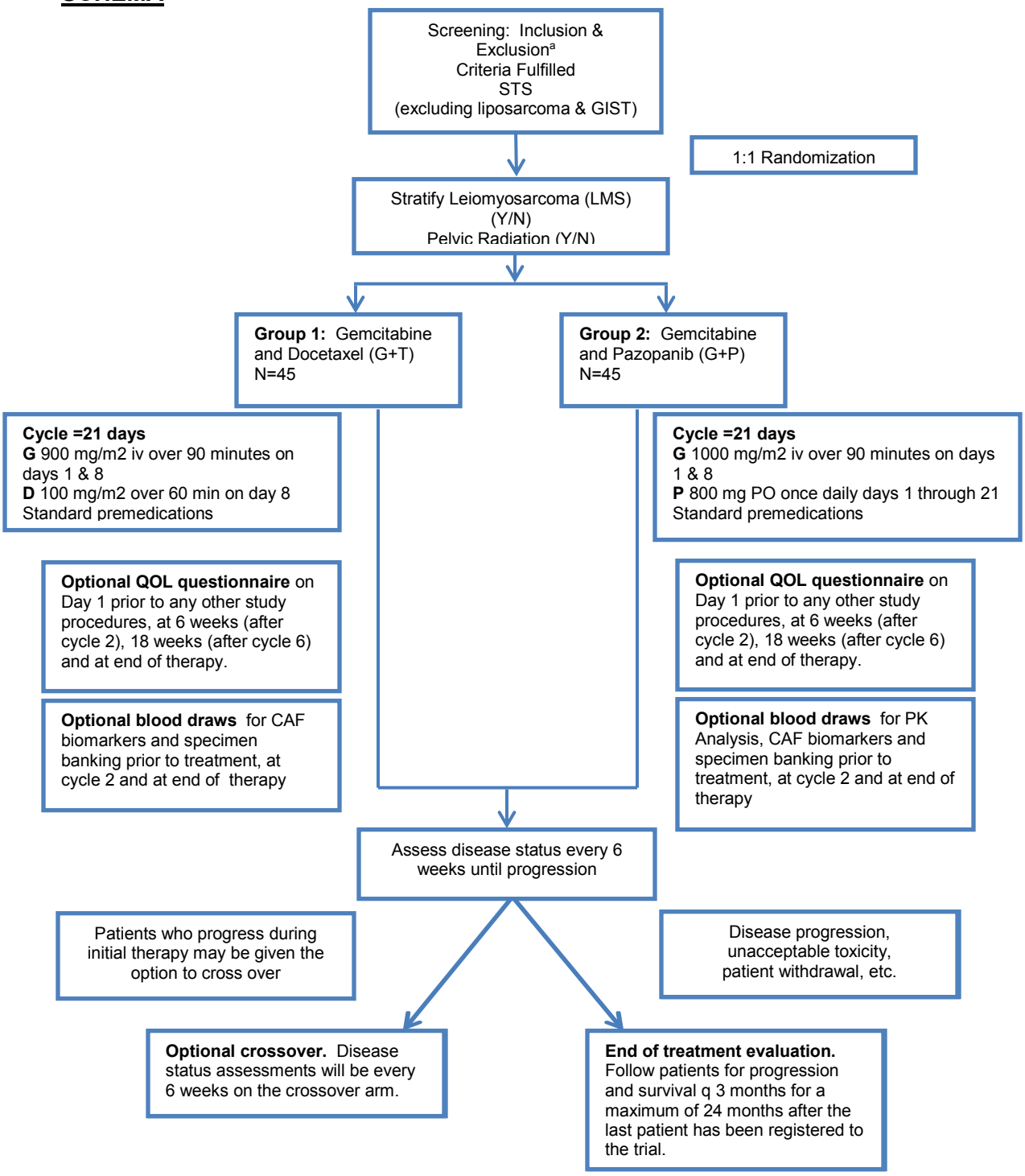

a. Baseline evaluations should be performed ≤ **14 days** before registration except for radiological evaluation of disease, which should be within **4 weeks** before registration. Pregnancy test when applicable should be **≤ 7 days** before registration.

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1 OBJECTIVES

1.1 Primary Objectives

- To estimate the progression-free survival (PFS) of the combination of gemcitabine plus pazopanib (G+P) and to estimate the PFS of the combination of gemcitabine plus docetaxel (G+T) in patients with metastatic and/or locally advanced or recurrent soft tissue sarcoma

- To estimate the rate of grade 3 or higher toxicity with G+P and G+T and to describe the type and grade of toxicities.

1.2 Secondary Objectives

- To estimate the hazard ratio comparing G+P vs. G+T in patients with metastatic and/or locally advanced or recurrent soft tissue sarcoma.

- To estimate the response rates of G+P and G+T in metastatic and/or locally advanced or recurrent soft tissue sarcoma patients.

- To examine quality of life (QOL) measures with both regimens (using EORTC QLQ-C30 version 3 and EuroQol questionnaires).

1.3 Correlative Objectives(s)

- An optional plasma biomarker study will be conducted for all patients randomized to either arm. The plasma biomarker study will evaluate circulating cytokine and angiogenesis factors (CAFs) that might include but are not limited to, IL-12, HGF, IL-16, IP-10, SDF-1α, IL-2Rα, IL-3, IFN-α2, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), M-CSF, and PIGF. Plasma will be collected at randomization (pre-treatment), cycle 2 and at time of progression to examine antiangiogenic biomarkers as predictors of response to G+P and G+T.

- An optional PK analysis will also be conducted for patients receiving G+P (includes consenting patients who are initially randomized to the G+P arm and consenting patients who crossover to the G+P arm after G+T). A plasma sample will be collected at randomization (pre-treatment), cycle 2 and at time of progression for consenting patients receiving pazopanib to assess pazopanib concentration for correlation.

- An optional blood banking study will also be offered to patients on either arm. An additional blood draw at prior to treatment, Cycle 2 and at disease progression will be obtained from consenting patients enrolled to either arm for specimen banking and future studies.

2 BACKGROUND

2.1 Soft Tissue Sarcomas (STS)

STS constitutes a heterogeneous group of malignancies arising in extraskeletal connective tissues (muscle, fat, fibrous tissue, blood vessels, or other mesenchymally-derived tissues), that comprise approximately 1% of all adult malignancies, while they give rise to 2% of total cancer related mortality. At present all these subtypes are usually grouped under the heading of STS for the purpose of treatment, although increasing options in the future might allow treatment directed specifically at individual subtypes.

Current treatment options for patients with STS vary with clinical stage, but may include surgery, radiotherapy and chemotherapy [1]. For patients with resectable disease, surgery is the standard treatment, as it results in the greatest chance for long-term disease-free survival. The addition of post-operative radiation appears to reduce the rate of local recurrence [2]. Radiation is also used as the primary treatment modality for inoperable tumors as well as for palliative purposes. However, even optimal local treatment does not prevent the occurrence of distant metastasis in many patients, especially those with high-grade tumors. Approximately 50% of patients present with or develop advanced or metastatic disease. STS metastasizes primarily to the lungs, but also to bone, liver and other organs depending on sub-type.

Chemotherapy is widely used in the treatment of non-resectable advanced disease, basically with palliative intent, as most initially chemotherapy sensitive patients will ultimately relapse. Despite available chemotherapy, the prognosis for these patients is very poor, with an estimated median survival of 8 to 13 months from the start of first-line anthracycline-based chemotherapy, as shown in randomized studies performed over the last 2 decades [3-6]. In addition these patients are often debilitated by their sarcoma as bulky disease might result in complications such as pain, intestinal obstruction and other symptoms leading to end-organ failure and death.

At present, initial standard chemotherapy for advanced or metastatic STS consists of an anthracycline (mainly doxorubicin) given as a single agent or in combination with ifosfamide [7]. The cumulative response rate in non-treated patients is 23% (15-30%) [8]. The use of doxorubicin is limited due to its risk of cumulative cardiac toxicity. The median survival for patients for whom conventional chemotherapy with an anthracycline and ifosfamide has failed is in the range of 6 months [9-13].

The combination of gemcitabine and docetaxel is another frequently used second-line regimen in soft tissue sarcomas and occasionally used front-line for leiomyosarcomas, the histology with the highest reported response rates to this combination. Maki et al, reported a phase II study in metastatic STS that suggested a survival benefit for the combination versus single agent gemcitabine [14]. The median progression-free survival (PFS) of gemcitabine therapy alone was 3 months; when combined with docetaxel, the median PFS increased to 6.2 months. However, the combination of gemcitabine and docetaxel is a relatively poorly tolerated regimen and 46% patients required at least one dose reduction and many of them discontinued therapy within 6 months due to toxicity.

The rate of gemcitabine administration may be crucial to maximizing the antitumor activity of this drug. The intracellular accumulation of gemcitabine triphosphate, the active form of

the drug, is saturated at gemcitabine dose rates that produce plasma gemcitabine concentration of 10 to 20 μmol/L. A gemcitabine dose of 900 mg/m2 given over a 90-minute infusion remains above a 10 μmol/L threshold approximately 50% longer versus the standard 30 minutes bolus infusion [14]. Gemcitabine is administered iv on days 1 and 8 of a 21-day cycle over 90 minutes in the treatment of STS.

There still remains a dearth of active agents in sarcoma and a great need to look for newer compounds and combinations with meaningful activity and hopefully a better toxicity profile. It has been reported that circulating angiogenic factor levels correlate with extent of disease and risk of recurrence in patients with soft tissue sarcoma [16]. Mean levels of VEGF and bFGF were significantly higher in patients compared to controls [17-19]. Sarcomas in general therefore appear to be a good target tumor type for evaluation of angiogenesis inhibitors, and particularly for those preventing VEGF action. In an EORTC phase II trial, 800 mg daily of oral pazopanib showed single-agent activity in soft tissue sarcomas, including leiomyosarcoma and synovial sarcomas, but not in adipocytic tumors [20]. Recently, results from PALETTE, a phase III study of pazopanib versus placebo in previously treated soft tissue sarcoma patients showed a statistically significant improvement in progression-free survival (PFS) with a median increase of 13 weeks, and the interim analysis for overall survival (OS) showed a trend toward improvement. [21]

2.2 Study Drug: Pazopanib

Numerous growth factors and cytokines are involved in the angiogenic process, i.e., the process of new blood vessel formation, important in the development and progression of malignancy. Among these factors, 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 [22-24].

Pazopanib, is a multi-target, small molecule inhibitor. It is an orally-bioavailable, ATP-competitive tyrosine kinase inhibitor of VEGFR (-1, -2, and -3), PDGFR (-α and -β), and c-Kit [25].

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

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

include hand-foot syndrome, mucositis/stomatitis, proteinuria, venous thrombotic events, and bleeding. Intestinal perforations and arterial thromboses were uncommon.

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

2.2.1 Safety in clinical studies with monotherapy pazopanib: Integrated data from Studies VEG105192, VEG102616, and VEG107769

The safety profile of pazopanib used in the treatment of RCC has been further defined in an integrated analysis of data from 593 subjects who received pazopanib across 3 RCC studies as of 09 January 2009. The database supporting the safety profile of pazopanib in subjects with RCC includes the completed placebo-controlled Phase III study VEG105192, with 290 subjects treated with pazopanib, a completed supportive Phase II study (VEG102616) in which 225 subjects were treated with pazopanib, and the ongoing open-label extension study VEG107769 (n=78).

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

Table 1: Adverse Events Reported for at Least 10% of Subjects (Safety Population) in Study VEG105192

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

a. AEs are ranked by incidence in the pazopanib arm. Any AE, any grade includes Grade 5 (fatal) events (12 [4%] subjects in the pazopanib arm and 4 [3%] subjects in the placebo arm).
b. One placebo subject had Grade 5 asthenia.
c. ALT= alanine aminotransferase; AST= aspartate aminotransferase

Table 2: Summary of Worst-case Hematologic Toxicity Grade Shift from Baseline (Safety Population) in Study VEG105192

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

a. Any grade increase from baseline. Subjects with missing baseline grade were assumed to have baseline grade of 0.
b. PTT= Partial thromboplastin time; INR= International Normalized ratio.

Table 3: Summary of Worst-Case Toxicity Grade Shift from Baseline for Clinical Chemistry Parameters (Safety Population) in Study VEG105192

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

a. Any grade increase from baseline.

2.2.2 Summary of Common Toxicities

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

Across the RCC database (N=593), 107 (18%) subjects had an elevation in ALT ≥ 3xULN as of 09 January 2009. ALT is a more specific indicator of hepatocellular injury than AST and was therefore used as a single criterion for evaluating outcomes. Liver enzyme elevations were reversible upon cessation of the drug and in some cases while continuing

on pazopanib. In an analysis performed across the RCC database, 96/106 (91%) subjects had full recovery. Recovery was defined as any ALT < 2.5xULN after the first elevation including post-therapy tests. Seven of the remaining 10 subjects had limited or no follow-up to determine recovery and 3 died of cancer progression with no follow-up ALT data. It was noted early in development that some of the subjects with elevated hepatic enzymes remained on study drug despite these elevations and had normalization of their transaminases while remaining on pazopanib ("adaptation"). Most subjects with transaminase elevations in whom dosing was interrupted could be successfully re-challenged.

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

Adaptation:

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

Re-challenge:

- 31 subjects who had a dose interruption following an ALT elevation to ≥ 3xULN were re-challenged; 4 (13%) at the same dose and 27 (87%) at a lower dose. The dose was reduced from 800 mg to 400 mg in 24 subjects and from 400 mg to 200 mg in 3 subjects.
- Median duration of interruption prior to re-challenge was 19 days (range 5-139 days).
- The median duration of re-treatment among all re-challenge subjects was 194 days (range 2-681 days). The maximum ALT before re-challenge and the latest ALT prior to interruption did not appear to correlate with the likelihood of recurrent elevations.
- 20 (65%) subjects did not experience an ALT ≥3xULN following a resumption of study drug;
- 10 (32%) subjects had recurrent elevations
- 2/10 (20%) subjects with recurrent elevations were continued on study drug and subsequently met the criteria for adaptation as defined above. Thus, these 2 subjects are counted both as re-challenges and as adaptations.
- 6/10 (60%) positive re-challenges recovered.
- 2/10 (20%) had inadequate follow-up to assess recovery.
- 1 (3%) subject had no follow-up data on the outcome of the re-challenge.

