A RANDOMIZED OPEN LABEL PHASE II STUDY OF WEEKLY GEMCITABINE PLUS PAZOPANIB VERSUS WEEKLY GEMCITABINE ALONE IN THE TREATMENT OF PATIENTS WITH PERSISTENT OR RELAPSED EPITHELIAL OVARIAN, FALLOPIAN TUBE OR PRIMARY PERITONEAL CARCINOMA

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IND Information: Exempt

Toxicity Grading: CTCAE v 4.0 will be utilized for this study.

NCT: NCT01610206

SCHEMA: Randomized open-label Phase II design

Regimen 1: Gemcitabine 1000 mg/m^2 administered weekly on days 1 and 8 (30-60 minutes IV infusion)

Regimen 2: Gemcitabine 1000 mg/m^2 administered weekly on days 1 and 8 (30-60 minutes IV infusion) with Pazopanib 800mg PO daily days 1-21

Until disease progression or adverse effects prohibit further therapy
Maximum body surface area used for dose calculations will be 2.0 mg/m^2
One cycle = 21 days

Patients will be stratified according to their second line platinum-free interval PFI (those with a PFI less than or equal to 182 days versus those with PFI greater than 182 days) and number of previous chemotherapy regimens (one *vs* two or more). PFI will be measured from the last ***day*** the platinum therapy was given to time of documented progression ***unless*** a subject does not achieve a Complete Response after first line platinum treatment then the subject is considered platinum resistant regardless of the PFI.

No biologic therapies aimed at treating the study cancer will be allowed while the patient is on study.

TABLE OF CONTENTS

		PAGE
1.0	OBJECTIVES	4
2.0	BACKGROUND AND RATIONALE	4
3.0	PATIENT ELIGIBILITY	14
4.0	STUDY MODALITIES	20
5.0	TREATMENT PLAN AND ENTRY PROCEDURE	27
6.0	TREATMENT MODIFICATIONS	32
7.0	STUDY PARAMETERS & SERIAL OBSERVATIONS	35
8.0	EVALUATION CRITERIA	36
9.0	DURATION OF STUDY	45
10.0	STUDY MONITORING & REPORTING PROCEDURE	45
11.0	DATA SAFETY AND MONITORING PLAN	51
12.0	STUDY MANAGEMENT	51
13.0	STATISTICAL CONSIDERATIONS	54
14.0	BIBLIOGRAPHY	58

APPENDIX I	-	New York Heart Association (NYHA) classification
APPENDIX II	-	Medications that may cause QTc Prolongation
APPENDIX II	-	Recommended Dose Modifications for pazopanib
APPENDIX IV	-	GOG General Chemotherapy Guidelines

1.0 OBJECTIVES

1.1 Primary Objectives:

1.11 To estimate the progression-free survival hazard ratio of the combination of weekly gemcitabine and pazopanib compared to weekly gemcitabine alone in patients with persistent or recurrent ovarian, fallopian tube, or primary peritoneal cancer

1.2 Secondary Objectives:

1.21 To determine the frequency and severity of adverse events as assessed by CTCAE v 4.0.

1.22 To obtain preliminary estimates of overall survival (OS), time to progression (TTP) and the duration of response in this patient population; and to estimate the respective hazard ratios of the combination to gemcitabine alone.

2.0 BACKGROUND AND RATIONALE

2.1 Ovarian Cancer

Ovarian cancer is the leading cause of gynecologic cancer deaths, and the fifth most common cause of cancer deaths in women. An estimated 15,460 women will die of ovarian cancer in 2011.[1] While approximately 75% of patients with epithelial ovarian cancer will respond to first-line chemotherapy with platinum and paclitaxel, most patients with advanced stage epithelial ovarian cancer will experience disease recurrence. While there are several active cytotoxic agents for the treatment of recurrent epithelial ovarian cancer, median survival after recurrence is about 2 years.[2] Therefore, there is a need for developing and testing novel agents in this population.

Novel agents are needed in both platinum sensitive and platinum resistant ovarian cancer, though response rates in the setting of platinum sensitive disease tend to be higher. In particular, there is a need to develop new agents and combinations in patients with platinum resistant or refractory ovarian cancer. The disease free interval from last platinum treatment is significant in predicting subsequent response to chemotherapy. Patients who experience recurrence greater than 6 months from last prior platinum are considered "platinum sensitive" and have a 50-60% response rate to second-line chemotherapy, while patients whose disease free interval is less than 6 months (platinum resistant) or who progress during primary therapy (platinum refractory) have a much lower response rate of 20-30% and 10% respectively.[3] It is in this platinum resistant/refractory group that novel compounds and combinations are most needed.

2.2 Pazopanib

Pazopanib is a potent and selective, orally bioavailable, adenosine triphosphate competitive, small molecule inhibitor of vascular endothelial growth factor receptor (VEGFR)-1, -2, and -3, platelet-derived growth factor receptor (PDGFR)-α, -β, and c-KIT tyrosine kinases (TKs) (Investigator's Brochure). In human umbilical vein endothelial cells (HUVECs), pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation and was 3- to 400-fold selective for VEGFRs compared to 23 other kinases tested. Pazopanib showed significant growth inhibition of a variety of human tumor xenografts in mice, and also inhibited angiogenesis in several different models of angiogenesis. Because angiogenesis is necessary for the growth and metastasis of solid

tumors, and VEGF is believed to have a pivotal role in this process, pazopanib treatment may have broad-spectrum clinical utility.

Mechanism of Action

Pazopanib inhibits VEGFR-1, -2, and -3 with concentrations causing 50% inhibition (IC_{50}) values of 10, 30, and 47 nM, respectively, and inhibits PDGFR-α, -β, and c-KIT with IC_{50} values of 71, 84, and 74 nM, respectively (Investigator's Brochure).[4,5]

In addition to their direct role in tumor cell growth and survival, several of the split-kinase domain RTKs, most notably VEGFR and PDGFR-β, play prominent roles in tumor neoangiogenesis.[6,7] Reported data suggest that combined pharmacologic disruption of PDGFR-β and VEGFR-2 signaling results in profound antiangiogenic effects in tumors.[8] Hence, although the pathogenesis of solid tumors and hematologic malignancies is complex, there is good rationale that inhibition of split-kinase domain RTK targets may result in direct effects against cancer cells expressing them.

Nonclinical Efficacy

Pazopanib selectively inhibited the proliferation of HUVECs stimulated with VEGF (IC_{50}=21 nM) compared to basic fibroblast growth factor (bFGF) (IC_{50}=721 nM). In a cell proliferation assay using a panel of 282 human tumor cell lines, pazopanib inhibited the proliferation of only 7 cell lines (IC_{50}<1000 nM), suggesting that pazopanib is a weak inhibitor of proliferation in the majority of human cell lines tested *in vitro*. Pazopanib also showed weak inhibitory activity in the colony forming unit assay induced by granulocyte-macrophage colony stimulating factor (GM-CSF) and Flt-3 ligand alone. However, the inhibition by pazopanib was enhanced by the addition of stem cell factor (a ligand for c-KIT), consistent with its activity against c-KIT kinase.

Inhibition of VEGFR-2 phosphorylation was studied in naive mice given an IV bolus administration of VEGF. The lungs of VEGF-treated mice showed increased phosphorylation of VEGF-2 compared to untreated control mice. Pre-treatment of mice with a single oral dose of pazopanib inhibited VEGF-induced VEGFR-2 phosphorylation in lungs in a dose- and time-dependent manner. The results from these studies suggest that plasma concentrations of ~40 mcM or higher are required for the optimal inhibition of VEGFR-2 phosphorylation in mice. This concentration is also consistent with the antiangiogenic and antitumor effects seen in mouse exposure studies. Pazopanib given orally at ≥30 mg/kg inhibited bFGF and VEGF-induced angiogenesis in a variety of animal models including the Matrigel plug and corneal micropocket models in Swiss nu/nu or C57B1/6 mice. Pazopanib also showed generally dose-dependent inhibition of aberrant ocular angiogenesis in laser-induced choroidal neovascularization in C57B1/6J mice (≥8 mg/kg orally) and Brown Norway rats (2.25 mg/kg, eye drops) as well as corneal neovascularization in a suture-induced model in New Zealand white rabbits (≥0.3 mg/kg, eye drops).