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

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

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

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

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

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

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

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

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

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

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

Proteinuria: Proteinuria is considered a class effect of VEGF inhibitors. In the placebo-controlled RCC study, 28 of 289 (10%) subjects treated with pazopanib with evaluable laboratory data had 3+ proteinuria post-baseline and 6 (2%) had 4+ proteinuria post-baseline.

2.2.3 Pazopanib in soft tissue sarcoma (STS)

2.2.3.1 Safety Profile of Pazopanib in STS

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

As of 09 September 2008, enrollment was completed with 142 adult subjects enrolled. Safety and efficacy analyses were completed by the European Organization for Research and Treatment of Cancer (EORTC) and described in a synoptic clinical pharmacology study report, with effective date of 24 September 2008, and published by Sleijfer et al [20].

All 142 subjects received pazopanib 800 mg once daily. AE data were available for all

142 subjects. The most frequent clinical adverse events (AEs) (≥30%), regardless of causality, were fatigue (70%), nausea (46%), diarrhea (46%), hypertension (45%), decreased appetite (39%), skin hypopigmentation (37%), vomiting (36%), weight decreased (31%), dyspnea (31%), cough (30%), and constipation (30%).

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

2.2.3.2 Pazopanib Efficacy in Sarcoma

Final efficacy data for the phase II study (VEG20002) of GW786034 in patients with relapsed or refractory soft tissue sarcoma study were published in 2009 [20]. Treatment response data are available for 138 subjects who received pazopanib 800 mg once daily. Ninety-nine percent of subjects had received prior chemotherapy: 35 subjects (25%) had received therapy in a (neo)-adjuvant setting, 83 (59%) had received therapy in an advanced setting, and 22 (16%) had received both.

The primary endpoint was the progression-free rate, using RECIST at 12 weeks after start of treatment. Patients with leiomyosarcoma, synovial sarcoma and “the other types of sarcoma” strata receiving pazopanib in VEG20002 experienced a 12-week progression-free rate of ≥ 40%, the pre-defined threshold indicating anti-tumor activity. The liposarcoma stratum did not meet its prespecified endpoint at the end of stage 1 and did not progress to stage 2.

Based on the results of the VEG20002, a Phase III randomized, double blind, placebo controlled study (VEG110727) of pazopanib versus placebo in subjects with soft tissue sarcoma (study excluded patients with GIST or liposarcoma) was initiated in 2008. Preliminary results of this study (PALLETE) were reported at ASCO 2011. Patients on the pazopanib arm showed a statistically significant improvement in progression-free survival (PFS) with a median increase of 13 weeks, and the interim analysis for overall survival (OS) showed a trend toward improvement [21].

2.3 Study Drug: Gemcitabine

Gemcitabine is a nucleoside metabolic inhibitor used in a variety of indications. The most common adverse reactions for the single-agent (≥20%) are nausea, vomiting, anemia, ALT, AST, neutropenia, leukopenia, alkaline phosphatase, proteinuria, fever, hematuria, rash, thrombocytopenia and dyspnea. Myelosuppression can be dose limiting.

Pulmonary toxicity has been reported and therapy should be discontinued immediately if lung injury is noted. Renal function also needs to be monitored. Cases of hemolytic uremic syndrome (HUS) and/or renal failure, some fatal, have occurred. Serious hepatotoxicity, including liver failure and death, has occurred. Gemcitabine can cause fetal harm. A pattern of tissue injury typically associated with radiation toxicity has been reported in association with concurrent and non-concurrent use of gemcitabine. Analysis of the data does not indicate enhanced toxicity when gemcitabine is administered more than 7 days before or after radiation,

other than radiation recall.

Increased toxicity has been noted with infusion time >60 minutes or dosing more frequently than once weekly. However, the rate of gemcitabine administration may be crucial to maximizing the antitumor activity of this drug. The intracellular accumulation of gemcitabine triphosphate, the active form of the drug, is saturated at gemcitabine dose rates that produce plasma gemcitabine concentration of 10 to 20 μmol/L. A gemcitabine dose of 900 mg/m^2 given over a 90-minute infusion remains above a 10 μmol/L threshold approximately 50% longer versus the standard 30 minutes bolus infusion [14]. For the treatment of sarcomas the gemcitabine is administered iv on days 1 and 8 of a 21-day cycle over 90 minutes as part of the standard gemcitabine and docetaxel regimen.

2.4 Study Drug: Docetaxel

The most common adverse reactions across all docetaxel (TAXOTERE) indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. Incidence varies depending on the indication. The most serious adverse reactions associated with docetaxel are toxic deaths, hepatotoxicity, neutropenia and fluid retention. In general, across all indications responding patients may not experience an improvement in performance status on therapy and may experience worsening. The relationship between changes in performance status, response to therapy, and treatment-related side effects has not been established.

The combination of gemcitabine and docetaxel has shown activity in soft tissue sarcomas with high response rates reported in the leiomyosarcoma sub-type and is commonly used as a second line regimen for STS or first line for leiomyosarcomas.

2.5 Rationale for this study

Pazopanib is an orally-bioavailable, ATP-competitive tyrosine kinase inhibitor of VEGFR (-1, -2, and -3), PDGFR (-α and -β) and c-Kit [25] that is approved for the treatment of advanced renal cell carcinoma (RCC) and is actively being studied in multiple other cancers. As described above, an EORTC phase II study and a recently reported phase III study showed activity of single-agent pazopanib in soft tissue sarcomas. The 800 mg daily dosing regimen is the established active monotherapy dose for subjects with RCC, providing optimal biologic and clinical effects associated with VEGFR inhibition and is generally well tolerated.

Antiangiogenic therapies such as pazopanib may work by inducing vascular normalization, thereby alleviating hypoxia and increasing the delivery of cytotoxic chemotherapies to cancer cells [Jain, 2005]. The increased penetration of drugs throughout the tumor could enhance the antitumor benefit of chemotherapy. This provides a rationale for combining pazopanib with cytotoxic chemotherapy. A phase I study of pazopanib in combination with gemcitabine has been completed and the recommended phase II dose was 800 mg PO of pazopanib daily with 1000 mg/m^2 of gemcitabine on days 1 and 8. [Pazopanib Investigator Brochure version 8.]

The goal for this study is (1) to examine the activity of pazopanib (P) as a treatment of sarcoma when combining with another active agent gemcitabine (G), and (2) to examine an alternative regimen to commonly used gemcitabine + taxotere (G + T) with fewer side effects and

increased ease of administration. The median progression-free survival (PFS) of G therapy when administered as a single agent was 3 months; when combined with T, the median PFS increased to 6.2 months [14]. However, 46% of patients receiving the combination required at least one dose reduction, and many of them discontinued therapy within 6 months due to toxicity. This suggests that a less toxic regimen would be preferred by both patients and physicians.

We hypothesize that G+P in combination would be a more desirable combination therapy for patients with soft tissue sarcoma. However, no formal statistical hypothesis will be tested. The primary objective is to estimate the PFS and rate of grade 3 and 4 toxicities in patients with advanced soft tissue sarcoma that are given G+P relative to G+T to assess whether the efficacy and tolerability warrants taking it forward into Phase III testing. Sample size was derived based on the precision of 95% confidence intervals for reporting toxicity rates and median PFS in each arm.

2.6 Dosing rationale for the investigational arm

Pazopanib 800 mg once daily is the recommended monotherapy dose based on clinical and preclinical results.

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

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

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

pazopanib 800 mg once daily results in plasma concentrations that provide optimal biologic effects associated with VEGFR inhibition in the greatest proportion of subjects.

Pazopanib in combination with gemcitabine was studied in an open-label, non-randomized, 2-part, dose-escalation, repeat-dose study using a standard cohort 3 + 3 design. Following the dose-escalation phase, 6 to 9 additional subjects (to achieve a total of 12 subjects) were to be enrolled in the expansion cohort. Successful evaluation of this expansion phase required dose-limiting toxicities (DLTs) in 2 of 12 subjects.

In the dose-escalation phase, treatment was administered at 3 dose levels: Dose Level 0 - pazopanib 400 mg orally once-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 orally once-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 orally once-daily and gemcitabine 1250 mg/m^2 by 30-minute infusion on Days 1 and 8 of a 21-day treatment cycle. In the cohort expansion phase, subjects received gemcitabine 1250 mg/m^2 alone on Cycle 1, Day 1 before starting pazopanib 800 mg once-daily on Day 2 of a 21-day treatment cycle. The recommended phase II dose suggested was 800 mg PO of pazopanib daily with 1000 mg/m^2 of gemcitabine on days 1 and 8, though escalation to higher dose was possible. Two DLTs were reported in 2 subjects during Cycle 1: Grade 4 thrombocytopenia (Paz400/Gem1000) and Grade 3 fatigue (Paz800/Gem1250).

2.7 Correlative Studies Background

To date there are no validated biomarkers for response to pazopanib. Circulating angiogenic factor levels have been reported to correlate with extent of disease and risk of recurrence in patients with soft tissue sarcoma [16]. Mean levels of VEGF and bFGF were found to be significantly higher in patients compared to controls [17-19].

Recently, Nikolinakos and colleagues have shown that baseline levels of 11 cytokine and angiogenic factors (CAFs) predicted tumor response in early stage NSCLC patients treated with pazopanib [27]. These included IL-12, HGF, IL-16, IP-10, SDF-1α, IL-2Rα, IL-3, IFN-α2, tumor necrosis factor–related apoptosis-inducing ligand (TRAIL), M-CSF, and PlGF. Plasma samples were collected before treatment and on the last day of therapy from 33 patients with early-stage NSCLC participating in a single-arm phase II trial. Levels of 31 CAFs were measured by suspension bead multiplex assays or ELISA and correlated with change in tumor volume. Pazopanib therapy was associated with significant changes of eight CAFs; sVEGFR2 showed the largest decrease, whereas placental growth factor underwent the largest increase. Increases were also observed in stromal cell–derived factor-1α, IP-10, cutaneous T-cell–attracting chemokine, monokine induced by IFN-γ, tumor necrosis factor–related apoptosis-inducing ligand, and IFN-α. Post-treatment changes in plasma sVEGFR2 and interleukin (IL)-4 significantly correlated with tumor shrinkage. Baseline levels of 11 CAFs significantly correlated with tumor shrinkage, with IL-12 showing the strongest association. Using multivariate classification, a baseline CAF signature consisting of hepatocyte growth factor and IL-12 was associated with tumor response to pazopanib and identified responding patients with 81% accuracy.

An optional plasma biomarker study will be conducted for all patients randomized to either arm. The plasma biomarker study will evaluate circulating cytokine and angiogenesis factors (CAFs) that might include but are not limited to, IL-12, HGF, IL-16, IP-10, SDF-1α, IL-2Rα, IL-3, IFN-

α2, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), M-CSF, and PIGF. Plasma will be collected at randomization (pre-treatment), cycle 2 and at time of progression to examine antiangiogenic biomarkers as predictors of response to G+P and G+T.

An optional blood banking study will also be offered to patients on either arm. An additional blood draw at prior to treatment, Cycle 2 and at disease progression will be obtained from consenting patients enrolled to either arm for specimen banking and future studies.

An optional PK analysis will also be conducted for patients receiving G+P (includes consenting patients who are initially randomized to the G+P arm and consenting patients who crossover to the G+P arm after G+T). A plasma sample will be collected at randomization (pre-treatment), cycle 2 and at time of progression for consenting patients receiving pazopanib to assess pazopanib concentration for correlation.

3 PATIENT SELECTION

3.1 Inclusion Criteria

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.

2. Age ≥ 18 years or legal age of consent if greater than 18 years.

3. Histologically or cytologically confirmed diagnosis of sarcoma of soft tissue. (Patients with liposarcoma, bone sarcoma or GIST will be excluded).

4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

5. Subjects must have metastatic and/or locally advanced or locally recurrent disease that is not amenable to curative surgical resection. If a patient declines surgery, they may be considered for this study.

6. A minimum of 1 and a maximum of 3 prior chemotherapy regimens, including adjuvant and neo-adjuvant therapy for the treatment of sarcoma. Patients eligible for an anthracycline should have received a prior anthracycline containing regimen. Patients who decline or are not eligible for anthracycline treatment may be considered for this protocol as a first line treatment.

7. Patients must have measurable disease by RECIST 1.1 or cutaneous disease amenable to serial measurements should be present. Measurable disease (a 'target' lesion) is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT (CT scan slice thickness no greater than 5 mm); ≥ 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable); and ≥ 20 mm by chest x-ray.

8. Able to swallow and retain oral medication.

9. Adequate organ system function as defined below.

Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.5 X 10^9/L
Hemoglobin[a]	≥9 g/dL (5.6 mmol/L)
Platelets	≥100 X 10^9/L
Coagulation.[b] Coagulation assessments should be completed according to institutional standards, which should include at least one of the following.	
International normalized ratio (INR)	≤1.2 X ULN
Prothrombin time (PT)	≤1.2 X ULN
Activated partial thromboplastin time (aPTT)	≤1.2 X ULN
Partial thromboplastin time (PTT)	≤1.2 X ULN
Hepatic	
Total bilirubin	≤ ULN
Alanine amino transferase (ALT) and Aspartate aminotransferase (AST)[c]	≤2.5 X ULN
Alkaline phosphatase	≤2.5 X ULN
Renal	
Serum creatinine	≤1.5 mg/dL (133 µmol/L)
Or, if serum creatinine >1.5 mg/dL: Calculated creatinine clearance (Cl_{CR}) (Appendix 2)	≥50 mL/min
Urine Protein to Creatinine Ratio (UPC; Appendix 3)[d]	<1
Or, 24-hour urine protein[d]	<1g

a) Subjects may not have had a transfusion within 7 days of screening assessment.
b) Subjects receiving anticoagulant therapy are eligible if their coagulation lab values are 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.

10. A female is eligible to enter and participate in this study if she is of:

    a. 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.

b. Childbearing potential, including any female who has had a negative serum pregnancy test within 7 days of registration and agrees to use adequate contraception. Acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as 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

1. Prior therapy with pazopanib, gemcitabine or docetaxel. Patients who have had prior treatment with gemcitabine or docetaxel for a prior malignancy are eligible if they meet the criteria in exclusion #3 and did not experience significant drug related toxicity.

2. Any concern for hypersensitivity to pazopanib, gemcitabine or docetaxel.

3. 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 or successfully treated in situ carcinoma are eligible.

4. 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 registration. 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.

5. 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 registration.

6. 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 and experiencing the "dumping" syndrome.

7. Presence of uncontrolled infection.

8. Prior mediastinal radiation.

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

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

11. Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA) (Appendix D).

12. Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥150 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg]. **Note**: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. BP must be re-assessed on two occasions that are separated by a minimum of 1 hour; on each of these occasions, the mean (of 3 readings) SBP / DBP values from each BP assessment must be <150/90 mmHg in order for a subject to be eligible for the study.

13. History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within 6 months of registration. **Note**: Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks prior to registration and are fully anti-coagulated are eligible.

14. Prior major surgery or trauma within 28 days prior to registration and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major). If the patient has a compression fracture secondary to tumor this should be treated and 28 days elapsed prior to entry on the protocol.

15. Evidence of active bleeding or bleeding diathesis.

16. Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels.

17. Hemoptysis in excess of 2.5 mL (or one half teaspoon) within 8 weeks of registration.

18. 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.

19. Unable or unwilling to discontinue use of prohibited medications listed in Section 5.2.3 for at least 14 days or five half-lives of a drug (whichever is longer) prior to registration and for the duration of the study.

20. Treatment with any of the following anti-cancer or non-oncologic investigational therapies:
    - radiation therapy, surgery or tumor embolization within 14 days prior to registration
    - chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days or 2.5 half-lives of a drug (whichever is longer) prior to registration.
    - non-oncologic investigational products within 30 days or 5 half-lives prior to registration, whichever is longer.

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

3.3 Inclusion of Women and Minorities

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

4 STUDY DESIGN & REGISTRATION PROCEDURES

4.1 Study Design

A randomized phase II approach will be used. Ninety patients will be randomized in a 1:1 ratio to either receive gemcitabine 1000mg/m^2 i.v. over 90 min on days 1 and 8 every 21 days along with pazopanib 800 mg PO once daily days 1 through 21 (G+P), or gemcitabine 900 mg/m^2 i.v. over 90 min on days 1 and 8 along with docetaxel 100 mg/m^2 i.v. over 60 min on day 8 every 21 days (G+T) till disease progression. Since G+T has shown good activity in leiomyosarcoma patients, to ensure a balance in the treatment arms being compared, prior to randomization, patients will be stratified by tumor type (leiomyosarcoma vs. other) and whether the patient has had prior pelvic radiation.

PFS and toxicity (defined as the incidence of grade 3 or 4 toxicity) will be the primary endpoints. We assume that accrual will occur over 18 months and that the last patient will be followed for 18 months. Interim analysis will allow early stopping in an arm for excessive toxicity. Patients will be allowed to cross-over to the other treatment arm upon progression. This will serve to encourage accrual and to evaluate PFS of G+P after exposure to G+T.

4.2 Registration procedure

The Hollings Cancer Center (HCC) Clinical Trials Network (CTN) program will provide centralized randomization and registration services for all patients at MUSC and participating multicenter sites. At a minimum, the CTN will conduct a patient eligibility audit review of all eligibility source documents prior to patient registration of the first three patients enrolled to a site. These procedures are outlined in the CTN Investigator Initiated Trial Multicenter Manual for this study. Upon completion of all the required baseline assessments, eligible subjects will be registered. They will then be stratified and randomly assigned to a treatment arm. A subject number will be assigned to each patient. The CTN will issue a patient registration confirmation email to the participating site at the time of registration. This confirmation will include the patient's assigned treatment arm and study ID number.

Once patients are randomized they should begin protocol treatment within 72 hours. Issues that would cause treatment delays should be discussed with the Principal Investigator.

Participating sites are not active to study enrollment until after the CTN has received the site's initial IRB approval and other start-up documents. The CTN will submit the initial request for study drug at the time of study activation. Any resupply orders for study drug will be made by the participating site per the instructions provided by Biologics, Inc. which has been subcontracted to handle the drug distribution for this study.

5 TREATMENT PLAN

5.1 Treatment schedule

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks for pazopanib, gemcitabine and docetaxel are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

For *BOTH* Arms, a cycle equals 21 days.

ARM 1: Gemcitabine (G) + Taxotere (T)

Gemcitabine at 900 mg/m^2 on DAYS 1 and 8 over 90 min (+/- 15 minutes), *and*
Taxotere 100 mg/m^2 on DAY 8 over 60 min (+/- 15 minutes) following the gemcitabine infusion.

Premedications:

Anti-emetic regimen at minimum should contain a 5-HT3 blocker i.v. and dexamethasone 12 mg i.v or equivalent on days 1 and 8. Dexamethasone 8 mg BID or equivalent on the day before and day after docetaxel

Growth factor support with pegfilgrastim (Neulasta TM) or filgrastim (Neupogen TM) will be given starting with cycle 1 per institutional guidelines. If the dose is held and not administered to the patient on day 1 or 8, the patient can be given growth factor support on day 1 or **ARM 2: Gemcitabine (G) + Pazopanib (P)**

Gemcitabine at 1000 mg/m^2 on days 1 and 8 over 90 min (+/- 15 minutes), *and*
Pazopanib at 800 mg (2x400mg or 4x200mg) once daily starting on day 1 through day 21. On days1 and 8 when Gemcitabine is also administered, Pazopanib can be given to the patient prior to gemcitabine administration. This relative timing to Gemcitabine administration is not required, but a recommendation. However, it is imperative that Pazopanib be taken orally per day without food at least one hour before or two hours after a meal. It is also important that the time of day Pazopanib is taken is relatively constant during study treatment.

Premedications:

Anti-emetic regimen at minimum should contain a 5-HT3 blocker i.v. and dexamethasone 12 mg i.v or equivalent on days 1 and 8.

If neutropenia is a problem in G+P during therapy then growth factor support with pegfilgrastim (Neulasta TM) or filgrastim (Neupogen TM) could be considered at the discretion of the treating physician. Growth factor support should be given following institutional guidelines. If the dose is held and not administered to the patient on day 1 or 8, the patient can be given growth factor support on day 1 or 8.

Patients will discontinue treatment if they have disease progression, intolerable toxicity or if treatment is interrupted for > 21 days. Patients may be allowed to crossover at the time of

progression.

5.2 PAZOPANIB Instructions

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

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

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

Pazopanib should be stored at room temperature between 20°C and 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Pazopanib will be supplied for the study as investigational stock. Pazopanib provided for this study should only be used exclusively for enrolled study patients. Appropriate patient specific drug accountability logs documenting the patient specific dispensing and return activity should be maintained by the participating institution.

5.3 GEMCITABINE premedications

Prophylactic anti-emetic regimen at minimum should contain a 5-HT3 blocker i.v. and dexamethasone 12 mg i.v or equivalent on days 1 and 8.

5.4 TAXOTERE premedications

All patients should be premedicated with oral corticosteroids in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. As outlined in 5.1., dexamethasone 12 mg i.v or equivalent on days 1 and 8, and dexamethasone 8 mg BID or equivalent may be given on the day before and day after docetaxel. Prophylactic anti-emetics should include an i.v. 5-HT3 blocker.

5.5 General Concomitant Medication and Supportive Care Guidelines

5.5.1 Permitted Medications

All subjects will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the 4 weeks prior to registration. The investigator must be informed as soon as possible about any new medication(s) taken during screening from 4 weeks prior to registration 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 and dates of administration.

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, analgesics, or bisphosphonates, when appropriate. Antiemetics (such as prochlorperazine, lorazepam, ondansetron or other 5-HT antagonists) may be administered prophylactically in the event of nausea. Anti-diarrheals, such as loperamide, may be administered as needed in the event of diarrhea (See Appendix E for Supportive care guidelines for nausea/vomiting and diarrhea). Although acetaminophen at doses of $\leq$2 g/day is permitted, it should be used with caution in subjects with impaired liver function. Glucocorticosteroids may be used as antiemetics and megestrol acetate may be used for appetite.

Use of Growth Factors
Prophylactic growth factor support with pegfilgrastim (Neulasta TMor filgrastim (Neupogen TM) will be given starting with cycle 1 in the G+T arm per institutional guidelines.

If neutropenia is a problem in G+P during therapy then growth factor support with pegfilgrastim (Neulasta TM) or filgrastim (Neupogen TM) can be added at the discretion of the treating physician per institutional guidelines.

If the dose is held and not administered to the patient on day 1 or 8, the patient can be given growth factor support on day 1 or 8.

Erythropoietin may be used at the discretion of the investigator, sub-investigator, or treating physician but is generally discouraged. Patients could be transfused with packed red blood cell transfusions as necessary.

5.5.2 Permitted Medications – Use with Caution

Specific recommendations regarding Simvastatin:

Concomitant use of pazopanib and simvastatin increases the incidence of ALT elevations. Across monotherapy studies with pazopanib, ALT > 3 ULN was reported in 126/895 (14%) of patients who did not use statins, compared with 11/41 (27%) of patients who had concomitant use of simvastatin. If a patient receiving concomitant simvastatin develops ALT elevations, follow dosing guidelines for pazopanib. Alternatively, consider discontinuing simvastatin. Insufficient data are available to assess the risk of concomitant administration of alternative statins and pazopanib.

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 on both arms should be monitored regularly for changes in relevant coagulation parameters as clinically indicated, as well as for any clinical bleeding episodes.

If a patient starts on anticoagulation therapy during treatment for reasons not attributable to study drug (e.g., underlying disease or port closing), study treatment should be held until desired level of anti-coagulation is reached. PT/INR and PTT/aPTT should be monitored until stable. Once stable, the patient can be restarted at the same dose level.

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 [26]. 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 as outlined in Section 10. Study calendar and as clinically indicated.

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

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, carbamazepine, phenobarbital, oxcarbazepine
- HIV antivirals: efavirenz, nevirapine
- Antibiotics: rifampin (rifampicin), rifabutin, rifapentine
- Miscellaneous: St. John's Wort, modafinil, pioglitazone

The Effects of Other Drugs on Docetaxel
Docetaxel is a CYP3A4 substrate. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. Substances that induce or inhibit CYP3A4 as listed above may alter the pharmacologic effects of docetaxel also and should be used with **CAUTION**.

5.5.3 Prohibited Medications

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

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

Subjects should not receive other anti-cancer therapy [cytotoxic, biologic, radiation, or hormonal (other than leuprolide or other GnRH agonists)] not specified in the protocol while on treatment in this study. Subjects should not receive any other investigational drug within 15 days of the last dose of study therapy.

5.6 End of Treatment

Treatment may continue on either arm until one of the following criteria applies:

- Evidence for disease progression.
- Inter-current illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree or require discontinuation of study drugs.
- Unacceptable toxicity.
- Death.
- Patient withdraws consent.
- Treatment delay greater than three weeks for any toxicity
- Concomitant treatment with a systemic anticancer drug that is not one of the study drugs.
- Patients who do not have satisfactory compliance with study procedures.

6 Patient Crossover

At the time that the patient is determined to have disease progression, the "*At time of progression/At end of treatment"* procedures outlined within the Section 10 study calendar should be completed within 7 days. Study assessments required at end of Study are outlined in Secrtion 10 Study Calendar. However, please note that a pregnancy test is only required at this end of study visit if the patient is expected to crossover.

All patients expected to continue with crossover study treatment must be registered with the HCC Clinical Trials Network (CTN).The assessments completed at the "*At time of progression/At end of treatment*" visit may be used for eligibility consideration for crossover registration.

All patients who crossover must complete the following procedures prior to HCC CTN crossover registration and beginning any crossover study therapy. Crossover procedures must be completed within 14 days prior to HCC CTN study crossover registration. Patients intending to crossover, must be registered to crossover therapy no later than 21 days after the "*At time of progression/At end of treatment*" visit.

Patients must meet the following criteria in order to continue into crossover study therapy.

6.1 Crossover Inclusion Criteria

1. The patient has documented disease progression after completing the initial therapy of this 101644 protocol.

2. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

3. Subjects must have metastatic and/or locally advanced or locally recurrent disease that is not amenable to curative surgical resection.

4. Patients must have measurable disease by RECIST 1.1. or cutaneous disease amenable to serial measurements should be present. Measurable disease (a 'target' lesion) is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT (CT scan slice thickness no greater than 5 mm); ≥ 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable); and ≥ 20 mm by chest x-ray.

5. Able to swallow and retain oral medication.

6. Adequate organ system function as defined in the table below.

Definitions for Adequate Organ Function

System	Laboratory Values
Hematologic	
Absolute neutrophil count (ANC)	≥1.5 X 10^9/L
Hemoglobin[a]	≥9 g/dL (5.6 mmol/L)
Platelets	≥100 X 10^9/L
Coagulation Tests[b] Coagulation assessments should be completed according to institutional standards, which should at least one of the following.	
International normalized ratio (INR)	≤1.2 X ULN
Prothrombin time (PT)	≤ 1.2X ULN
Activated partial thromboplastin time (aPTT)	≤1.2 X ULN
Partial thromboplastin time (PTT)	≤1.2 X ULN
Hepatic[c]	
Total bilirubin[c]	≤ ULN
Alanine amino transferase (ALT) and Aspartate aminotransferase (AST)[c]	≤2.5 X ULN
Alkaline phosphatase	≤2.5 X ULN
Renal	
Serum creatinine	≤1.5 mg/dL (133 µmol/L)
Or, if serum creatinine >1.5 mg/dL: Calculated creatinine clearance (Cl_{CR}) (Appendix 2)	≥50 mL/min
Urine Protein to Creatinine Ratio (UPC; Appendix 3)[d]	<1
Or, 24-hour urine protein[d]	<1g

a) Subjects may not have had a transfusion within 7 days of screening assessment.
b) Coagulation tests are only required for crossover registration for those patients crossing over into the Gem+Paz arm. Subjects receiving anticoagulant therapy are eligible if their coagulation lab values are 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. UPC tests are only required for crossover registration for those patients crossing over into the Gem+Paz arm.

6.2 Crossover Exclusion Criteria

1. Patients who end initial 101644 therapy due to grade 3 or greater toxicity are not eligible to cross-over.

2. Patients who choose to discontinue treatment on an arm (or who are removed for other reasons than progression such as toxicity) will not be allowed to cross over to the other treatment arm.

3. Positive pregnancy test.

4. Any concern for hypersensitivity to pazopanib, gemcitabine or docetaxel.

5. 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 crossover registration. Screening prior to crossover registration 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.

6. 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 of crossover registration.

7. 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 and experiencing the "dumping" syndrome.

8. Presence of uncontrolled infection.

9. If crossing over to Gemcitabine + Pazopanib, corrected QT interval (QTc) > 480 msecs using Bazett's formula.

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

11. Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA) (Appendix D).

12. Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥150 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg].

    Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. BP must be re-assessed on two occasions that are separated by a minimum of 1

hour; on each of these occasions, the mean (of 3 readings) SBP/ DBP values from each BP assessment must be <150/90 mmHg in order for a subject to be eligible for the study.

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

    Note: Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks prior to crossover registration and are fully anti-coagulated are eligible.

14. Prior major surgery or trauma within 28 days of crossover registration and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major).

15. Evidence of active bleeding or bleeding diathesis.

16. Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels.

17. Hemoptysis in excess of 2.5 mL (or one half teaspoon) within 8 weeks of crossover registration.

18. 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.

6.3 Crossover Procedures

At the time of screening for crossover registration, the following procedures are required within 14 days of crossover registration. The exception is the pregnancy test for WOCBP which is required within 7 days of crossover registration. These assessments include:

- Medical history/Physical exam
- Review of concomitant medication
- Vital signs
- ECOG performance status
- Review of adverse events
- CBCD
- LFT
- Chemistries
- Pregnancy test for WOCBP (within 7 days)

For patients who were originally randomized to the G+T arm and plan to cross over to the G+P arm, the following assessments must be completed in addition to the End of Treatment assessments.

- EKG
- Urinalysis/ UPC

- PT/INR or PTT/aPTT
- T4, TSH

Upon completion of crossover assessments and verification of crossover eligibility, the following crossover registration documents should be completed and submitted to the HCC CTN. All documents are posted to the HCC CTN workbench. Please fax documents to 843-792-5123.

- 101644 Crossover Enrollment Packet
- 101644 Crossover Eligibility Criteria Checklist.
- Radiographic assessment and RECIST source document (if applicable) of the patient's last radiographic response assessment.

Upon review and approval of the crossover registration, an email registration confirmation will be forwarded to the registering site. This confirmation should be filed within the patient research record. The patient should follow the assessments as outlined within the Section 10 Study calendar for crossover therapy.

6.4 Crossover Correlative Studies

For patients who consented to the optional CAF biomarker, optional blood specimen banking, and optional quality of life assessment, these evaluations only apply to the initial study therapy. These studies will not be completed during the study's crossover therapy.

For patients who consented to the optional Pazopanib PK sampling and are planned to receive Gemcitabine and Pazopanib as part of crossover study therapy, PK draws will occur at the following timepoints during crossover therapy: 1) after crossover registration but prior to Pazopanib start, 2) at cycle two of crossover therapy, and 3) at time of progression after crossover therapy.

6.5 Crossover Therapy and Dose Level

If a Gemcitabine dose reduction was implemented during initial study therapy, the same dose level should be used during the crossover therapy portion of the study. The Gemcitabine dose level should not be increased. Please refer to Table 6.1.1 and Table 6.1.2 for description of the dose levels.

For example, if a patient initially randomized to G+T was dose reduced to dose level -1 and received Gemcitabine 700 mg/m^2 during initial study therapy, then the patient should continue at dose level -1 in the crossover therapy of G+P and receive Gemcitabine at 800 mg/m^2. Thus, the Gemcitabine dose level used at the time that the patient ended initial therapy should continue when starting crossover therapy.

The same dose modifications guidelines should be used for initial and crossover therapy.

6.6 Duration of Follow Up

The follow-up period begins after a patient completes initial therapy and does not continue to crossover therapy or after the patient completes crossover therapy. During follow-up, patients

will be followed every 3 months until progression; after progression is documented, patients should be followed every 3 months for survival until 24 months after the last patient is enrolled to the study. All attempts will be made to document progression and survival every 3 months, but if any of the timepoints are missed, it will not be considered a protocol deviation.

6.7 Crossover Criteria for removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.3 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

7 DOSING DELAYS/DOSE MODIFICATIONS

7.1 General principles

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

The NCI-CTCAE, v4.0 must be used to grade the severity of AEs except for hypertension and palmar-plantar erythrodysesthesia syndrome: grading for these events is described in the Table 6.3.1. Specific recommendations for management of pazopanib related AEs along with guidelines for dose interruption, modification, or discontinuation are provided in Table 6.3.1. In the event of treatment emergent hepatotoxicity, the guidelines for management of hepatotoxicity provided in Table 6.4.1 and 6.4.2 should be followed. Refer to Tables 6.2.1, 6.2.2 and 6.2.3 for dose modifications for hematologic toxicities. **Patients requiring any of the drug treatments to be held > 21 days must discontinue protocol treatment.**

Dose reductions for **non- hematologic toxicities** with G, P and T will be permanent with the following exceptions. The investigator will be allowed to dose modify at their discretion for minor AEs or AEs that may be corrected by other measures. Examples of minor non-hematological toxicities include alopecia, nausea, vomiting, fever without grade IV neutropenia, or metabolic imbalances that may be corrected by provision of supportive care (e.g. hypokalemia and provision of potassium). For minor AEs in which the patient recovers, the investigator will be allowed to re-escalate.

Dose reductions for G, P and T for **treatment related hematologic toxicities** will allow re-escalation to one level higher if the counts permit. If a second reduction is required subsequently this will then be a permanent reduction**.**

Treatment will be held for all non-hematologic $\geq$ grade 3 toxicities except for minor non-hematological toxicities as described previously. Please refer to the dose level tables (6.1.1 and 6.1.2) below for each arm to guide the dose reduction. Patients unable to tolerate dose level -2 or requiring treatment held beyond 3 weeks, must discontinue protocol treatment.

Table 4: G+P Dose Levels

G+P	Gemcitabine	Pazopanib
Dose level 1 (DL 1)	1000 mg/m2	800 mg
Dose level -1 (DL-1)	800 mg/m2	600 mg
Dose level -2 (DL-2)	675 mg/m2	400 mg

Table 5: G+T Dose Levels

G+T	Gemcitabine	Docetaxel
Dose level 1 (DL 1)	900 mg/m2	100 mg/m2
Dose level -1 (DL-1)	700 mg/m2	75 mg/m2
Dose level -2 (DL-2)	600 mg/m2	60 mg/m2

7.2 Hematologic toxicities:

Table 6 Adjustments based on blood counts on day 1 of a treatment cycle

ANC		Platelets	Gemcitabine Dose
≥ 1,000	and	≥ 100,000	100% of current dose level
<1,000	or	<100,000	Hold treatment and resume at 100% of current dose level if counts recover to ANC ≥1,500 and platelets ≥ 100,000 within a week. Consider G-CSF or GM-CSF prophylaxis (per section 5.1) if not already on it. If a delay of >1week but less than 3 weeks is required for recovery of counts, then reduce dose of agent/s by one dose level based on Tables 4 & 5. Investigators' discretion can be used to decide whether one or both agents need dose reduction.

Table 7 Adjustments based on blood counts on day 8 of a treatment cycle.

ANC		Platelets	Chemotherapy Dose %
≥ 1,500	and	≥ 100,000	**G+T:** 100% of the G dose given on day 1 and 100% of T dose. **G+P:** 100% of the G dose given on day 1. P dose stays the same.
750 to 1499	or	75,000 to 99,999	**G+T:** Reduce dose by one dose level. Investigators' discretion can be used to decide whether one or both agents need dose reduction. **G+P:** Reduce dose by one dose level. Investigators' discretion can be used to decide whether one or both agents need dose reduction. **Both Arms:** At the discretion of the investigator, if patient is on dose level -2, hold until recovery of counts and continue treatment at current dose level. The patient will be removed from study if drug is held greater than 3 weeks for the recovery of counts.
< 750	or	<75,000	**G+T:** Hold G and T. Repeat counts in 1 week and treat according to ANC and Platelet level. If still not recovered to higher level after 1 week, skip day 8 treatments and reduce dose of G and T in the

			subsequent cycles by one dose level on days 1 and 8. **G+P:** Hold G and P and repeat counts weekly till ANC ≥ 750 and Platelets ≥ 75,000 and then re-start at the next lower dose level. However, if counts still not recovered to higher level after 1 week, skip day 8 treatment with G and reduce dose of G in the subsequent cycles by one dose level on days 1 and 8. Resume P at the lower dose when ANC ≥ 750 and Platelets > 75,000. **Both Arms:** At the discretion of the investigator, if patient is on dose level -2, hold until recovery of counts and continue treatment at current dose level. The patient will be removed from study if drug is held greater than 3 weeks for the recovery of counts.

Table 8 Adjustments based on blood counts on Cycle 1 Day 15 of a treatment cycle (Pazopanib related only)

Platelets	Modification
≥50,000	Continue with current dose; monitor as clinically indicated
<50,000	Interrupt P until toxicity resolves to < grade 2. Restart P at reduced dose level and monitor as clinically indicated If no recovery to < grade 2 or recurrent grade 3 or 4 platelet count decrease, discontinue study treatment.

7.2.1 Adjustments for febrile neutropenia and sepsis

If febrile neutropenia or sepsis occurs, G-CSF or GM-CSF may be instituted until the resolution of the febrile neutropenia or septic episode if adverse prognostic factors exist (according to ASCO Guidelines). Prophylactic G-CSF or GM-CSF should be strongly considered in G+P as per section 5.1. In the G+T arm prophylactic G-CSF or GM-CSF is recommended beginning with cycle 1.

7.2.2 Adjustment for Anemia

Erythropoietin may be used at the discretion of the investigator, sub-investigator, or treating physician but is generally discouraged. Patients could be transfused packed red blood cell transfusions as necessary**.**

7.3 Dose Interruptions/Modifications Specific for Pazopanib Related Toxicities, Excluding Liver Toxicities

If dose reduction is necessary, two dose reductions will be permitted in a stepwise fashion (refer

to tables 6.1.1 & 6.1.2 for dose levels).

Table 9 Dose Modification Algorithms for Potential Pazopanib-Related Adverse Events

AE Terms & Descriptions	Dose Modification Algorithms
Hypertension	
(1) Asymptomatic and persistent SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or a clinically significant increase in DBP of 20 mmHg (but still below 110 mmHg).	**Step 1.** Continue pazopanib at the current dose. **Step 2.** Adjust current or initiate new antihypertensive medication(s). **Step 3.** Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[a] BP. If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (2).
(2) Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or failure to achieve well-controlled[a] BP within 2 weeks in scenario (A).	**Step 1.** Consider reducing or interrupting pazopanib as clinically indicated. **Step 2.** Adjust current or initiate new antihypertensive medication(s). **Step 3.** Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. **Step 4.** Once BP is well-controlled, restart pazopanib at the next lower dose level, if pazopanib was interrupted.
(3) Symptomatic hypertension or recurring SBP ≥160 mmHg, or DBP ≥100 mmHg, despite modification of antihypertensive medication(s).	**Step 1.** Interrupt pazopanib. **Step 2.** Adjust current or initiate new antihypertensive medication(s). **Step 3.** Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is also recommended. **Step 4.** Once BP is well-controlled, restart pazopanib dose-reduced to the next lower dose level.
(4) Refractory hypertension unresponsive to above interventions or ≤ 2 dose reductions.	Discontinue pazopanib and continue follow-up per protocol.
Prolongation of QTc Interval:	
QTc ≥ 480 < 500 msec	Continue pazopanib at the current dose; monitor as clinically indicated.
QTc ≥ 500 msec	Discontinue pazopanib and continue follow-up per protocol.
Proteinuria	
UPC <3	Continue pazopanib at the current dose; monitor as clinically indicated.

AE Terms & Descriptions	Dose Modification Algorithms
Proteinuria	
UPC ≥ 3 or 24-rine protein ≥ 3g	**Step 1.** Interrupt pazopanib. **Step 2.** Weekly UPC or 24-hr urine protein monitoring until UPC is < 3 or 24-hr urine protein is < 3 grams. Then restart pazopanib at the next lower dose level. **Step 3.** If UPC > 3 or 24-h urine protein ≥ 3g recurs, repeat steps 1 and 2 **Step 4.** If UPC ≥ 3 or 24-hr urine protein ≥ 3 recurs and the pazopanib dose can no longer be reduced, discontinue pazopanib and continue follow-up per protocol.
Hemorrhage /Bleeding: Investigate and document underlying etiology of the bleeding	
Grade 1	For hemoptysis, interrupt pazopanib and contact the Principal Investigator to discuss whether further treatment with pazopanib is appropriate. For other Grade I hemorrhage/bleeding events, continue pazopanib at the current dose; monitor as clinically indicated.
Grade 2	**Step 1.** If pulmonary or GI bleed (other than hemorrhoidal bleeding), discontinue pazopanib and continue follow-up per protocol. Otherwise, interrupt pazopanib until the AE resolves to ≤ Grade 1. **Step 2.** Restart pazopanib; consider reducing dose and monitor as clinically indicated.
Grade 3 or 4, or recurrent ≥ Grade 2 event after dose interruption/reduction.	Discontinue pazopanib and continue with follow-up per protocol.
Venous Thrombosis (DVT, PE)	
Grade 2	Continue pazopanib at the current dose; monitor and treat as clinically indicated.

AE Terms & Descriptions	Dose Modification Algorithms
Venous Thrombosis (DVT, PE)	
Grade 3	**Step 1.** Interrupt pazopanib treatment. **Step 2.** Initiate and monitor anticoagulation as clinically indicated. **Step 3.** Resume pazopanib treatment at the same dose only if all of the following criteria are met: – The subject must have been treated with anticoagulant at the desired level of anticoagulation for at least one week. – No Grade 3 or 4 or clinically significant Grade 2, hemorrhagic events have occurred while on anticoagulation treatment. Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment. When treating with warfarin, INR should be monitored within three to five days after any change in pazopanib dosing (e.g., re-initiating, escalating/de-escalating, or discontinuing pazopanib), and then at least weekly until the INR is stable. The dose of warfarin (or its derivatives) may need to be adjusted to maintain the desired level of anticoagulation.
Grade 4 and/or PE	Discontinue pazopanib and continue follow-up per protocol.
Arterial Thrombosis/Ischemia	
Any Grade	Discontinue pazopanib and continue follow-up per protocol.
Palmar-plantar Erythrodysesthesia Syndrome	
Grade 1 Minimal skin changes or dermatitis without pain (erythema, edema, hyperkeratosis)	**Step 1.** Continue pazopanib at present dose **Step 2.** Initiate supportive care with emollient lotions
Grade 2 Skin changes with pain; limiting instrumental activities of daily living (ADLs) (peeling, blisters, edema, bleed, hyperkeratosis)	**Step 1.** Hold pazopanib **Step 2.** Treat as clinically appropriate: emollient lotions, limiting tight shoes and heels **Step 3.** Upon resolution to Grade 1 or better, restart pazopanib at one lower dose level **Step 4.** If recurrent consider a further dose reduction to dose level -2 or discontinuation if already at dose level -2
Grade 3 Severe skin changes with pain and limiting self care ADLs	Discontinue pazopanib
Other Clinically Significant Adverse Events attributable to Pazopanib[b]	
Grade 1	Continue pazopanib; monitor as clinically indicated.