Pazopanib has been evaluated in human tumor xenograft models in mice as a single agent as well as in combination with other TK inhibitors and with various chemotherapeutic agents. The combination with lapatinib (an EGFR/ErbB2 TK inhibitor) showed a modest increase in tumor growth inhibition of both BT474 and in NCI-H322 tumor xenografts in SCID mice compared to either agent alone; however, the differences were not statistically significant. Pazopanib has also been evaluated in

combination with various other chemotherapeutic agents (e.g., topotecan, irinotecan, 5-fluorouracil, oxaliplatin, or docetaxel) against HT29 tumor xenografts. The effect of any of the combinations on tumor growth was not significantly different from that of either agent alone.

The combination of pazopanib with AKT and B-Raf kinase inhibitors was evaluated in human colon, ovarian, and renal xenografts in mice. There was no increase in tumor growth inhibition in colon and renal xenografts with the combination as compared to the best single agent. However, an increased inhibition was seen in the ovarian carcinoma model at the highest dose of both compounds in combination compared to either agent alone. Pazopanib in combination with a B-raf inhibitor, SB-590885, in mutant B-raf ^{V600E} xenografts showed a modest increase in tumor inhibition with the combination compared to either agent alone. The combination of pazopanib and bevacizumab was studied in human colon tumor xenografts: RKO, SW620, and HT29. A modest increase in tumor inhibition was observed with the combination compared to either agent alone, suggesting a potential benefit of combining the two agents. In human ovarian cancer cells as well as in OVCAR-3 mice xenografts, pazopanib compared to paclitaxel exerted different effects on the expression and secretion of CA-125 and was not always associated with changes in tumor burden, suggesting cautious use of CA-125 as an independent marker of antitumor activity of pazopanib in clinical studies.

Nonclinical Pharmacology and Toxicology

In safety pharmacology studies, there were no pazopanib-related central and peripheral nervous system, respiratory, or cardiovascular effects in rats or monkeys given single oral doses of up to 300 mg/kg and 500 mg/kg. However, following a single IV dose of 3.75 mg/kg to monkeys, a mild, reversible decrease in heart rate was observed with no effects on arterial pressures, body temperature, or ECG waveform changes. At the limit of pazopanib solubility for *in vitro* assays, there was minimal (~19%) inhibition of hERG tail current repolarization and no treatment-related effects on isolated dog Purkinje fibers. The toxicity profile of pazopanib has been defined in single-dose studies in rats and dogs and repeat dose studies in mice (13 weeks), rats (26 weeks), and monkeys (52 weeks). The principal nonclinical toxicities are believed to be directly associated with VEGFR-2 inhibition and include effects on bone and bone marrow, incisor teeth, ovary, kidney, pancreas, nails, testes, adrenal, pituitary, trachea, hematologic tissues, salivary glands, and developing embryo/fetus. The onset of these effects varied with dose and systemic exposure with the earliest onset seen after 4 days of dosing in the rat. Neither rats nor monkeys tolerated oral doses in the range of 300-500 mg/kg/day for >4 weeks, both experiencing severe weight loss and morbidity. Hepatic effects have also been noted occasionally in rodents.

Nonclinical reproductive toxicology studies indicate reduced female fertility, fetal teratogenic effects, and reduced fetal body weight in pregnant rats and/or rabbits given pazopanib. In rats, pazopanib caused a reduction in the number of stage I-V round spermatids at ≥300 mg/kg/day, resulted in female reproductive tract target organs effects at 300 mg/kg/day, and caused early embryo resorptions. The agent was found to be non-mutagenic and non-clastogenic in a range of genetic toxicity tests.

Nonclinical Pharmacokinetics and Drug Metabolism

Mean bioavailability ranged from 47% in dogs to 72% in rats. There was a 4- to 5-fold decrease in exposure in fed compared to fasting dogs, but in monkeys the exposure did not change substantially on feeding. Pazopanib is highly (>98.8%) plasma protein bound in mouse, rat, dog, monkey, and human plasma. *In vitro* data indicate that pazopanib is highly permeable across membranes and is a substrate for the P-glycoprotein (P-gp) transporter and breast cancer resistant protein (BCRP). Following oral administration of radiolabeled pazopanib, excretion of drug-related material was rapid and essentially complete. Circulating metabolites observed in humans were minor and were also noted in the nonclinical species. Metabolism appeared to be predominantly mediated by CYP3A4 and to a lesser extent by CYP1A2 and CYP2C8. The majority of the dose was excreted via feces in humans, rats, and monkeys.

Clinical Experience

Over 6000 subjects with cancer have been enrolled in clinical studies of pazopanib as of September 2011. In October 2009, the FDA approved pazopanib tablets for the treatment of subjects with advanced renal cell carcinoma (RCC). In addition, several clinical studies evaluating pazopanib in non-small cell lung cancer (NSCLC), ovarian cancer, breast cancer, soft tissue sarcoma (STS), carcinosarcoma of the uterus, cervical cancer, hepatocellular cancer (HCC), multiple myeloma (MM), and glioma are in progress or have been completed.

Clinical Efficacy

In a randomized, double-blind, placebo-controlled phase 3 study evaluating the efficacy and safety of pazopanib monotherapy in treatment-naive and cytokine-pretreated subjects with advanced RCC, the median progression-free-survival (PFS) was significantly prolonged with pazopanib compared with placebo in the overall study population (9.2 vs. 4.2 months). The objective response rate (RR) was 30% with pazopanib and only 3% with placebo.[9] In subjects with ovarian cancer, 31% of subjects experienced a CA-125 response to pazopanib, with a median time to response of 29 days and median duration of response of 113 days (Investigator's Brochure).[10] Median PFS was 84 days and the overall RR was 18%. In advanced or metastatic STS, the rate of PFS at 12 weeks was 43.9% for leiomyosarcoma, 48.6% for synovial sarcoma, 26.3% for adipocytic sarcoma, and 39% for other types of sarcoma.[11] In a phase 2 trial of subjects with early-stage NSCLC, 86% of subjects experienced a reduction in tumor volume after short-term, preoperative use of pazopanib (~2-6 weeks) as assessed by high-resolution CT scanning.[12] Interim results from a phase 2 study of pazopanib in subjects with recurrent or metastatic breast invasive breast cancer showed that the clinical benefit rate was 26%.[13] The median TTP was 3.7 months, and 50% of subjects with measurable target lesions had some decrease in size. PFS at 3 and 6 months was 55% and 28%, respectively. Preliminary results from a randomized study in subjects with first-line advanced ErbB2-positive advanced or metastatic breast cancer showed that a higher response rate (36.2% vs. 22.2%) was observed in subjects on combination lapatinib 1000 mg once daily + pazopanib 400 mg once daily compared to monotherapy lapatinib 1500 mg once daily.[14] In a randomized phase 2 study of pazopanib vs. lapatinib vs. the combination of pazopanib/lapatinib in advanced and recurrent cervical cancer, there was a 34% reduction in risk for progression in subjects receiving pazopanib relative to lapatinib. The median PFS was 17.1 weeks in the lapatinib group and 18.1 weeks in the pazopanib group.[15] Interim analysis of data from 26 subjects showed that pazopanib has both a favorable toxicity profile and promising clinical

activity in subjects with advanced and progressive differentiated thyroid cancers.[16] Five confirmed partial responses (PRs) (19%) were reported. Pazopanib has not shown efficacy in phase 2 studies conducted in MM or glioma (Investigator's Brochure)

Safety

The randomized, phase 3 study in RCC subjects provided a key comparison of safety with pazopanib compared to placebo.[9] The overall frequency of adverse events (AEs) reported during the study was higher in the pazopanib arm (92%) compared with placebo (74%). The most common AEs reported in >20% of subjects in the pazopanib arm were diarrhea (52%), hypertension (40%), hair color change (depigmentation; 38%), nausea (26%), anorexia (22%), and vomiting (21%). Most of the events were grade 1 or 2. A higher number of grade 3 AEs were reported in the pazopanib arm (33%) compared with the placebo arm (14%). The most frequent grade 3 AEs in the pazopanib arm were increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), hypertension, and diarrhea. The frequency of grade 4 and grade 5 AEs was similar between the pazopanib and placebo arms: grade 4 in 7% and 6%, respectively; grade 5 in 4% and 3%, respectively.

A comprehensive review of all completed and ongoing pazopanib clinical trials with a cut-off date of September 2009, lists 15 most commonly occurring serious AEs (SAEs) (Investigator's Brochure). Vomiting and diarrhea are the most commonly reported SAEs across all the pazopanib studies. As a consequence of this, dehydration is also seen with pazopanib treatment. For most reports, the AEs resolved after supportive treatment such as antiemetics, antidiarrheal agents, and IV fluids. GI perforation is commonly associated with VEGF pathway inhibitors. This may manifest as abdominal pain which is not uncommon in cancer subjects for many reasons. Of the 42 subjects in pazopanib trials with SAEs of abdominal pain, only three had a documented underlying intestinal perforation. In July 2006, the DCTD, NCI, issued an Action Letter to investigators using pazopanib describing the occurrence of bowel perforations in subjects on pazopanib clinical trials.