AE Terms & Descriptions	Dose Modification Algorithms
Grade 2 or 3, if clinically significant	**Step 1.** Interrupt pazopanib until toxicity resolves to ≤ Grade 1. **Step 2.** Restart pazopanib at a lower dose level and monitor as clinically indicated
Other Clinically Significant Adverse Events attributable to Pazopanib[b]	
Grade 4	Discontinue pazopanib and continue follow-up per protocol.

a. Well-controlled BP defined as SBP <140 mmHg and mean DBP <90 mmHg.
b. AEs are graded according to NCI Common Terminology Criteria for Adverse Events v4.0 (NCI CTCAE v4)

7.4 Dose Interruptions/Modifications for Hepatotoxicity

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 ensure all are recorded in the CRF), and (b) identify and discontinue those with known hepatotoxicity and replace with a non-hepatotoxic equivalent for the same indication if necessary. If hepatotoxicity occurs and the suspected cause is from alcohol use, this should be documented within the comments of the adverse event case report form. 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 10 Guidelines for Management of Treatment Emergent Hepatotoxicity in G+P arm

Event	Dose Modification Algorithms
A). ALT and AST of ≤ 3.0 x ULN	Continue G+P at current dose with full panel LFTsa monitored as per protocol. Study calendar (section 10)
B). ALT and/or AST >3.0 x ULN to ≤5.0 x ULN without bilirubin elevation (defined as total bilirubinb <2.0 x ULN or direct bilirubin ≤35%) and without hypersensitivity symptoms (e.g., fever, rash)	Liver Event Monitoring Criteria: (1) Continue G + P at current dose levels. (2) Monitor subject closely for clinical signs and symptoms; perform full panel LFTsa weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1.
C) ALT and/or AST >5.0 x ULN to ≤ 8 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)** Interrupt G + P until toxicity resolves to ≤Grade 1 or baseline. **(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.

Event	Dose Modification Algorithms
D). 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 G + P until toxicity resolves to ≤ Grade 1 or baseline. **Report the event to Novartis as an SAE within 24 hours of learning of its**. 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 or baseline. **(4)** If the subject is benefiting from the study treatment, contact Principal Investigator for possible re-challenge with P. Re-treatment may be considered if ALL following criteria are met: – ALT/AST reduced to Grade 1 or baseline – Total bilirubin <1.5 x ULN or direct bilirubin ≤ 35% – No hypersensitivity signs or symptoms – Subject is benefiting from therapy. **Recurrence – Liver Event Stopping Criteria:** Discontinue study treatment and monitor subject closely for clinical signs and symptoms; perform full panel LFTs [a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1 or baseline. At the time of the recurrence, complete the CRF liver event forms. P should be permanently discontinued and further treatment off study will be at the discretion of the treating physician.
E). ALT or AST >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 pazopanib immediately; report the event to Novartis as an SAE within 24 hours of learning of its occurrence.** Make every reasonable attempt to have subjects return to the clinic for repeat liver chemistries and liver event follow up assessments. **(2)** Monitor subject closely for clinical signs and symptoms; record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form. Perform full panel LFTs [a] weekly or more frequently if clinically indicated until LFTs are reduced to Grade 1.
For isolated total bilirubin[b] elevation without concurrent ALT /AST increases (defined as ALT and AST<3 X ULN).	**(1)** Isolated hyperbilirubinemia (i.e., in the absence of elevated ALT/AST or other signs/symptoms of liver injury) does not require dose modification. Pazopanib inhibits UGT1A1 and OATP1B1, which can cause elevation of indirect (unconjugated) bilirubin in the absence of liver injury. **(2)** If bilirubin is >1.5 x ULN in the absence of ALT 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 ≥2 x ULN, then the event should be promptly reported as an SAE.

Table 11 Guidelines for Management of Treatment Emergent Hepatotoxicity in G+T arm

Bilirubin		Alkaline phosphatase		ALT/AST		Dose
>ULN	AND/ OR	>5 x ULN	AND/ OR	>5 x ULN	Hold until recovered (recheck weekly) then restart treatment*:	
					Docetaxel	Next lower dose level
					Gemcitabine	100% of current dose
≤ ULN	AND	> 2.5 but ≤ 5 x ULN	AND	> 2.5 but ≤ 5 x ULN	Hold until recovered (recheck weekly) then restart treatment*:	
					Docetaxel	Next lower dose level
					Gemcitabine	100% of the current dose
≤ ULN	AND	> 2.5 but ≤ 5 x ULN	OR	> 2.5 but ≤ 5 x ULN	Docetaxel	Next lower dose level
					Gemcitabine	100% of the current dose

* If bilirubin ≤ ULN *and* alkaline phosphatase ≤ 3 x ULN *and* SGOT/SGPT ≤ 3 x ULN

7.5 Dose Interruptions/Modifications Specific for Non-Hematologic Toxicities, Excluding Liver Toxicities

Table 12 Adjustments for drugs based on stomatitis, esophagitis, or dysphagia on day 1 of a treatment cycle

Grade	Arm	Dose %
0, 1, 2	G+P	100% of the current dose level
	G+T	100% of the current dose level
3, 4	G+P	**1st occurrence:** No change in the dose of P. Delay G dose by 1 week, and if grade lowers to ≤ 2, then resume at the next lower dose level. **2nd occurrence or if still not recovered after 1 week then**: reduce dose of P to the next lower level and reassess weekly. If toxicity grade ≤ 2, then administer G at the next lower dose level.
	G+T	Delay dose by 1 week, and if grade lowers to ≤ 2, then administer the G at 100% of the current dose. If still not recovered to grade ≤ 2 after 1 week, reassess weekly and if toxicity grade ≤ 2, then administer G at the next lower dose level.

Table 13 Adjustments for drugs based on stomatitis, esophagitis, or dysphagia on day 8 of a treatment cycle

Grade	Arm	Dose %
1-2	G+P	100% of the current dose level
	G+T	100% of the current dose level
≥ 3	G+P	No change in the dose of P Delay G dose by 1 week, and if grade lowers to ≤ 2, then resume at the next lower dose level. If still not recovered to grade ≤ 2 after 1 week, skip day 8 treatment and reduce dose in subsequent cycles by one dose level on days 1 and 8.
	G+T	Delay dose of G and T by 1 week, and if toxicity grade ≤ 2, then administer the G and T at the next lower dose level. If still not recovered to grade ≤ 2 after 1 week, skip day 8 treatment and reduce dose in subsequent cycles by one dose level on days 1 and 8.

Table 14 Adjustments for all drugs based on dyspnea or pneumonitis on day 1 or day 8 of a treatment cycle

Dyspnea Grade (due to Drug Toxicity)		Dose %
1	All drugs	100
≥2	All drugs	Discontinue Protocol Therapy
Pneumonitis Grade		Dose %
1	All drugs	100%
≥2	All drugs	Discontinue protocol therapy

7.5.1 Hypersensitivity reaction

Allergic reactions may follow administration of any of the chemotherapy drugs. See Appendix F for treatment of hypersensitivity reactions. Treatment should be discontinued for grade 4 hypersensitivity reactions. There are no dose reductions for hypersensitivity reactions.

7.5.2 Peripheral neuropathy:

Table 15 Adjustments for docetaxel based on peripheral neuropathy on day 8 of a treatment cycle

Grade		Dose
1-2	All drugs	100%
≥3	Hold until symptoms ≤ grade 1, then restart as follows:	
	Docetaxel	Reduce by one dose level

7.5.3 Fluid retention or Hyperlacrimation

For patients receiving docetaxel: See Appendix G and H**.**

7.5.4 Other treatment related non-hematologic toxicity:

Exception nausea/vomiting, alopecia, and fever without grade IV neutropenia and other metabolic imbalances. Please see Section 7.1 for additional detail:

Table 16 Adjustments for G and T based on any other treatment related non-hematologic toxicity on day 1 or 8 of a treatment cycle (See 6.1 for exceptions)

CTC Grade	**Chemotherapy dose (%)**
1	100
2	Hold*
3	Hold**
4	Discontinue Protocol Therapy
* Give 100% upon improvement to grade 1 ** Reduce by one dose level upon improvement to grade 1	

8 STUDY AGENT INFORMATION

8.1 Investigational agent: Pazopanib

8.1.1 Formulation, product identification, package and labeling

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

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

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

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

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

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

8.1.2 Destruction of drug

Any unused, used and expired study drug will be destroyed at the site per Institutional SOPs unless otherwise specified. A copy of the final drug accountability log noting the drug destruction must be forwarded to the HCC Clinical Trials Network.

8.1.3 Records to be kept at site, dispensing and accountability

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

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

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

Study patients receiving Pazopanib must be instructed to complete a Pazopanib drug diary to document the daily administration of Pazopanib. The drug diary is available on the HCC-CTN workbench online repository. Patients should be counseled at the beginning of and throughout study participation to comply with the following activities for patient safety and monitoring:

1. Administer Pazopanib as outlined in section 8.1.1.2 *Route of administration*
2. Complete the provided Pazopanib drug diary.
3. Return the completed Pazopanib drug diary and pill bottle with any remaining study drug to the study site at each visit.

If the treating investigator suspects a patient's failure to comply with proper administration of Pazopanib, the patient should be immediately counseled and may be removed from study if warranted per the treating investigator's discretion.

8.1.4 Treatment of Investigational Product Overdose

No maximum tolerated dose (MTD) was reached in the dose escalation study of pazopanib administered as a single agent at repeated doses of up to 2000 mg/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 Principal Investigator- Dr. Andrew Kraft.

Decisions regarding pazopanib dose modifications or interruptions will be made by the investigator in consultation with the Principal Investigator based on the clinical evaluation of the subject.

Following an overdose, additional monitoring of the subject for AEs/SAEs and laboratory abnormalities should be considered. A plasma sample for pharmacokinetic analysis for pazopanib may be requested by the Principal Investigator on a case-by-case basis. This plasma sample 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.

8.2 Commercial Agent(s)

8.2.1 Gemcitabine

Gemcitabine is commercially available. For product description and handling information, please refer to the package insert for Gemcitabine.

Route of administration:
In the treatment of sarcoma, gemcitabine is administered as an infusion over 90 minutes on Days 1 and 8 of each 21-day cycle.

Side effects:
The most common adverse reactions for the single-agent (≥20%) are nausea and vomiting, anemia, neutropenia, leukopenia, proteinuria, fever, hematuria, rash, thrombocytopenia, dyspnea, ALT, AST and alkaline phosphatase elevation. Please refer to the package insert for additional details.

8.2.2 Docetaxel (Taxotere)

Taxotere is commercially available. For product description and handling information, please refer to the package insert for taxotere.

Route of administration: The final TAXOTERE dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature and lighting conditions.

9 CORRELATIVE/SPECIAL STUDIES

Correlative studies will be performed on all patients on either arm who give consent for the correlative studies outlined below. Refer to the MUSC 101644 Correlatives Manual for processing, handling and shipping instructions.

9.1 Cytokine and Angiogenesis Factors Biomarker Studies

Cytokine and angiogenesis factors (CAFs) correlative studies will be performed to all patients on either arm who give consent for the optional biomarker study to investigate possible biomarkers for response or resistance. One 10 ml tube of blood will be collected after randomization (prior to C1D1 treatment), upon completion of cycle 2 and at the end of therapy**.** CAFs measured may include but are not limited to IL-12, HGF, IL-16, IP-10, SDF-1α, IL-2Rα, IL-3, IFN-α2, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), M-CSF, PIGF and sVEGFR will be assessed.

9.2 Specimen Banking Study

An additional blood draw will be completed for all patients on either arm who consent to the optional specimen banking. One 10 ml tube of blood will be collected after randomization (prior to C1D1 treatment), upon completion of cycle 2 and at end of therapy.

9.3 Pharmacokinetic Study

A plasma sample will also be collected after randomization (prior to C1D1treatment), upon completion of cycle 2 and end of therapy to assess pazopanib concentration in patients receiving pazopanib, who have consented for the biomarker analysis for correlation. Blood samples for the determination of plasma pazopanib concentrations will be collected into a 3mL EDTA vacutainer The study will provide all tubes for blood collection, storage, and labels with the visit name and time of sample collection. An initial supply of kits will be provided to the site at the time of study activation..

To request a resupply order of PK kits, please complete the PK materials re-order form and as outlined in the 101644 Correlatives Manual. Although resupply requests will be accommodated as expedient as possible, please monitor PK kit supplies at your site and allow 10 business days for processing PK kit resupply orders. Refer to the 101644 Correlative Studies Manual for detailed instructions.

9.4 Quality of Life Assessment

For patients who consent to the optional Quality of Life study, Quality of Life will be assessed using two questionnaires that all patients will be asked to fill out at 4 different time points. See section 9.2. The questionnaires are available in Appendices I and J.

The European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) is a questionnaire with 30 questions developed to assess the quality of life of cancer patients. QLQ-C30 Version 3.0 is the most recent version that will be used. The Euroqol questionnaire (EQ-5D-3L) is a standardized instrument for use as

a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. It is a descriptive system consisting of 5 dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension has 3 levels designated simply as no problem, some problem, or extreme problem, and subjects are asked to check the level most descriptive of their current level of function or experience on each dimension.

The EORTC QLQ-C30 and EQ-5D questionnaire will be completed by each patient at baseline (on the day of first treatment, prior to any other study specific procedures), at 6 weeks (after 2 cycles), 18 weeks (after 6 cycles) and at the end of therapy. The questionnaires will be administered and collected by the study coordinator on the day of the clinic visit, prior to any other study specific procedure or treatment.

10 Study Assessments

See next page for study calendar and assessment guidelines.

10.1 STUDY CALENDAR- GROUP 1: GEMCITABINE + DOCETAXEL

Patients receiving Gemcitabine + Docetaxel during initial or crossover therapy will follow this calendar

		All Cycles		Cycle 1 only			
	Screening[a]	Day 1 [a, k]	Day 8 [k]	Day 15	Every 6 weeks *(end of every 2 cycles)*	Progression/ End of Treatment[i]	Follow-up
Gemcitabine		X	X				
Docetaxel			X				
Informed Consent	X						
Medical History/ Physical Exam	X	X				X	
Concomitant Medications Assessment[k]	X[k]	X	X			X	
Vitals signs	X	X	X			X	
Height	X						
Weight	X	X					
ECOG Performance Status	X	X				X	
Toxicity Assessment[c]		X----------					----X
CBCD, LFTs, chemistries [c, d]	X	X	X[c]	X		X	
Pregnancy test (WOCBP only)	X[a]					X[i]	
UPC	X					X[i]	
Thyroid function test (T4, TSH)	X					X[i]	
Coagulation tests	X	X[d]				X[i]	
EKG	X					X[i]	
Radiographic Assessment [f, k]	X				X[e]	X[e]	
Optional CAF Biomarker Blood Draw (initial treatment only)[f]	X[f]				X [f]	X	
Optional Blood Specimen Banking (initial treatment only)[f]	X [f]				X [f]	X	
Optional QOL Assessment (initial treatment only)[g]	X				X	X	
Follow up[h]							X[h]

a. Baseline evaluations are to be done within 14 days of registration, except for informed consent, radiographic disease and concomitant medication assessments that should be done within 4 weeks of registration, and serum pregnancy test that should be within 7 days of registration. After randomization, patients should begin treatment within 72 hours. Screening assessments completed within 48 hours of starting Cycle 1 Day 1 treatment do not need to be repeated unless deemed appropriate by the treating

physician.

b. Toxicity will be evaluated at every clinic visit and day 1 of every cycle. Any interim toxicities requiring treatment should be reported to the study coordinator or study physician and documented. Use CTCAE v4.0 to grade AEs, except for hypertension and palmarplantar erythrodysesthia syndrome (See Table9). Refer to section 7 for instructions regarding dose modifications. If patient is experiencing liver function toxicities (LFTs), weekly monitoring may be required depending on levels.

c. On subsequent cycles after cycle 1, only CBC with differential and LFTs will be required on day 8. Repeat any other laboratory tests as necessary. Any abnormal LFTs (Total Bili, AST, ALT, Alkaline phosphatase) should be repeated within a week and followed thereafter per the treating physicians recommendations. Chemistries include sodium, potassium, chloride, bicarbonate, BUN, creatinine and glucose. Laboratory assessments may be carried out within 3 days before the actual treatment administration to allow flexibility in scheduling.

d. Coagulation test should be repeated after a week of starting therapy on any patient who is on stable therapeutic anticoagulation per institutional standards. It should be then followed till documentation of stabilization while on protocol therapy. If anti-coagulation therapy is initiated on study for reasons not related to study drug, study drug should be held and the patient should be monitored until desired level of anti-coagulation is reached.

e. Radiographic Assessment: CT scans to cover bodily areas in which there is disease or suspected disease. Restaging scans should be repeated every 6 weeks or 2 cycles until progression. If dose holds cause a delay in the start or end of a cycle, scans should remain scheduled every 6 weeks. Attempts should be made to obtain radiographic assessment at the end of treatment visit if there is no prior radiographic confirmation of disease progression. If a patient crosses study arms, radiographic assessments will continue to be performed according to the same schedule. MRIs may be substituted in place of CT scan for clinical reasons such as patient intolerance of intravenous contrast material. The same method of assessment (i.e. CT, MRI) and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Use RECIST 1.1 guidelines. Refer to Section 11.

f. An additional blood draw will be collected from patients who provide informed consent to the optional biomarker and banking correlative studies and are receiving treatment during initial study therapy. CAF Biomarker and specimen banking samples will not be collected for patients in crossover therapy. Blood draws will occur at three time points: after randomization but prior to treatment, upon completion of cycle 2 (after day 15 of cycle 2 and before treatment on day 1 of cycle 3), and at the time of progression. Refer to 101644 Correlative Manual for processing and handling instructions.

g. Quality of Life Questionnaires will be administered to patients who provided consent and are receiving initial study therapy at the following four time points: (1) at baseline (on the day of first treatment and prior to any other study specific procedures), (2) at 6 weeks (after 2 cycles), (3) 18 weeks (after 6 cycles), and (4) at the end of therapy. The questionnaires will be administered and collected by the study coordinator on the day of the clinic visit, prior to any other study specific procedure or treatment. Quality of life assessments will not be administered for patients in crossover therapy.

h. Patients will be followed every3 months for documentation of progression and survival status for a maximum of 24 months after the last patient has been registered to the trial.

i. Patients will be given the opportunity to crossover to the other treatment arm upon progression if deemed appropriate by the investigator. If the patient does crossover, the patient must complete the end of treatment evaluations and submit a crossover registration packet to the Hollings Cancer Center CTN. A pregnancy test, urinalysis, UPC, coagulation tests, EKG, T4 and TSH are only required at this end of study visit if the patient is expected to crossover to the Gem+Paz arm. Refer to Section 5.4 Patient Crossover for more details.

j. Concomitant medications should be assessed during screening from 28 days prior to registration through completion of the end of therapy visit. Assess indication, dose information and dates of administration. Prohibited medications should be stopped 14 days prior to registration until discontinuation from study (Refer to Section 5.2.3).

k. To allow for scheduling or holiday issues, patient assessments and drug administration may be done +/- 3 days. Radiographic assessments may be done +/- 7 days. Patient assessments must be completed prior to administration of Gemcitabine or Docetaxel.

10.2

STUDY CALENDAR- GEMCITABINE + PAZOPANIB

Patients receiving Gemcitabine + Pazopanib during initial or crossover therapy will follow this calendar

	Screening[a]	All Cycles[n]		Cycle 1 Only	1st 24 weeks *(8 cycles)*	After week 24 *(end of cycle 8)*	Progression / End of Treatment[k]	Follow-up
		Day 1[a]	Day 8	Day 15	Every 6 weeks *(end of every 2 cycles)*	Every 12 weeks *(end of every 4 cycles)*		
Gemcitabine		X	X					
Pazopanib		X[n]----------X[n]						
Informed Consent	X							
History/ Physical Exam	X	X					X	
Concomitant Medications Assessment[L]	X[L]	X	X				X	
Vitals signs	X	X	X	X[b]			X	
Height	X							
Weight	X	X						
ECOG Performance Status	X	X					X	
Toxicity Assessment[c]		X----------X						
CBCD, LFTs, chemistries [d]	X	X	X[d]	X			X	
Pregnancy test (WOCBP only)	X[a]						X	
UPC	X				X	X		
Thyroid function test (T4, TSH)	X				X	X		
Coagulation tests	X	X[f]						
EKG [e]	X				X	X[e]		
Radiographic Assessment [g,n]	X	X[g]					X[g]	
Pazopanib Drug Diary Review[m]		X	X	X			X	
Optional CAF Biomarker Blood Draw (initial therapy only)[h]	X[h]				X[h]		X	
Optional Blood Specimen Banking (initial therapy only)[h]	X[h]				X[h]		X	
Optional QOL Assessment (initial therapy only) [i]	X				X		X	
Optional Pazopanib PK Plasma Sample[h]	X[h]				X[h]		X	
Follow up[j]								X[j]

a. Baseline evaluations are to be done within 14 days of registration, except for informed consent, radiographic disease and concomitant medication assessments that should be done within 4 weeks of registration and serum pregnancy test that should be within 7 days of registration. After randomization, patients should begin treatment within 72 hours. Screening assessments completed within 48 hours of starting Cycle 1 Day 1 treatment do not need to be repeated unless deemed appropriate by the

treating physician.

b. Monitoring of BP: A measurement of BP should be taken on day Cycle 1 day 15. The BP measurement can be done in clinic or self-reported by patient.

c. Toxicity will be evaluated at every clinic visit and day 1 of every cycle. Any interim toxicities requiring treatment should be reported to the study coordinator or study physician and documented. Use CTCAE v4.0 to grade AEs, except for hypertension and palmarplantar erythrodysesthia syndrome (See Table9). Refer to section 7 for instructions regarding dose modifications. If patient is experiencing liver function toxicities (LFTs), weekly monitoring may be required depending on levels.

d. On subsequent cycles after cycle 1, only CBC with differential and LFTs will be required on day 8. Repeat any other laboratory tests as necessary. Any abnormal LFTs (Total Bili, AST, ALT, Alkaline phosphatase) should be repeated within a week and followed thereafter per the treating physicians recommendations. Chemistries include sodium, potassium, chloride, bicarbonate, BUN, creatinine and glucose. Laboratory assessments may be carried out within 3 days before the actual treatment administration to allow flexibility in scheduling.

e. After 1 year on study, ECGs will be performed every 6 months.

f. Coagulation tests should be repeated after a week of starting therapy on any patient who is on stable therapeutic anticoagulation per institutional standards. It should be then followed till documentation of stabilization while on protocol therapy. If anti-coagulation therapy is initiated on study for reasons not related to study drug, study drug should be held and the patient should be monitored until desired level of anti-coagulation is reached. See Section 5.5.1

g. Radiographic Assessment: CT scans to cover bodily areas in which there is disease or suspected disease. Restaging scans should be repeated every 6 weeks or 2 cycles until progression. If dose holds cause a delay in the start or end of a cycle, scans should remain scheduled every 6 weeks. Attempts should be made to obtain radiographic assessment at the end of treatment visit if there is no prior radiographic confirmation of disease progression. If a patient crosses study arms, radiographic assessments will continue to be performed according to the same schedule. MRIs may be substituted in place of CT scan for clinical reasons such as patient intolerance of intravenous contrast material. The same method of assessment (i.e. CT, MRI) and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Use RECIST 1.1 guidelines. Refer to Section 11.

h. An additional blood draw will be collected from patients who provide informed consent to the optional correlative studies and are receiving initial study treatment. The CAF biomarker and specimen banking do not apply to crossover therapy. The Pazopanib PK studies will be collected from patients in the initial or crossover study phase who provide informed consent to the optional PK study. All blood draws will occur at three time points: after randomization but prior to treatment, upon completion of cycle 2 (after day 15 of cycle 2 and before treatment on day 1 of cycle 3), and at the time of progression. Refer to 101644 Correlative Manual for processing and handling instructions.

i. Quality of Life Questionnaires will be administered to patients at four time points: (1) at baseline (on the day of first treatment and prior to any other study specific procedures), (2) at 6 weeks (after 2 cycles), (3) 18 weeks (after 6 cycles), and (4) at the end of therapy. The questionnaires will be administered and collected by the study coordinator on the day of the clinic visit, prior to any other study specific procedure or treatment. Quality of life assessments will not be administered for patients in crossover therapy.

j. Patients will be followed every3 months for documentation of progression and survival status, for a maximum of 24 months after the last patient has been registered to the trial.

k. Patients will be given the opportunity to crossover to the other treatment arm upon progression. If the patient does crossover, the patient must complete the end of treatment evaluations and submit a crossover registration packet to the Hollings Cancer Center CTN. A pregnancy test is only required at this end of study visit if the patient is expected to crossover. Refer to Section 5.4 Patient Crossover for more details.

L. Concomitant medications should be assessed during screening from 28 days prior starting study therapy through completion of the end of therapy visit. Assess indication, dose information and dates of administration. Prohibited medications should be stopped 14 days prior to first dose of study drug until discontinuation from study (Refer to Section 5.5.3).

m. Pazopanib drug diaries should be collected and reviewed on Day 1 of each cycle. Patients should be instructed to bring their diaries and pill bottles with them to the each visit and patient compliance should be assessed. If patient non-compliance is present, the patient should be re-educated and counseled on drug compliance. Any unused medication should be collected and returned to the facilities pharmacy for destruction per institutional policies.

a. To allow for scheduling or holiday issues, patient assessments and drug administration may be done +/- 3 days. Radiographic assessments may be done +/- 7 days. Patient assessments must be completed prior to administration of Gemcitabine. Patients should also continue taking Pazopanib during any scheduling delays.

11 MEASURES OF EFFECT

Response Evaluation Criteria in Solid Tumors (RECIST)

The Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria will be used for objective tumor response assessment. Assessments will be performed *after every two cycles* of treatments. Attempts should be made to obtain radiographic assessment at the end of treatment visit if there is no prior radiographic confirmation of disease progression. If a patient crosses study arms, radiographic assessments will continue to be performed after every two cycles of treatments. Once protocol treatment has been completed subjects will be assessed every three months or sooner as indicated and judged by treating physicians.

11.1 Definitions

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

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

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

11.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. Sarcomas arising in a previously irradiated site will be considered measurable. Sarcoma lesions that have been treated with therapeutic intent will be considered measurable if they have increased in size by more than 20%.

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial

effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

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

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

11.3 Methods for Evaluation of Measurable Disease

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

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

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

CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI

is also acceptable in certain situations (e.g. for body scans).

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

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

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

11.4 Response Criteria

Evaluation of Target Lesions

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

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

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

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

Evaluation of Non-Target Lesions

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

Non-CR/Non-PD: Persistence of one or more non-target lesion(s).

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

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

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.

Table 17 For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR

SD	Non-CR/Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD***	Yes or No	PD
Any	Any	Yes	PD
* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.			

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

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

11.5 Duration of Response

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

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

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

11.6 Progression-Free Survival

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

12 DATA REPORTING / REGULATORY REQUIREMENTS

12.1 Adverse events

An adverse event is any unintended or undesirable experience that occurs during the course of the clinical investigation whether or not it is considered to be drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

At each evaluation patients should be interviewed in a non-directed manner to elicit potential adverse reactions from the patient. The occurrence of an adverse event will be based on changes in the patient's physical examination, laboratory results, and/or signs and symptoms.

All adverse events, regardless of causal relationship, will be recorded in the case report form and source documentation. The investigator, sub-investigator, or treating physician must determine the intensity of any adverse events according to the NCI Common Terminology Criteria for Adverse Events v4.0 and their causal relationship.

Adverse events will be followed until resolution while the patient remains on-study. Once the patients is removed from study, events thought to be related to the study medication will be followed until resolution or until the patient starts a new treatment regimen.

12.2 Serious adverse events (SAE)

Serious adverse events will be defined as an adverse event occurring while on study or within 30 days of the last study drug administration that result in any of the following outcomes:

- Death.
- A life-threatening adverse drug experience.
- A persistent or significant disability/incapacity.
- Inpatient hospitalization or prolongation of existing hospitalization. For the purposes of this study inpatient hospitalization or prolongation of existing hospitalization for the following reasons are not considered to be events for reporting: transfusion support, or other elective procedures associated with conventional medical practice, unless associated with other serious adverse events.
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Any pregnancies occurring during or within 30 days of the last study drug administration should also be considered serious adverse events and reported to the sponsor.