Dyspnea is also frequently seen in pazopanib-treated subjects and may reflect the underlying disease under treatment. Anemia is commonly seen in cancer subjects in association with chemotherapy, hemorrhage, or infection. The SAEs of pyrexia were attributed to multiple causes: concurrent infections, the underlying malignancy, hepatic events, other concomitant medications, and unknown causes. Hepatic events are thought to be on-target tyrosine kinase inhibitor (TKI) class effects, as hepatic enzyme elevations have been seen with other agents of this class. Careful clinical evaluation is, therefore, warranted in subjects with hepatic abnormalities. Pneumonia can be a complication of chemotherapy or can result from debilitation and advanced disease. Review of the 33 SAEs showed the presence of an underlying cause other than pazopanib in 19 of the 30 subjects. Fatigue and asthenia are commonly reported and have multiple causes.

Hypertension observed with pazopanib is a known class effect. There have been 30 SAEs of hypertension and 3 SAEs of hypertensive crisis in pazopanib clinical trials. There were 28 subjects who were effectively treated with antihypertensive medication initiation or dose adjustment, while 4 had no such treatment. Although there were 29 SAEs of pleural effusion, the body of data does not suggest that any of these cases were

due to pazopanib. There have been 24 SAEs of pulmonary embolism (PE) reported in pazopanib trials. This is of particular relevance since other members of this class have been associated with PE and other venous thromboembolic events.

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

Clinical Pharmacokinetics

The oral bioavailability of pazopanib reflects absorption that is limited by solubility above doses of 800 mg once daily (Investigator's Brochure).[17] Increases in doses above 800 mg to 2000 mg in the fasted state will not result in increased systemic exposure. Geometric mean pazopanib $t_{½}$ values ranged from 18.1-52.3 hours. The mean $t_{½}$ was 30.9 hours in the 800 mg once daily group, in phase 2 and 3 trials. Oral absorption is significantly enhanced when dosed with food; therefore, it is recommended to administer pazopanib on an empty stomach, at least 1-2 hours after a meal.

Preliminary information on the pharmacokinetics (PK) of pazopanib administered in combination with lapatinib has been reported.[18] Thirty-three subjects received doses of lapatinib ranging from 750-1500 mg once daily along with pazopanib at doses of 200-500 mg daily. Preliminary mean plasma concentrations 24 hours after administration (C_{24}) on day 22 were ~19 mcg/mL and 23 mcg/mL after pazopanib doses of 250 mg and 500 mg, respectively. These values are similar to the mean C_{24} values observed after administration of 800 mg pazopanib alone (23.1 mcg/mL). Plasma lapatinib concentrations at 750-1500 mg daily were similar to those observed after monotherapy. Concurrent administration of pazopanib and lapatinib was generally well tolerated; coadministration of lapatinib may alter the PK of pazopanib.[18]

Preliminary PK information on the combination of pazopanib and paclitaxel administered to subjects with advanced cancer has been reported.[19] Twelve subjects received paclitaxel (15-80 mg/m^2 on days 1, 8, and 15 every 28 days) and pazopanib at 400 or 800 mg/day starting on day 2 of the first cycle. Coadministration of pazopanib increased paclitaxel mean C_{max} and AUC_{0-8} approximately 20-35%.[19]

Age, body weight, gender, and race had no significant influence on pazopanib PK.

Potential Drug Interactions

Pazopanib is metabolized primarily by CYP3A4, and systemic exposure to pazopanib is altered by inhibitors and inducers of this enzyme. The concomitant use of strong CYP3A4 inhibitors should be avoided. If co-administration of a strong CYP3A4 inhibitor is warranted, a dose reduction to 400 mg is recommended. Grapefruit may also increase plasma concentrations of pazopanib and should be avoided. CYP3A4 inducers such as rifampicin may decrease plasma concentrations; therefore, an alternative concurrent medication with none or minimal enzyme induction should be used. Concomitant use of medications that have narrow therapeutic windows and that are substrates of CYP3A4, CYP2D6 or CYP2C8 should occur only with caution.

Concomitant medications that have narrow therapeutic windows ***and*** are substrates of CYP3A4, CYP2D6 or CYP2C8 should be used with caution. If possible, medications

that are not substrates for these enzymes and/or do not have narrow therapeutic windows should be substituted.

Dose Selection

Pharmacodynamic data indicate that pazopanib, at a monotherapy dose of 800 mg once daily, results in effects consistent with inhibition of the VEGF receptors and angiogenic factors (Investigator's Brochure). Concentration-effect relationships were observed between trough plasma pazopanib concentrations and the development of hypertension as well as the percent change from baseline to the nadir of soluble VEGFR2 (sVEGFR2), a marker of VEGFR inhibition. Decreases in sVEGFR2 have been correlated with increased clinical benefit in RCC with other small molecule TKIs.[20] The trough plasma pazopanib concentrations associated with the EC_{50} in both concentration-effect relationships were similar (15.3 mcg/mL for hypertension and 21.3 mcg/mL for sVEGFR2). Pazopanib monotherapy has been approved as an 800 mg once daily dose for the treatment of advanced RCC in the US. In a phase 1 dose-finding study in subjects with HCC, the maximum tolerated dose (MTD) for single-agent pazopanib in subjects was determined to be 600 mg once daily (Investigator's Brochure). The 800 mg once daily dose was not well tolerated resulting in 40% of subjects experiencing dose-limiting toxicities (DLTs). No DLTs were observed at 600 mg once daily among the six subjects enrolled in the dose-escalation phase. However, in the cohort expansion phase at 600 mg, one subject had a grade 4 GI hemorrhage and grade 4 transaminase increases.

2.3 Rationale for the use of pazopanib in ovarian, peritoneal and tubal cancers

Angiogenesis targeting and Pericyte targeting

Currently, the GOG (in concert with CTEP and/or the pharmaceutical companies) is running several single arm phase II biologic agent trials in the 170-queue. To date, clinical activity has been reported in seven. One of these agents has demonstrated clinical activity considered significant for further clinical development, bevacizumab (GOG-0170D).[21] It is not a surprise that agents targeting the processes of angiogenesis would be of some importance in this disease, which has been documented both pre-clinically and clinically to be vulnerable to inhibition of VEGF and/or its receptors and be associated prognostically with fluctuating levels of pVEGF. Multiple reports have shown that angiogenesis, as measured by microvessel density, is associated with worse survival for ovarian cancer patients.[22-26] Bevacizumab is already in front-line and recurrent phase III investigation, and has been shown to increase the progression-free survival by 3.8 months in the upfront setting. Burger et al. demonstrated a 21% response rate with a median response duration of 10 months for patients with recurrent epithelial ovarian cancer treated with single agent bevacizumab.[21] Nevertheless, new agents are vitally necessary, specifically those that may offer clinical response in women previously exposed to VEGF targeted therapy by targeting other factors in the tumor microenvironment, such as pericytes and stromal growth factors.

Pericyte homeostasis has been demonstrated to be an important factor in maintaining normal and maturing vasculature.[27] This homeostasis is controlled by a ligand-receptor system, which is amplified in many human tumor cells and pericytes and leads to bizarre morphology and dysfunction of these supporting vascular cells. Pericytes have also been implicated in protecting endothelial cells from the effects of anti-VEGF therapy.[28] Unfortunately, targeting just the pericyte with PDGF inhibitors has led to

little or no effect on tumor growth, and in some clinical trials has led to undesirable toxicities, such as fluid accumulation – largely explained by the reversion of a more immature vascular phenotype devoid of pericytes.[29] Nevertheless, it has been hypothesized that dual targeting of VEGF and PDGF would lead to enhanced anti-angiogenesis therapy. Preclinical models using specific agents (fusion proteins against VEGF and PDGF) or multi-targeted (SU6668) agents have supported this effect in various tumor models.[27,28] Another study reported efficacy in controlling malignant ascites from ovarian cancers in a murine model.[30] Clinically, trials are ongoing in ovarian cancer with agents targeting VEGFR and PDGFR. Recently, a phase II trial of sunitinib demonstrated a response rate of 13%- 1 partial response and 3 CA125 responses.[31] In addition, a phase II study of sorafenib, a multi-targeted receptor kinase inhibitor, including VEGFR and PDGFR in combination with gemcitabine demonstrated an objective response rate of 4%, and a CA125 response of 28%. 23% of patients were progression free for at least 6 months.[32] Sorafenib also demonstrated modest single-agent activity, with substantial toxicity, in GOG 170F where 69 patients were enrolled.[33] PRs were observed in 3% of measurable patients and nearly 24% were non-progressive at 6 months.

As mentioned previously, pazopanib is a potent angiogenic small molecular inhibitor of the tyrosine kinases VEGRF-1, -2, -3, PDGFR, and c-kit which has been evidenced by inhibition VEGFR-2 phosphorylation and endothelial cell migration.[34-36] Friedlander et al. studied pazopanib in 36 patients with recurrent platinum sensitive and resistant epithelial ovarian, fallopian tube and primary peritoneal cancers.[10] Patients with elevated CA125 with or without non-bulky (no mass > 4cm) measurable disease were eligible. The CA125 response rate was 31%, median time to response was 29 days and median response duration was 113 days. The most common adverse events included fatigue, gastrointestinal issues (nausea, vomiting, diarrhea) and headache. Only 1 patient had a grade 4 toxicity- peripheral edema.[10]

2.4 Weekly Gemcitabine and Safety of Combination Weekly Gemcitabine/Pazopanib

Gemcitabine (2',2' – difluorodeoxycytidine, dFdC) is a nucleoside analog of cytidine with a wide-range activity in solid tumors. Gemcitabine has undergone investigation in a series of phase I and phase II trials as single agent for second line therapy. Gemcitabine was approved for use in recurrent ovarian cancer by the FDA in 2006. Response rates have ranged from 11-60%.[37-54] Very few and well tolerated side effects were observed.

The earliest 3 trials were reported between 1995 and 1998. Lund et al treated 51 women with recurrent ovarian cancer.[45] Gemcitabine dose was 800 mg/m^2 and treatment was given weekly for 3 weeks followed by 1 week off. In this study a 19% PR rate was reported (no CR). In 1996 Shapiro et al reported 38 women with recurrent ovarian cancer treated on the same schedule with a dose of 1000 mg/m^2.[52] In this study the RR was 13%. Friedlander et al reported 38 patients with recurrent ovarian cancer treated with a dose of 1200 mg/m^2.[40] Two patients had CR, 3 had PR for overall RR of 13.9%. Notably, there was stable disease in 50% of patients. The most common toxicities seen in this study were neutropenia and leukopenia.

Subsequent studies were more rigorous about defining platinum sensitivity status and confining studies to platinum resistant (and in many cases paclitaxel resistant) disease.

The retrospective review published by Safra et al highlights the different response rates between platinum resistant and platinum sensitive patients.[51] In this series, most women were heavily pretreated, with a mean of 3 prior regimens (range 2-8). Single agent gemcitabine was given at 1000 mg/m^2 for 3 weeks with 1 week off. Forty three total patients were treated: 22 platinum sensitive and 21 platinum resistant. In the platinum sensitive group, there were 45% PR and 45% SD. Median time to progression (TTP) was 5 months and median survival was 16.5 months. In the platinum resistant group, the PR rate was only 5% but there were 43% of patients with SD. Median TTP was 2.8 months and median survival 6.3 months.

Other prospective studies suggest a higher response rate for single agent gemcitabine in the platinum resistant population. The phase II study reported by Markman et al had very stringent criteria for establishing platinum resistance and included only patients that were both platinum and paclitaxel resistant.[48] In that study 51 patients were treated in a 3 out of 4 week schedule. These patients had been treated with a median of 3 prior therapies (range 1-6). The gemcitabine dose started at 1250 mg/m^2 but after the first 10 patients was decreased to 1000 mg/m^2 due to toxicity. Even at 1000 mg/m^2 dose modifications were required in 50% of patients. In this very highly platinum resistant population, there were 4 PR's by RECIST and 4 patients with greater than 75% drop in CA 125 for an ORR of 16%. There were no CR's. The median duration of response was 4 months and overall survival 7 months.

Overall, when all studies of single agent gemcitabine are combined, the response rate is 19%.[42,43] In the majority, but not all of these studies, the participants were likely to have platinum-resistant disease and were heavily pretreated. Doses higher than 1000 mg/m^2 in heavily pretreated patients are not advised because of the risk of severe myelosuppression[42,43] It is notable that an additional 30% of patients experienced stable disease, for an overall clinical benefit rate of approximately 50%.

Gemcitabine toxicity is mild, transient, and noncumulative.[55] It includes myelosuprresion (dose-limiting), flu-like symptoms, fatigue, fever, peripheral edema, proteinuria, cutaneous reactions, and respiratory and GI effects. There have been rare reports of HUS and cardiac dysfunction, including MI, CHF, and atrial fibrillation. Overall, gemcitabine toxicity is rarely severe or a cause for discontinuing drug. The myelosuppression is easily managed by lowering the dosage.

The combination of pazopanib and gemcitabine has been studied in a phase I trial and the results reported in the most updated pazopanib IB (Version 9.0, January 25, 2012). The primary goal of the phase I study was to determine the OTR (defined as the highest dosing regimen that resulted in a DLT in no more than 1 of 6 subjects) of oral pazopanib administered once daily plus gemcitabine on days 1 and 8 of a 21 day treatment cycle. A total of 22 subjects with advanced solid tumors were enrolled in 3 consecutive dose cohorts.

For cohort Paz800/gem 1000 there were no DLTs observed in any subject during cycle 1. Paz800/Gem1250 was identified as the OTR.

The most commonly reported Aes (>50%) in enrolled subjects, regardless of causality, were: fatigeu (82%), nausea (68%), decreased appetite (59%), neutropenia (59%), and diarrhea (55%).

A phase II trial (NCT01080248) is currently open at Washington University evaluating gemcitabine and pazopanib in pancreatic cancer. The doses in this study are gemcitabine 1000 mg/m^2 IV over 30 minutes on Days 1, 8 and 15 (of a 28 day cycle) and pazopanib 800 mg po daily every 28 days.

The OTR has not yet been defined.

2.5 Translational Research

There are no planned translational endpoints for this study.

2.6 Rationale for Clinical Trial Design

This is an open label, randomized phase II trial. All patients will receive IV gemcitabine on days 1 and 8, every 21 days in combination with either oral pazopanib or no oral treatment.

2.7 Inclusion of Women and Minorities

The University of Virginia will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire ovarian, fallopian tube and primary peritoneal cancer population treated.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

3.11 Patients must have recurrent or persistent epithelial ovarian, fallopian tube or primary peritoneal carcinoma. Histologic documentation of the original primary tumor is required via the pathology report.

3.12 Patients must have measurable disease or detectable (non-measurable) disease:

3.121 Measurable disease 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 greater than or equal to 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or greater than or equal to 20 mm when measured by chest x-ray. Lymph nodes must be greater than or equal to 15 mm in short axis when measured by CT or MRI.

3.122 Detectable disease in a patient is defined as one who does not have measurable disease but has baseline value of CA-125 at least 2 x ULN

3.13 Patients who have measurable disease must have at least one "target lesion" to be used to assess response on this protocol as defined by RECIST 1.1. Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

3.15 Patients who have received one prior regimen must have an ECOG Performance Status of 0, 1, or 2.

Patients who have received two or three prior regimens must have an ECOG Performance Status of 0 or 1.

3.16 Recovery from effects of recent surgery, radiotherapy, or chemotherapy:

3.161 Patients should be free of active infection requiring antibiotics (with the exception of uncomplicated UTI).

3.162 Any hormonal therapy directed at the malignant tumor must be discontinued at least one week prior to registration.

3.163 Any other prior therapy directed at the malignant tumor, including chemotherapy, biological/targeted and immunologic agents (including small molecules and murine monoclonal antibodies), must be discontinued at least three weeks prior to registration. Chimeric or human or humanized monoclonal antibodies (including bevacizumab) or VEGF receptor fusion proteins (including VEGF TRAP/aflibercept) must be discontinued for at least 8 weeks prior to registration.

3.164 At least 4 weeks must have elapsed since the patient underwent any major surgery (e.g., major: laparotomy, laparoscopy, thoracotomy, video assisted thorascopic surgery (VATS); minor: central venous access catheter placement, ureteral stent placement or exchange, paracentesis, thoracentesis).

3.17 Prior therapy

3.171 Patients must have had one prior platinum-based chemotherapeutic regimen for management of primary disease containing carboplatin, cisplatin, or another organoplatinum compound. This initial treatment may have included intraperitoneal therapy, consolidation, non-cytotoxic agents (biologic/targeted agents, such as bevacizumab) or extended therapy administered after surgical or non-surgical assessment. If patients were treated with paclitaxel for their primary disease, this can have been given weekly or every 3 weeks.