In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

Also considered serious for the purposes of this Study:

- ALT >3.0 x ULN with concomitant elevation in bilirubin (defined as total bilirubin ³2.0 x ULN, with direct bilirubin >35%) or with hypersensitivity symptoms (e.g., fever, rash) – bilirubin fractionation should be performed if testing available

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

12.3 Reporting of SAE's

Any serious adverse events which occur during the clinical study or within 30 days of receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator.

Adverse events classified as serious require expeditious handling and reporting to IRBs and designated IRB or ethics board policies should be followed.

Sponsor Reporting: Within 24 hours of becoming aware of a SAE, the investigator must file a MEDWatch Form FDA 3500A (www.fda.gov/medwatch/getforms.htm) to Novartis and MUSC Sponsor Investigator per the information below:

All serious adverse events must be reported within 24 hours to Novartis:
US CPO DS&E
Fax: (877)778-9739
If unable to fax: clinicalsafetyop.phuseh@novartis.com
Novartis study code: CPZP034BUS21T

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.

Copies of the submission to Novartis must also be submitted to the Medical University of South Carolina

ATTN: HCC CTN
Re: CTO #101644
Fax: 843-792-5123
Email: Anderton@musc.edu

The following items should be included at the time of forwarding the SAE notification to the HCC-CTN office.

- SAE cover sheet and case report form – within case report form packet
- Completed MedWatch Form FDA 3500A – available online at www.fda.gov/medwatch/getforms.htm
- Novartis fax confirmation of SAE submission
- IRB submission, if applicable per designated IRB policies
- Any de-identified supporting clinical documents serving as source document of the SAE as deemed important by the site or as requested by the coordinating center.

The site should receive confirmation from MUSC that the SAE report was received. If not, please contact the HCC CTN immediately.

12.4 Data and Safety Monitoring

The Principal Investigators will be responsible for monitoring the safety and efficacy of the trial, executing the DSM plan, and complying with all reporting requirements. This will be accomplished under the oversight of the Data Safety Monitoring Committee (DSMC) of the Hollings Cancer Center (HCC).

The HCC DSMC is responsible for monitoring data quality and patient safety for all interventional investigator-initiated trials (IIT's) at Hollings Cancer Center (HCC). The HCC DSMC will have oversight of this protocol. The HCC DSMC will meet at a minimum on an annual basis to discuss the investigator-initiated trial. Also, the IIT will be audited by the DSMC auditor or external agency (if within 6 months of the IIT's anniversary) at least once a year.

The DSMC reviews all IRB reportable serious adverse events, monitoring/ auditing reports, and protocol deviations and has the authority to recommend closure and/or suspension for trials on which there are safety or trial conduct issues and may submit recommendations for corrective actions. The DSMC recommendations for modifications to the trial (if requested) are forwarded to the principal investigator. The principal investigator is notified of this recommendation in order that he/she may alert all investigators involved in the trial with regard to the potential action. At this time the principal investigators may submit to the DSMC additional information that could affect the Committee's decision.

All IRB reportable serious adverse events, monitoring/ auditing reports will be reviewed by the HCC DSMC for review during the DSMC monthly meetings. The HCC CTN will forward the event report to the HCC DSMC so that the information can be reviewed at the next available DSMB meeting. During the DSMB review, the DSMB can make recommendations for any further study action. The HCC CTN will maintain a copy of the DSMB approval letters for each event review within this study's central file.

12.5 Data Collection

Electronic and hard copy CRF's will be provided for the recording of data. With the exception of hard copy case report forms utilized for expedited reporting requirements as described in section 12.3 Reporting of SAE's, the remainder of patient data will be collected and submitted via electronic CRFs. All data should be substantiated by clinical source documents organized within a patient research record. ICH Good Clinical Practices are to be followed.

During the course of the study, data quality will be monitored by random inspection of the completed forms by a designated monitor. Any problems detected will be discussed with the PI. If necessary, re-training of data collectors will be conducted.

The study will be subject to a yearly internal audit via the DSMC at a minimum and audits may occur more frequently at the request of the DSMC.

13 STATISTICAL CONSIDERATIONS

13.1 Primary Endpoint(s):

1. Progression-free survival, defined as the time from randomization until documented progression or death. For patients who are alive and progression-free upon discontinuing the study, their time to progression will be censored at the last clinic visit at which the patient was progression-free.
2. Grade 3 or higher toxicity, defined as the occurrence of any grade 3 or higher hematologic or non-hematologic toxicity, felt to be related to study treatment. Adverse events will be classified using CTCAE v4.0.

13.2 Secondary Endpoint(s):

1. Tumor response defined using RECIST v1.1. Patient will be considered to be a responder if s/he experiences a complete or partial response while on study.
2. Quality of life. Quality of life outcomes are the continuous scores from the EORTC QLQ-C30 and EQ-5D-3L).

13.3 Sample size justification

Sample size was derived based on the precision of 95% confidence intervals for reporting toxicity rates and median PFS in each arm. Hypothesis testing is not implemented due to the uncertainty in choosing a historical control PFS rate. With 45 patients per arm and assuming an observed toxicity rate of less than 30%, the maximum half-width of the 95% confidence interval is <14%. For PFS, the precision of the 95% confidence interval will depend heavily on the observed median PFS. With observed median PFS of 3, 6 or 8 months, the estimated half-widths of 95% confidence interval would be expected to be 1.4, 2.9, or 3.9 months, respectively, based on results from Kaplan-Meier curves and using Greenwood's formula for variance. These estimates would be considered sufficiently precise for determining whether or not the efficacy and safety profile warrant further exploration of G+P as combined therapy.

Statistical Analysis: PFS will be analyzed in each arm by generating Kaplan-Meier curves, and reporting the median PFS with their 95% confidence intervals. The proportion of patients in each arm with grade 3 or higher related toxicities will be reported with their 95% confidence intervals.

Early stopping for safety: To ensure safety of patients, we will stop an arm early if there is significant toxicity defined as an unacceptable rate of grade 3 or higher toxicity. Unacceptable toxicity is defined as any grade 3 or higher hematologic or non-hematologic toxicity (CTCAE v4.0) that is related to study treatment, with the following exceptions:

1. Lymphocytopenia and anemia
2. Grade 3 fatigue that persists for ≤ 7 days
3. Grade 3 or 4 nausea, anorexia, vomiting, stomatitis/mucositis or diarrhea, unless they persist despite maximum supportive care
4. Grade 4 neutropenia or thrombocytopenia unless it lasts for > 7 days, or is associated with a fever > 38.5 °C and grade > 1 bleeding, respectively
5. Grade 3 neutropenia or thrombocytopenia, unless it is associated with a fever >38.5°C and grade > 1 bleeding, respectively.

6. Elevated AST, ALT or bilirubin < 10 x ULN.

We would consider an acceptable level to be 15% (alternative hypothesis) and an unacceptable rate to be 30% (null hypothesis) of patients experiencing adverse events as defined above. We will use a sequential probability ratio test that allows stopping for strong evidence that the rate is 30% (vs. 15%). The safety monitoring is based on the sequential probability ratio test and the threshold is defined by a likelihood ratio value of 10 or greater in favor of the null. This procedure has a 74% chance of early stopping if the true rate of patients experiencing grade 3 or higher event as described above is 0.30 and only a 6% chance of early stopping if the true rate of patients experiencing grade 3 or higher event as described above is 0.15 and is based on the binomial log-likelihood.

Number of patients with SAE	Total number of patients treated	Point estimate of SAE rate	Likelihood Ratio favoring H_0 vs H_1
4	4-6	≥ 0.67	≥ 10.9
5	7-10	≥ 0.50	≥ 12.1
6	11-15	≥ 0.40	≥ 11.2
7	16-20	≥0.35	≥ 10.3
8	21-24	≥ 0.33	≥ 11.5
9	25-29	≥ 0.31	≥ 10.5
10	30-33	≥ 0.30	≥ 11.8
11	34-38	≥ 0.29	≥ 10.8
12	39-42	≥ 0.29	≥ 12.1
13	43-44	≥ 0.30	≥ 16.4

In the event of a death occurring during study treatment or within 30 days of the last dose of study treatment that is considered related or possibly related, the event must be reviewed by the HCC Data Safety Monitoring Board (DSMB) at the next available meeting. Please see section 14.1.3 for additional DSMB reporting detail.

13.4 Sample Size/Accrual Rate

Ninety patients will participate in this study with 45 patients on each arm. We expect overall accrual to be approximately 5 patients per month across all sites. Accrual should be completed in 18 months from start of study.

13.5 Stratification Factors

Since G+T has shown good activity in leiomyosarcoma patients, to ensure a balance in the treatment arms being compared, we will include stratified randomization. At the time of patient registration, we will request information regarding sarcoma type and prior pelvic radiation treatment. Because there is interest in the potential for differential response by sarcoma type and prior pelvic radiation treatment, the above analyses will be repeated within each subtype. However, we do not have a large enough sample size per type to estimate parameters with sufficient precision. As such, these will be considered exploratory and may yield results that are interesting and worth pursuing in a future study.

13.6 Analysis of Secondary Endpoints

The hazard ratio (HR) will be estimated between the two groups for planning of future studies of these treatment combinations. This will be done using Cox regression. With median PFS in the of G+P vs. G+T of 8 months vs. 6 months the estimated HR would be 0.75 and the expected 95% confidence interval range from 0.48 to 1.15. With median PFS in the of G+P vs. G+T of 6 months vs. 3 months, the estimated HR would be 0.50 and the expected 95% confidence interval range from 0.32 to 0.79. These correspond to half-widths for the 95% confidence intervals of 0.34 and 0.22 for these two scenarios.

Response rate per arm will be estimated with its 95% confidence interval. Overall survival will be described using Kaplan-Meier curves and median survival per arm with 95% confidence intervals. Comparative tests will not be performed. Toxicity profiles will be described by estimating the SAE rate per arm and tabulating toxicities per arm by type and grade. Quality of life measurements and markers of angiogenesis will be evaluated by estimating the difference from baseline to follow-up assessments. These changes will be displayed graphically per arm and summary statistics will be used to demonstrate average change from baseline. Biomarkers from serum will also be analyzed by performing Cox regression, predicting PFS using biomarker expression as a covariate in each arm. Graphical displays will be used to evaluate proportionality assumption of the proportional hazards model.

13.7 Reporting and Exclusions

Evaluation of toxicity. All patients, who were treated on one of the two treatment groups, will be evaluable for toxicity from the time of their first treatment on study.

Evaluation of response. All randomized patients (intention-to-treat population) will be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories:

1) complete response
2) partial response
3) stable disease
4) progressive disease
5) early death from malignant disease
6) early death from toxicity
7) early death because of other cause
8) unknown (not assessable, insufficient data)

[Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database.]

All of the patients who meet the eligibility criteria and are treated with study-directed therapy will be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

14 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

14.1 Monitoring and Regulatory Compliance

The Principal Investigator and the Clinical Research Coordinator assigned to the case will be primarily responsible for maintaining all study related documents including the clinical research forms. All CRF entries will be verified with source documentation. The review of medical records will be done in a manner to assure that patient confidentiality is maintained.

The Hollings Cancer Center Data Safety Monitoring Committee (HCC DSMC) will be reviewing all monitoring reports generated for the study.

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, Health Canada, any applicable local health authority, and Institutional Review Board (IRB) or Ethics Committee requirements.

This study must have the approval of a properly constituted IRB or Ethics Committee. Before the investigational drug is shipped to the Investigator, the Investigator or designee will provide Novartis with a copy of the IRB or Ethics Committee approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

The Investigator or designee will be responsible for obtaining annual IRB or Ethics Committee reapproval throughout the duration of the study. Copies of the Investigator's annual report to the IRB or Ethics Committee and copies of the IRB or Ethics Committee continuance of approval must be provided to Novartis.

The Investigator is also responsible for notifying their IRB or Ethics Committee of any significant adverse events that are serious and/or unexpected.

As received by Novartis, MUSC will provide study sites with any expedited safety reports generated from any ongoing studies with changes to the pazopanib Investigator's Brochure, and any other safety information which changes the risk/benefit profile of pazopanib during the conduct of the study, to allow him/her to fulfill his/her obligation for timely reporting to the IRB/ECs and other Investigators participating in the study. Upon completion of the trial, the Investigator must provide the IRB or Ethics Committee and Novartis with a summary of the trial's outcome.

14.2 Subsite Monitoring

The Medical University of South Carolina will be responsible for the monitoring of study patient data and records. Monitoring will be performed centrally. All monitoring reports will be kept by the Hollings Cancer Center (HCC) – Clinical Trials Network (CTN) to ensure that all reports are contained in a central study file. The HCC - CTN manager or HCC internal auditor will be responsible for conducting the review of monitoring packets. A final monitoring report will be generated and issued to the site and will be kept in the central study file by the CTN. The HCC CTN will be responsible for forwarding the final monitoring reports to the HCC Data Safety Monitoring Committee (DSMB) for review.

14.3 Frequency of Reviews

The first three patients at each participating center will have their eligibility criteria reviewed prior to enrollment by the CTN. Additional patients eligibility may be reviewed prior to enrollment at the discretion of the CTN.

During the course of the study, each site will be selected for an audit approximately once a year. The number of cases reviewed will be commensurate with the site's rate of enrollment. However, at a minimum, at least 10% of the patient cases enrolled at a participating center will be selected for random audit by the completion of the entire study period.

14.4 Data Safety Monitoring Board

The Hollings Cancer Center Data Safety Monitoring Board will have oversight of the protocol. The HCC DSMB will meet at a minimum on an annual basis to discuss the investigator-initiated trial. Also, the IIT will be audited by the DSMB auditor or external agency (if within 6 months of the IIT's anniversary) at least once a year.

In addition, all study deaths, protocol deviations and SAEs as defined above will be reviewed by the HCC DSMB for review during the DSMB monthly meetings. The coordinating center will review protocol deviation and SAE events for form completion and provide assistance in communicating to the subsite if more information is warranted. The HCC CTN will forward the event report to the HCC DSMB so that the information can be reviewed at the next available DSMB meeting. During the DSMB review, the DSMB can make recommendations for any further study action. The HCC CTN will maintain a copy of the DSMB approval letters for each event reviewed and will distribute to the subsite, if applicable.