3.172 Patients are allowed to receive, but are not required to receive, two additional cytotoxic regimens for management of recurrent or persistent disease.

3.173 Patients are allowed to receive, but are not required to receive, non-cytotoxic (biologic/targeted agents, such as bevacizumab) therapy as part of their primary treatment regimen. Patients are allowed to receive, but are not required to receive, PARP inhibitors for management of primary or recurrent/persistent disease (either alone or in combination with cytotoxic chemotherapy). PARP inhibitors or non-cytotoxic therapies do NOT count as a prior regimen when given alone.

3.18 Patients must have adequate:

3.181 Bone marrow function:

- Absolute neutrophil count (ANC) greater than or equal to 1,500/mcl.
- Platelets greater than or equal to 100,000/mcl.
- Hemoglobin greater than or equal to 9 g/dL. Patients may not have had a transfusion within 7 days of screening assessment.

3.182 Blood coagulation parameters: PT such that international normalized ratio (INR) is less than or equal to 1.2 x ULN (or an in-range INR, usually between 2 and 3, if a patient is on a stable dose of therapeutic warfarin) and a PTT less than or equal to 1.2 x ULN.

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

3.183 Renal function: Creatinine less than or equal to 1.5 mg/dL, or if >1.5 mg/dL, creatinine clearance must be at least 50 ml/min

3.184 Urine Protein: Urine Protein to urine creatinine ratio (UPC) should be less than 1. If greater than 1, then 24 hour urine protein must be less than 1g for patient to be eligible.

3.185 Hepatic function:

- Bilirubin less than or equal to 1.5 x ULN.
- AST (SGOT) *and* ALT (SGPT) less than or equal to 2.5 x ULN

- Subjects who have **BOTH** bilirubin greater than ULN *and* AST/ALT greater than 1.0 x ULN are not eligible

3.186 Thyroid function: Patients should have normal baseline TSH. Patients with elevated TSH level (between 4.5-10 mU/L in the absence of symptoms of hypothyroidism) must have a normal free thyroxine (T4). TSH that is 10 mU/L or higher is exclusionary.

- A history of hypothyroidism and/or hyperthyroidism is allowed, as long as the patient has stable well-controlled thyroid function for a minimum of 2 months.

3.19 Patients of childbearing potential must have a negative pregnancy test prior to the study entry and be practicing an effective form of contraception. Pregnant women are excluded from this study because of the potential for teratogenic or abortifacient effects.

3.110 Patients must have signed an approved informed consent and authorization permitting the release of personal health information.

3.111 Patients must meet pre-entry requirements as specified in section 7.0.

3.112 Patients must be greater than or equal to 18 years of age.

3.113 Patients must be capable of taking and absorbing oral medications. A patient must be clear of the following:

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

3.114 Any concomitant medications that are associated with a risk of QTc prolongation and/or Torsades de Pointes should be discontinued or replaced with drugs that do not carry these risks, if possible. Patients who must take medication with a risk of possible risk of Torsades de Pointes should be watched carefully for symptoms of QTc prolongation, such as syncope. *See Appendix II for a list of medications that may cause QTc prolongation.*

Patients with personal or family history of congenital long QTc syndrome are NOT eligible.

3.115 CYP3A4 Inhibitors: **Strong inhibitors of CYP3A4 are prohibited.** Grapefruit juice is an inhibitor of CYP450 and should not be taken with pazopanib.

CYP3A4 Inducers: **Strong inducers of CYP3A4 are prohibited.**

CYP Substrates: Concomitant use of agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended.

3.116 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
- a bilateral tubal ligation
- is post-menopausal

b. Childbearing potential, including any female who has had a negative serum pregnancy test within 2 weeks prior to the first dose of study treatment, preferably as close to the first dose as possible, and agrees to use adequate contraception. GSK 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
- estrogenic vaginal ring
- percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (ISU) with a documented failure rate of less than 1% per year
- male partner sterilization (vasectomy with documentation of azzospermia) 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)

3.2 Exclusion Criteria

3.21 Patient who have had previous treatment with pazopanib or with weekly gemcitabine for recurrent or persistent disease.

3.22 Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer and other specific malignancies as noted in Section 3.23 and 3.24, are excluded if there is any evidence of other malignancy being present within the last two years. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.

3.23 Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis within the last three years are excluded. Prior vaginal brachytherapy is allowed. Prior radiation for localized cancer of the breast, head and neck, or skin is permitted, provided that it was completed more than two years prior to registration, and the patient remains free of recurrent or metastatic disease.

3.24 Patients who have received prior chemotherapy for any abdominal or pelvic tumor OTHER THAN for the treatment of ovarian, fallopian tube, or primary peritoneal cancer within the last three years are excluded. Patients may have received prior adjuvant chemotherapy for localized breast cancer, provided that it was completed more than three years prior to registration, and the patient remains free of recurrent or metastatic disease.

3.25 Patients with clinically significant cardiovascular disease. This includes:

3.251 Uncontrolled hypertension, defined as systolic greater than 150 mm Hg or diastolic greater than 90 mm Hg

Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry.

3.252 Congenital long QT syndrome or baseline QTc greater than 480 milliseconds.

3.253 Myocardial infarction or unstable angina within 6 months prior to registration.

3.254 New York Heart Association (NYHA) Class III or greater congestive heart failure. (see Appendix I)

3.255 History of serious ventricular arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation) or serious cardiac arrhythmia requiring medication. This does not include asymptomatic, atrial fibrillation with controlled ventricular rate.

3.256 Patients who have received prior treatment with an anthracycline (including doxorubicin, excluding liposomal doxorubicin) must have an echocardiogram or MUGA assessment and are excluded if they have an ejection fraction less than 50%.

3.257 CTCAE v.4.0 Grade 2 or greater peripheral vascular disease (at least brief less than 24 hrs) episodes of ischemia managed non-surgically and without permanent deficit.

3.258 History of cardiac angioplasty or stenting within 6 months prior to registration. History of coronary artery bypass graft surgery within 6 months prior to registration.

3.259 Arterial thrombosis within 6 months prior to registration.

3.26 Patients with serious non-healing wound, ulcer, or bone fracture. This includes history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 28 days prior to the first date of study treatment.

Note: Deliberate surgically created abdominal fistula is acceptable.

3.27 Patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder, coagulopathy, or tumor involving major vessels

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

3.29 History of allergic reactions attributed to compounds of similar chemical or biologic composition to pazopanib.

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

3.211 Patients with any condition that may increase the risk of gastrointestinal bleeding or gastrointestinal perforation, including:

- active peptic ulcer disease
- known gastrointestinal intraluminal metastatic lesions (gastrointestinal serosa metastatic lesions are permitted)
- inflammatory bowel disease (e.g., ulcerative colitis, Crohn's disease) or other gastrointestinal conditions with increased risk of perforation
- patients with clinical symptoms or signs of gastrointestinal obstruction and patients who require parenteral hydration and/or nutrition.

3.212 Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product, including but not limited to.

- malabsorption syndrome
- major resection of the stomach or small bowel

3.213 Patients who are pregnant or nursing.

3.214 History of hemoptysis in excess of 2.5 mL (1/2 teaspoon) within 8 weeks prior to first dose of pazopanib.

3.215 Uncontrolled intercurrent illness including, but not limited to, psychiatric illness/social situations that would limit compliance with study requirements.

3.216 Any ongoing toxicity from prior anti-cancer therapy that is greater than grade 1 and/or that is progressing in severity, except alopecia.

3.217 Unable or unwilling to discontinue use of prohibited medications listed in Section 4.211 for at least 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of study drug and for the duration of the study.

4.0 STUDY MODALITIES

4.1 Gemcitabine, Gemzar ® (NSC #613327)

4.11 Formulation: Gemcitabine HCl is a nucleoside analog that exhibits anti-tumor activity.

4.12 Supplier/How Supplied: Gemcitabine HCl is commercially available from Eli Lilly and Co. Gemcitabine is supplied as a white lyophilized powder in sterile single use vials containing 200mg (10 ml) or 1000 mg (50 ml) of gemcitabine as the hydrochloride salt.

4.13 Stability/Storage: Unopened vials of gemcitabine are stable until the expiration date indicated on the package when stored at controlled room temperature between 20 to 25ºC (68 to 77°F).

4.14 Preparation: To reconstitute, add 5 ml of 0.9% Sodium Chloride Injection to the 200 mg vials or 25 ml to the 1000 mg vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/ml which includes accounting for the displacement volume of the lyophilized powder. The total volume upon reconstitution will be 5.26 ml or 26.3 ml, respectively. Complete withdrawal of the contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/ml. The solution should be clear, colorless to slightly straw colored. Do not administer if discoloration or particulate matter is found. Once the drug has been reconstituted, it should be stored at controlled room temperature and used within 24 hours.

4.15 Administration: The mixed solution will be continuously infused over 30-60 minutes minutes (see Section 5.2).

4.16 Adverse effects:

Hematologic: The following Grade 3 and 4 toxicities can be expected after single agent therapy with doses between 800 and 1250 mg/m^2: neutropenia 25%, leukopenia 9%, anemia 8%, and thrombocytopenia 5%. Infection occurred in 16% of patients; sepsis occurred in less than 1%. 17% of patients experienced hemorrhage of Grade 2 or less.
Gastrointestinal: Nausea and vomiting is frequent, up to 69%, but usually mild to moderate. Grade 3 and 4 nausea and vomiting were noted in 14%. Diarrhea was seen in 19%, stomatitis in 11%, and constipation in 23%.
Pulmonary: Dyspnea was seen in 23%, severe in 3%. Rarely parenchymal toxicity including pneumonitis has been reported. Treatment should be discontinued immediately, if suspicious symptoms occur.

Hepatic: Transient elevation of hepatic enzymes was seen in 70%, however, this was not dose dependent and no increase was noted during prolonged therapy. Serious hepatotoxicity, including liver failure and death, has been reported very rarely.
Fever: This is seen in up to 41%, but usually of a mild degree. Fever may be accompanied by flu-like symptoms in 19%.
Renal: Reversible proteinuria, hematuria are frequent; increased BUN and creatinine in 16% and 8% of patients, respectively. However, renal insufficiency or hemolytic uremic syndrome is very rare. If suspicious symptoms are noted therapy should be discontinued immediately.
Dermatologic/Skin: Alopecia is seen in 15%; a reversible macular or macularpapular rash is seen in 30%; pruritus occurs in 13%. Peripheral edema is seen in up to 20% of the patients treated. Infusion site reactions occurred in 4% of patients.
Neurologic: There was a 10% incidence of mild paresthesias; somnolence occurred in 11% of patients.
Pain at the site of injection: Seen in 48% of patients; Grade 3 in 9%.
Other: Cardiovascular or allergic reactions are seen very rarely.

*See FDA-approved gemcitabine package insert for a comprehensive list of adverse events associated with gemcitabine.

4.2 Pazopanib (CTEP IND#75648, NSC#737754)
All investigators who receive a copy of the protocol will also receive a copy of the Investigator's Brochure (IB).

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

4.22 Classification: VEGFR tyrosine kinase inhibitor

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

4.24 Molecular Formula and Weight: $C_{21}H_{23}N_7O_2S$-HCl **M.W.:** 474.0 (monohydrochloride salt); 437.5 (free base)

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

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

4.27 How Supplied**:** pazopanib is supplied as aqueous film-coated tablets containing the equivalent of 200 mg. Each bottle will contain 34 oval-shaped, white, tablets.

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

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

4.29 Stability: Stability studies are ongoing.

4.210 Administration**:** Oral Administration will be performed on an outpatient basis. Pazopanib will be dispensed as tablets at the beginning of each treatment cycle (Day 1, every 21 days). Pazopanib should be taken on an empty stomach either 1 hour before or 2 hours after meals. The tablets should be swallowed whole and cannot be crushed or broken. If a dose is missed by > 12 hours, then the patient should skip that dose. If a dose is missed by ≤ 12 hours then the patient can take the missed dose when remembered.

4.211 Potential Drug Interactions: Additional information for drug interactions with cytochrome P450 isoenzymes may be found at: http://medicine.iupui.edu/flockhart/

Pazopanib is primarily metabolized by the human CYP3A4 isoenzyme. **Strong CYP3A4 inducers and inhibitors are prohibited on pazopanib trials.**

Medications that strongly inhibit CYP3A4 include (but are not limited to):

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

Medications that strongly induce CYP3A4 include (but are not limited to):

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

Pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6. Drugs that have narrow therapeutic windows and are substrates for these enzymes **should be administered with extreme caution.** Because of pazopanib's long half-life, caution should continue to be exercised for at least 7 days and up to 15 days after the last dose of pazopanib when administering these medications.

Medications that are substrates for these enzymes *and* have narrow therapeutic windows include (but are not limited to):

- Ergot derivatives: dihydroergotamine, ergonovine, ergotamine, methylergonovine (potential increased risk for developing ergot toxicity that includes severe vasospasm leading to peripheral as well as cerebral ischemia)
- Neuroleptics: pimozide (potential increased risk for QT interval prolongation, ventricular arrhythmia, and sudden death)
- Antiarrhythmics: bepridil, flecainide, lidocaine, mexiletine, amiodarone, quinidine, propafenone (potential increased risk for QT interval prolongation and Torsade de Pointes)
- Immune modulators: cyclosporine, tacrolimus, sirolimus (potential increased risk for nephrotoxicity and neurotoxicity)
- Miscellaneous: quetiapine, risperidone, clozapine, atomoxetine.

Note: Zofran (ondansetron) is a CYP3A4 substrate but does not have a narrow therapeutic window and so can be given to patients for treatment of emesis.

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

Pazopanib may increase bleeding. All patients receiving pazopanib will be monitored for signs of bleeding with CBC and vital sign assesments performed on days 1 and 8 of every cycle.

Pazopanib may cause decrease glucose. Patients receiving pazopanib and hypoglycemia agents should be monitored for hypoglycemia.

Pregnant women are excluded from this study because pazopanib is an antiangiogenic agent which has produced teratogenic effects and reduced fetal body weight in pregnant rats and/or rabbits, and therefore has the potential for teratogenic or abortifacient effects in humans. Because there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with pazopanib, breastfeeding should be discontinued if the mother is treated with pazopanib. These potential risks may also apply to other agents used in this study.

4.212 Availability:
Pazopanib is an investigational agent supplied by Novartis.

4.213 Clinical Supplies / Drug Ordering
Clinical Supplies**:** pazopanib (NSC 737754) will be provided by Novartis and distributed to the University of Virginia Investigational Drug Pharmacy. UVA Investigational Drug Pharmacy will supply each site with full bottles for distribution by their pharmacy according to each pharmacy/state's regulations.

Drug Ordering:
Once a site has been activated, the site will receive a 2-cycle/8-week supply as an initial shipment. Sites may reorder additional drug as needed by completing the provided Drug Request form and faxing it to UVA. All drug orders will be shipped directly to the individual site's investigational pharmacy.

4.214 Drug Accountability:
Sites must use an NCI DARF or an accountability form approved by the NCI. UVA will review the site's DARF (if not an NCI DARF) prior to dispensing drug.

4.215 Drug Returns**:** Only undispensed clinical supplies should be returned to the UVA investigational pharmacy.

Drug Transfers**:** Bottles **MAY NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers must be approved in advance by the UVA investigational pharmacy and the UVA PI.

4.216 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pazopanib (GW786034, NSC 737754)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. *Frequency is provided based on 1019 patients.* Below is the CAEPR for pazopanib (GW786034).

Version 2.2, March 18, 2010[1]

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 4.0 Term) [n= 1019]			**EXPECTED AEs FOR OnCore REPORTING Agent Specific Adverse Event List**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	***Expected (up to grade 3)***
CARDIAC DISORDERS			
		Left ventricular systolic dysfunction	
		Myocardial infarction	
ENDOCRINE DISORDERS			
	Hypothyroidism		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain***
	Constipation		
Diarrhea			***Diarrhea***
		Gastrointestinal fistula[2]	***Gastrointestinal fistula[2]***
		Gastrointestinal hemorrhage[3]	
		Gastrointestinal perforation[4]	***Gastrointestinal perforation[4]***
Nausea			***Nausea***
Vomiting			***Vomiting***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased***
	Blood bilirubin increased		***Blood bilirubin increased***
		Electrocardiogram QTc interval prolonged (accompanied by Torsades de pointes)	
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased***
	Neutrophil count decreased		***Neutrophil count decreased***
	Platelet count decreased		***Platelet count decreased***
	Serum amylase increased		
	Weight loss		
	White blood cell decreased		***White blood cell decreased***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia***
	Dehydration		***Dehydration***
	Hyperglycemia		***Hyperglycemia***
	Hypermagnesemia		
	Hypoglycemia		***Hypoglycemia***
	Hypomagnesemia		
	Hypophosphatemia		***Hypophosphatemia***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia***
	Myalgia		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			