14.5 Study Initiation Requirements

Participating study sites cannot begin enrollment until an initiation letter has been issued from the MUSC-Hollings Cancer Center. Each center is required to participate in an initiation conference call.

Before the start of this study and the shipment of study drug to a participating study site, the following documents must be on file at MUSC-Hollings Cancer Center. Participating sites will be responsible for forwarding the initiation documents to:

Hollings Cancer Center
ATTN: Clinical Trials Network
86 Jonathan Lucas Street, Suite 373
MSC 955
Charleston, SC 29425-9550

Documents can also be submitted via email to cogginca@musc.edu or via fax at (843) 792-5123. Please ensure that the fax cover page clearly identifies the site, study identifier and is addressed to ATTN: CTN.

These documents are required to be submitted by each participating center:

1. U.S. Food and Drug Administration (FDA) Form 1572, signed by the Principal Investigator at the participating center.
2. The names of any sub-investigators at the participating center must appear on this form. Investigators must also complete all regulatory documentation as required by local regulations. This includes any required human subjects training required by the site's local IRB.
3. Current curricula vitae and documentation of professional licensure of the Principal Investigator and co-Investigators listed on the 1572.
4. Resumes and human subject protections documentation (e.g. NIH, CITI) for all research personnel (e.g. study coordinators, data managers and other research personnel).
5. A signed and dated investigator brochure acceptance form.
6. Written documentation of IRB approval of protocol (identified by title, protocol version and date of approval) for each site.
7. IRB approved study informed consent and HIPAA consent form. HIPAA consent language can be included within the study informed consent. Please note that all informed consent forms should be reviewed and approved by the HCC Clinical Trials Network office prior to submission to the site's designated IRB.
8. A signed Confidentiality Agreement.
9. A signed Clinical Trial Agreement for each site.
10. Laboratory certifications (CAP, CLIAs) and laboratory reference value ranges for each laboratory listed on the site's 1572.
11. The Hollings Cancer Center Clinical Trials Network site specific forms as specified in the 101644 investigator-initiated multicenter manual.

14.6 Study Completion

The following data and materials are required by MUSC-Hollings Cancer Center and Novartis before a study can be considered complete or terminated:

1. Copies of protocol amendments and IRB approval/notification, if appropriate.
2. Copies of the IRB final report, documentation of submission to the IRB.
3. A summary of the study prepared by the Principal Investigator (Study report, manuscript and/or abstract).
4. All regulatory documents (e.g., updated curriculum vitae for each Principal Investigator, updated U.S. FDA Form 1572 for each site).

14.7 Protocol Modifications

No modifications will be made to the protocol without the agreement of the sponsor-investigator. Changes that significantly affect the safety of the patients, the scope of the investigation, or the scientific quality of the study will require Institutional Review Board approval prior to implementation, except where the modification is necessary to eliminate apparent immediate hazard to human subjects. Any departures from the protocol must be fully documented in the protocol deviation case report form and the source documentation.

14.8 Protocol Deviations and Safety Reporting

A Protocol Deviation is any variance from the protocol involving a subject or subjects that is not approved by the IRB prior to its initiation or implementation, and occurs when a member of the study team departs from the IRB-approved protocol in any way without the investigator first obtaining IRB approval.

Any protocol deviation or serious adverse event will be reported by the subsite within 10 days of notification. Protocol Deviations will be reported by completion of the hard copy Protocol Deviation Report form. Serious Adverse Events will be reported by completion of a MedWatch 3500A form and hard copy Serious Adverse Event form. For both Protocol Deviations and Serious Adverse Events, all required forms and any supporting clinical documentation should be submitted to the Clinical Trials Network office within 10 days of notification.

14.9 Patient Privacy

In order to maintain patient confidentiality, all case report forms, study reports and communications relating to the study will identify patients by initials and assigned patient numbers. The US Food and Drug Administration (FDA) may also request access to all study records, including source documentation for inspection.

Subject medical information obtained as part of this study is confidential, and must not be disclosed to third parties, except as noted below. The subject may request in writing that medical information be given to his/her personal physician.

The Investigator/Institution will permit direct access to source data and documents by Novartis, its designee, the FDA and/or other applicable regulatory authority. The access may consist of trial-related monitoring, audits, IRB or Ethics Committee reviews, and FDA inspections.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

14.10 Publication Policy

The Investigators plan to publish and present the information obtained from the study.

15 ETHICAL CONSIDERATIONS

15.1 Informed Consent

The investigator will obtain written informed consent from all participating patients or their authorized representatives. Obtaining informed consent must be done according to International Conference on Harmonization- Good Clinical Practice Guidelines (ICH GCP). Copies of the signed document will be given to the patient and filed in the Investigator's study file, as well as the patient's medical record if in conformance with the institution's Standard Operating Procedures.

15.2 Institutional Review Board

The trial will not be initiated without approval of the appropriate Institutional Review Board (IRB). All administrative requirements of the governing body of the institution will be fully complied with. This protocol, consent procedures, and any amendments must be approved by the IRB in compliance with current regulations of the Food and Drug Administration. A letter of approval will be sent to the institution(s) funding the study prior to initiation of the study and when any subsequent modifications are made. The IRB will be kept informed by the Investigator as to the progress of the study as well as to any serious or unusual adverse events.

16 DATA HANDLING AND RECORD KEEPING

16.1 Data recording and quality control

The Clinical Research Coordinator and Investigator will be responsible for the recording of all data on the Case Report Forms (CRF's).

The Investigator will provide access to his/her original records to permit a representative from the funding or auditing institution(s) to verify the proper transcription of data. Data submission will be electronically via the REDCap database.

16.2 Record retention

Federal law requires that an Investigator maintain all study records for two years after the investigation is discontinued.

17 DATA COLLECTION

Data will be reported by electronic case report forms in the REDCap database. REDCap is an electronic data capture system. All data should be substantiated by clinical source documents organized within a patient research record. ICH Good Clinical Practices are to be followed.

During the course of the study, data quality will be monitored by random inspection of the completed forms by a designated monitor. Any problems detected will be discussed with the PI. If necessary, re-training of data collectors will be conducted.

The study will be subject to a yearly internal audit via the DSMC at a minimum and audits may occur more frequently at the request of the DSMC.

18 RECRUITMENT PROCEDURE

All patients referred to or seeking treatment for advanced stage soft tissue sarcoma (excluding GIST and liposarcoma) will be offered this trial.

Women and men will be recruited, and are anticipated to be equally represented in the trial.

Persons equal to or over the age of 18 are eligible for trial participation if they have a performance status of 0-2, thus by NIH criteria, children are eligible for trial participation. However, the median age of persons with soft tissue sarcoma is 41 years, and the vast majority of participants will be above the age of 21.

Minority participation will be especially encouraged. About 26% of patients seeking their care at MUSC are African American.

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APPENDIX A: Performance Status Criteria

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints.
1	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).	90	Able to carry on normal activities; minor signs or symptoms of disease.
		80	Normal activity with effort
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	70	Cares for self; unable to carry on normal activity or to do active work.
		60	Requires occasional assistance but is able to care for most of his/her needs.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	50	Requires considerable assistance and frequent medical care.
		40	Disabled, requires special care and assistance.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	30	Severely disabled, hospitalization indicated. Death not imminent.
		20	Very sick, hospitalization indicated. Active supportive treatment necessary.
		10	Moribund.
5	Dead.	0	Dead.

http://oncologypro.esmo.org/Guidelines-Practice/Practice-Tools/Performance-Scales

APPENDIX B: Determination of Creatinine Clearance (ClCR)

Estimation of creatinine clearance using Cockroft and Gault method:

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

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

For SI units:

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

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:

12 $Cl_{CR} = \frac{C_U \cdot V}{C_{CR}}$

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

APPENDIX C: Urine Protein Creatinine Ratio (UPC)

Clinical meaning of UPC

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

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

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

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

Calculating UPC

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

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

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

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

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

Units for UPC ratio

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

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

References:

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APPENDIX D: New York Heart Association (NYHA) Classification of Congestive heart failure

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

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

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

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

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

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

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

Management Guidelines
Uncomplicated diarrhea of CTCAE Grade 1 or 2:

- Hydration: have subject drink 8 to 10 large glasses (approximately 2 liters) of clear non-caffeinated liquids a day (e.g., broth or electrolyte-containing sports drinks).
- If Grade 2 diarrhea, consider dose reduction of investigational products.
- Dietary modifications: have subject stop all lactose-containing products and eat frequent, small meals
- Pharmacologic intervention using loperamide:

- Begin loperamide at initial dose of 4 mg followed by 2 mg every 4 hours or after every unformed stool. The recommended maximum daily dose of loperamide is 16 mg/day.
- Continuation of loperamide is suggested until diarrhea-free for 12 hours.
- If mild to moderate diarrhea persists for more than 24 hours, administer loperamide 2 mg every 2 hours and pursue evaluation for other treatable causes.
- If mild to moderate diarrhea persists after 48 hours total treatment with loperamide, discontinue study drug(s) and consider initiation of second-line agents (lomotil, octreotide).

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

- Subject must call study site physician immediately in response to any event of severe diarrhea with or without complications as listed above.
- Hospitalization may be required for subjects most at risk for life-threatening complications.
- Interrupt investigational products until symptoms resolve; consider reintroducing at a reduced dose (discuss with Sponsor-Investigator).
- If loperamide has not been initiated, begin loperamide usage immediately at an initial dose of 4 mg followed by 2 mg every 2 hours or after every unformed stool. The recommended maximum daily dose of loperamide is 16 mg/day.
- If no improvement in severity after 24-hours of maximal loperamide dosing, subject must visit study site and be evaluated:
- For dehydration, use intravenous fluids as appropriate.
- Antibiotic therapy should be considered in patients, who present with signs and symptoms of bacterial diarrhea such as fever, bloody diarrhea, and presence of fecal leukocytes. Investigators should have a low threshold to start such treatment in patients with Grade 3 or Grade 4 neutropenia.
- Before initiation of antimicrobial therapy, stool cultures should be obtained. When bacterial etiology for diarrhea is suspected, study-treatment and anti-motility agents (loperamide or others) should be held.
- Intervention 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 fluoropyrimidine-based chemotherapy regimens when administered as an escalating dose by continuous infusion or subcutaneous injection. Octreotide can be administered per the current package insert and institutional guidelines.

Nausea and Vomiting

Every attempt should be made to control nausea and vomiting in subjects who have emesis and are

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

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

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

APPENDIX F : Management of acute hypersensitivity

The table below outlines the required dose modifications for these events. Also included are suggested treatment guidelines; however sites may follow their institutional standards for the treatment of hypersensitivity.

Severity of Symptoms	Treatment Guidelines
Mild symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash	Consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient. Then, complete infusion at the slowed rate.
Moderate symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mm Hg	Interrupt infusion. Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor patient until resolution of symptoms. Resume chemotherapy infusion after recovery of symptoms; depending on the physician's assessment of the patient. Chemotherapy infusion should be resumed at a slower rate, then, increased incrementally to the initial planned rate, (i.e., infuse at an 8-hr rate for 5 minutes, then at a 4-hr rate for 5 minutes, then at a 2-hr rate for 5 minutes, then finally, resume at the 1-hr infusion rate). Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the next cycle of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hr infusion, (i.e., infuse at an 8-hr rate for 5 minutes, then at a 4-hr rate for 5 minutes, then at a 2-hr rate for 5 minutes, and finally, administer at the 1-hr infusion rate).
Severe symptoms: any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80mm Hg, angioedema	Immediately discontinue infusion. Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor patient until resolution of symptoms. The same treatment guidelines outlined under moderate symptoms (i.e., the third and fourth bullets) should be followed.
Anaphylaxis: (grade 4 reaction)	NO FURTHER STUDY DRUG THERAPY

APPENDIX G: Management of edema/fluid retention

No dose reduction is required. Patients developing new onset edema, progression of existing edema, or another sign of fluid retention (i.e., 2 pound weight gain) are to be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to docetaxel are listed below.

Diazide (or generic equivalent) one capsule po qd up to tid.

Furosemide 40 mg po daily if edema progresses despite Diazide (or equivalent) therapy. Potassium supplementation should be given as needed.

Furosemide 20 mg po daily plus metolazone 2.5 mg po daily may be needed if, after a two-week trial, furosemide 40 mg po qd is ineffective. The patient may be treated with potassium supplementation as needed.

Further therapy should be customized depending upon the clinical situation. The clinical tolerance of the patient, the overall tumor response and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment.

APPENDIX H: Management of hyperlacrimation

The excessive lacrimation (epiphora) seen in some patients receiving weekly docetaxel appears to be related to cumulative dose (median~300 mg/m2) and resolves rapidly after treatment cessation.

Excessive lacrimation seems to be the result of a chemical conjunctivitis and/or chemical inflammation (with edema) of the lacrimal duct epithelium (producing a reversible lacrimal duct stenosis). Consequently, investigators in clinical trials have treated such patients with (a) artificial tears and/or (b) saline eye wash and/or (c) steroid based eye drops.

It is suggested that the following approach be taken to patients experiencing clinically significant hyperlacrimation:

Grade	Dose
0 - 2	100
3 - 4	Reduce by 1 dose level
	Recommend patient see an ophthalmologist.

Dose modifications will be permanent. Only one dose reduction per patient is allowed for all toxicities.

APPENDIX I: THE QLQ-C30 VERSION 3.0

PT STUDY NUMBER: 101644 - __ __ __ __ __ - __ __

DATE COMPLETED (MM/DD/YYY):_____

WE ARE INTERESTED IN SOME THINGS ABOUT YOU AND YOUR HEALTH. PLEASE ANSWER ALL OF THE QUESTIONS YOURSELF BY CIRCLING THE NUMBER THAT BEST APPLIES TO YOU. THERE ARE NO "RIGHT" OR "WRONG" ANSWERS. THE INFORMATION THAT YOU PROVIDE WILL REMAIN STRICTLY CONFIDENTIAL.

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a **long** walk?	1	2	3	4
3. Do you have any trouble take a **short** walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at all	A little	Quite a bit	Very much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with you daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your **family** life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your **social** activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

FOR THE FOLLOWING QUESTIONS PLEASE CIRCLE THE NUMBER BETWEEN 1 AND 7 THAT BEST APPLIES TO YOU

29. How would you rate your overall **health** during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall **quality of life** during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

APPENDIX J: EQ-5D questionnaire

PT STUDY NUMBER: 101644 - __ __ __ __ __ - __ __

DATE COMPLETED (MM/DD/YYY):_____

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today