	Tumor pain		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness***
	Dysgeusia		
	Extrapyramidal disorder		
	Headache		***Headache***
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
	Proteinuria		***Proteinuria***
		Urinary fistula	***Urinary fistula***
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
		Female genital tract fistula	***Female genital tract fistula***
		Uterine fistula	***Uterine fistula***
		Vaginal fistula	***Vaginal fistula***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
	Respiratory hemorrhage[5]		***Respiratory hemorrhage[5]***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia***
		Palmar-plantar erythrodysesthesia syndrome	
	Rash maculo-papular		***Rash maculo-papular***
Skin hypopigmentation			***Skin hypopigmentation***
VASCULAR DISORDERS			
Hypertension			***Hypertension***
		Thromboembolic event (venous)[6]	
		Vascular disorders – other (arterial thromboembolic event)[6]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

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

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

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

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

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

Also reported on pazopanib (GW786034) trials but with the relationship to pazopanib (GW786034) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia
CARDIAC DISORDERS - Atrial fibrillation; Sinus bradycardia
EYE DISORDERS - Blurred vision
GASTROINTESTINAL DISORDERS - Dyspepsia; Dysphagia; Flatulence; Pancreatitis; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Fever; Non-cardiac chest pain
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alkaline phosphatase increased; Creatinine increased; INR increased
METABOLISM AND NUTRITION DISORDERS - Hyperkalemia; Hypernatremia; Hypocalcemia; Hypokalemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Generalized muscle weakness
NERVOUS SYSTEM DISORDERS - Intracranial hemorrhage
PSYCHIATRIC DISORDERS - Confusion
RENAL AND URINARY DISORDERS - Hematuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pharyngolaryngeal pain; Pleuritic pain; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Pruritus

Note: Pazopanib (GW786034) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

5.0 TREATMENT PLAN AND ENTRY PROCEDURE

5.1 Patient Entry and Registration

All eligible participants must sign an informed consent form. Consented patients should be entered in the Cancer Center Clinical Trials Database (OnCore) prior to randomization. Prior to randomization, the signed informed consent, completed eligibility checklist along with supporting documentation should be submitted to the Sponsor (UVa) for review. Detailed registration information is included in a study procedures manual.

Randomization will be discussed with subjects during the process of informed consent and informed consent must be documented prior to randomization. All participants who meet the inclusion/exclusion criteria may be randomized. Randomization will be based on equal allocation among arms. Randomization will not be stratified by institution. The randomization codes are generated by the study statisticians and stored in the UVa Cancer Center Clinical Trials Database (OnCore). Randomization occurs at the time of registration into the Cancer Center database. Randomization will not occur more than 1 day (+/- 2 days to allow for weekends and/or holidays) prior to the anticipated treatment date.

This study will be conducted on an outpatient basis.

5.2 Treatment Plan

5.21 Eligible patients will receive:

Regimen 1: Gemcitabine 1000 mg/m^2 administered weekly on days 1 and 8 (30-60 minutes IV infusion)

Regimen 2: Gemcitabine 1000 mg/m^2 administered weekly on days 1 and 8 (30-60 minutes IV infusion) with Pazopanib 800mg PO daily for 21 days

One cycle equals 21 days.
Maximum body surface area used for gemcitabine dose calculations will be 2.0 m^2

Chemotherapy doses will be based on the subject's weight at baseline and will remain the same throughout the study. However, the doses will be recalculated if the patient has a weight change of greater than or equal to 10% from baseline.

Patients are instructed to swallow tablets once a day (preferably in the morning) on an empty stomach, either 1 hour before or 2 hours after food with about 1 cup (240 mL) water. Tablets should be swallowed whole; they must not be chewed, broken, or crushed.

Patients will be given a Patient Medication Calendar to complete daily.. The Patient Tablet Calendar should be reviewed prior to the start of each cycle.

All prescription and over-the-counter medications as well as alternative medicines that have been taken within 4 weeks prior to the first dose of pazopanib should be reviewed for potential drug-drug interactions (see Section 4.211, 5.33 and Appendices III).

5.211 Recommended preparative regimen for gemcitabine (to reduce the risk associated with hypersensitivity reactions): This regimen should include a standard dose of dexamethasone (either IV or PO), an anti-histamine H1 (diphenhydramine 25-50 mg IV or orally, or an equivalent dose of an alternate H1blocker such as loratadine or fexofenadine), and a standard dose of antihistamine H2 IV (such as cimetidine, ranitidine, or famotidine). Dexamethasone is allowed here as a preparative treatment despite the CYP3A4 interactions. The preparative regimen can be altered at the discretion of the treating investigator.

5.22 If side effects are not severe, a patient may remain on study indefinitely until evidence of disease progression or unacceptable toxicity.

5.3 Concomitant Medications: **Information for drug interactions with cytochrome P450 isoenzymes may be found at http://medicine.iupui.edu/flockhart/**
Additional information can be found in Appendix II and Section 4.211.

5.31 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). Subjects taking concomitant anticoagulant therapy should be monitored regularly for changes in relevant coagulation parameters as clinically indicated, as well as for any clinical bleeding episodes.

5.32 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 (British Journal of Cancer 2008: 99, 1380). Such changes may require an adjustment in the dose of hypoglycemic and/or insulin therapy. Subjects should be advised to report symptoms of hypoglycemia (e.g. confusion, visual disturbances, palpitations, sweating). Serum glucose should be tested during treatment with pazopanib as outlined in the protocol and as clinically indicated.

5.33 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 secondary to the inhibition of specific CYP enzymes by pazopanib.

See Section 4.211. Additional information for drug interactions with cytochrome P450 isoenzymes may be found at http://medicine.iupui.edu/flockhart/

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.

5.34 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**.

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

Medications that inhibit CYP3A4 may result in increased plasma pazopanib concentrations. Selection of an alternate concomitant medication with no or minimal potential to inhibit CYP3A4 is recommended.

See Section 4.211. Additional information for drug interactions with cytochrome P450 isoenzymes may be found at http://medicine.iupui.edu/flockhart/

5.4 Precautions/Warnings (See Appendix II)

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

5.411 **Intensive QTc monitoring. A baseline** ECG **is required prior to study registration, and subjects with QTc > 480 msec are excluded**. Repeat ECG must be performed during the day 1, cycle 2 visit. If the QTc interval at 3 weeks is ≥ 500 msec, the subject should be removed from the study.

5.412 Subjects must be questioned about family history of prolonged QTc, personal history of prolonged QTc, cardiac disease, and concomitant medications which are associated with a high risk of causing QTc prolongation prior to study registration (see sections 3.114 and 3.25).

5.413 Concomitant treatment with drugs that are associated with a high risk of causing QTc prolongation should be changed to similar agents that do not pose such a risk, if possible, prior to a subject receiving the first dose of pazopanib. A comprehensive list of agents that are associated with a risk of prolonging the QTc interval is provided in Appendix II. Subjects who begin any drugs with a high risk for QTc prolongation while receiving pazopanib should be monitored carefully for signs of potential problems with QTc prolongation (syncope, *etc*.). An ECG is not mandated in this circumstance; however, it should be performed at the treating physician's discretion.

5.42 Hypertension is an important AE associated with pazopanib. **Frequent blood pressure (BP) monitoring is important** in subjects receiving pazopanib starting on day 8 and continuing until subject is off study. Experience to date suggests that increases in BP may occur following dosing with pazopanib for a number of weeks and that these increases may occur relatively quickly. It is imperative that the investigator institute appropriate measures to control BP. This may necessitate changes to existing antihypertensive medication, addition of new medication(s) and/or interruption/withdrawal of pazopanib. **Recommendations for hypertension management are presented in Appendix II**.

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

5.5 Criteria for removal from treatment

5.51 Inability to tolerate the lowest doses of gemcitabine or pazopanib because of toxicity.

5.52 Patient may withdraw from study at any time for any reason. Patients with evidence of progressive disease or patients with significant side effects will be removed from study treatment.

5.53 Patient may be withdrawn from the study treatment at any time at the discretion of the Primary Investigator.

6.0 TREATMENT MODIFICATIONS

Study Drug	**Initial dose level**	**1 level reduction**	**2 level reduction**
Gemcitabine	1000 mg/m^2	800 mg/m^2	600 mg/m^2
Pazopanib	800 mg PO	600 mg PO	400 mg PO

Please note all CTCAE grading below refers to version 4.0.

6.1 Hematologic toxicity

6.11 Initial treatment modifications will consist of cycle delay and/or dose reduction as indicated below. The use of hematopoietic cytokines and protective reagents are restricted as noted:

6.111 Patients will NOT receive prophylactic growth factors [filgrastim (G-CSF), sargramostim (GM-CSF), pegfilgrastim (Neulasta)] unless they experience recurrent neutropenic complications after treatment modifications specified below.

6.112 Patients will NOT receive prophylactic thrombopoietic agents.

6.113 Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia. Treating physicians should be aware of prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival, and that these agents are administered only to avoid red blood cell transfusions. They do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted.
http://www.fda.gov/Medwatch/safety/2007/safety07.htm

6.114 Patients may NOT receive amifostine or other protective reagents.

6.12 Treatment decisions will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC).

6.13 Subsequent cycles of therapy will not begin (Day 1 of each cycle) until the ANC is ≥ 1500 cells/mcl and the platelet count is ≥ 100,000/mcl. Therapy will be delayed for a maximum of two weeks until these values are achieved. Patients who fail to recover adequate counts within a two week delay will be removed from study. In the event a patients counts do not qualify for gemcitabine treatment, but are sufficient for pazopanib (See Appendix), pazopanib may be continued while gemcitabine is held. This will be considered a continuation of the previous cycle. A new cycle is defined by gemcitabine administration.

Day 8 gemcitabine treatment will not be given unless ANC is ≥ 1000 cells/mcl and the platelet count is ≥ 75,000/mcl. If Day 8 is held, it should not be made up.

6.14 Patients requiring greater than two dose reductions of gemcitabine for any cause will result in discontinuation of study treatment. Patients requiring greater than two dose reductions of pazopanib for any cause will result in discontinuation of pazopanib (with continuation of gemcitabine, if appropriate, until unacceptable toxicity or progression of disease). Patients who have received at least one study treatment will continue to be followed and included in the primary analysis.

6.15 Dose modification for gemcitabine:

	ANC[1]	**PLT**	**ACTION**
Day 1	<1500	< 100,000	Delay. Monitor counts weekly until adequate for gemcitabine treatment. Restart when counts are adequate for treatment; reduce gemcitabine one dose level. If counts do not recover after 2 weeks delay, remove from study.
Day 8	< 1000	< 75,000	Hold gemcitabine Reduce gemcitabine one dose level at subsequent cycle day 1
[1]For febrile neutropenia, and/or documented grade 4 neutropenia persisting greater than or equal to 7 days, reduce gemcitabine by one dose level on subsequent cycles.			

6.2 <u>Dose interruption and modification of pazopanib</u>

Recommendations of dose modifications and management of patients experiencing adverse events, including but not limited to liver toxicity, hypertension and QTc prolongation, are provided in Tables A and B in Appendix II.

6.3 Dose and Treatment Modifications for Gemcitabine Non-Hematologic Toxicity

6.31 Grade 2 (or greater) renal toxicity requires reduction of one dose level and delay in subsequent therapy for a maximum of 2 weeks until recovered to Grade 1. Patients who fail to recover from Grade 2 or worse renal toxicity to Grade 1 or less will discontinue gemcitabine. Patients may continue with pazopanib as a single agent. For both groups, imaging studies (CT scans) should continue to be done on time (approximately every 6 weeks) in order to document time to progression.

6.32 There will be no dose modifications for alopecia or fatigue.

6.33 It is expected that patients with nausea, emesis, diarrhea, or constipation will receive appropriate medical management without dose modification. However, patients with persistent (greater than 24 hours) grade 3 (or greater) toxicity in spite of optimal medical management require reduction of one dose level of both drugs and delay in subsequent therapy for a maximum of 2 weeks until recovered to grade 1.

6.34 Unless otherwise specified within this protocol, non-hematologic toxicities with an impact on organ function of grade 2 (or greater) require reduction of one dose level and delay in subsequent therapy for a maximum of 2 weeks until recovered to grade 1, or pre-therapy baseline.

6.4 Dose escalations

There will be no dose escalations or re-escalations on this study.

7.0 STUDY PARAMETERS & SERIAL OBSERVATIONS

Parameter	Pre-Study	Prior to Each Cycle[1]	Day 8 of each cycle	Every other cycle	Follow up[2]
History & Physical	X[3]	X[17]			X
Vital signs (BP, HR, temp)[4]	X[3]	X	X		
CBC/Differential/Platelets[5]	X[6]	X[7]	X		
PT/INR and PTT[8]	X[6]				
Electrolytes, BUN, creatinine, Ca, Mg, PO_4	X[6]	X[7]			
Urine protein-creatinine ratio (UPCR)	X[9]			X[10]	
Bilirubin, AST (SGOT), ALT (SGPT), Alkaline Phosphatase	X[6]	X[7]	X[18]		
Thyroid Function test (TSH)	X[6]				
Serum Pregnancy Test (WOCBP)	X[6]				
Electrocardiogram (ECG)	X[3,11]	X[12]			
LVEF Testing	X[3,13]				
Chest imaging (x-ray or CT chest)	X[3]			X[14]	X[14]
Radiographic tumor measurement	X[3, 15]			X[15]	X[15]
Performance Status	X[3]	X[17]			
Clinical tumor measurement	X[3,16]	X[16]			X[16]
CA-125	X[6]	X			X
Toxicity Assessment	X[6]	X	X		X
Patient Tablet Calendar		X			

[1] Can be done on Day 1 of the cycle
[2] Follow-up until progression of disease every three months for 2 yrs, every 6 months for 1 year and then yearly for 2 years for a maximum of 5 years. AEs are collected through 30 days post last treatment dose. A visit should take place within this time frame to ensure all AEs are reported
[3] Must be done within 28 days prior to therapy..
[4] On day 15 of every cycle, patients taking pazopanib should have BP measured and recorded
[5] If grade 4 neutropenia is documented (ANC <500/µl), obtain twice per week until resolved to grade 3
[6] Must be done within 14 days prior to therapy.
[7] Must be done within 4 days of re-treatment with protocol therapy; ANC must be ≥ 1500 cells/µl and platelets ≥ 100,000/µl. Cycle 1 day 1 labs do not need to be repeated if screening labs were performed within 14 days of treatment.
[8] Patients on prophylactic or therapeutic anticoagulation with warfarin should have PT/INR monitored after starting and stopping pazopanib (e.g., weekly for the first cycle and weekly for a minimum of 2 weeks following discontinuation of pazopanib) and weekly for the first cycle of treatment following a warfarin or pazopanib dose modification
[9] If protein is 1+ or higher, 24-hour urine protein should be obtained and the level must be <1000 mg (<1 g/24hrs)
[10] Urine protein-creatinine ratio (UPCR) should be performed prior to every other cycle in subjects taking pazopanib. See the guidelines provided in Appendix III, Table A regarding treatment with pazopanib and proteinuria
[11] Baseline QTc must be < 480 ms
[12] In subjects taking pazopanib, ECG should be performed on day 1 of cycle 2 only. If QTc is > 500 ms, then subject is discontinued
[13] Required for patients who have received prior treatment with an anthracycline (including doxorubicin, excluding liposomal doxorubicin)
[14] Repeat chest imaging if initially abnormal or if required to monitor tumor response
[15] CT scan or MRI if used to follow lesion for measurable disease every other cycle during treatment and then every 3 months thereafter until disease progression is confirmed; also repeat at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease or rising serum tumor marker levels. Responses (CR and PR) require confirmation at greater than or equal to 4 weeks from initial documentation (Section 8).
[16] Every other cycle for those patients whose disease can be evaluated by physical examination according to RECIST 1.1 (Section 8)
[17] Cycle 1 day 1 Physical Exam and Performance status do not need to be repeated if performed within 5 days of treatment. Pelvic exam will be performed every other cycle, if clinically indicated
[18] In subjects taking pazopanib, testing should be performed on Day 8 of Cycle 1, 2 and 3.

8.0 EVALUATION CRITERIA

8.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

8.11 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 ≥10 mm with CT scan, as ≥20 mm by chest x-ray, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters.

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

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. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal/pelvic masses (identified by physical exam and not CT or MRI), are considered as non-measurable.

Notes:
Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

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, and 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.

8.12 Methods for Evaluation of Measurable Disease

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

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions,

documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

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, subsequent image acquisitions should use the same type of scanner and follow the baseline imaging protocol as closely as possible. If possible, body scans should be performed with breath-hold scanning techniques.

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. PET-CT scans are not always done with oral and IV contrast. In addition, the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed. **For these reasons, this study will not allow PET-CT use for RECIST 1.1 response criteria.**

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.

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

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

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

CA-125 (Ovarian, fallopian tube and primary peritoneal cancer trials): CA125 alone cannot be used to assess response. If CA125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response. Specific guidelines for CA-125 response (in recurrent ovarian cancer) have been published [*JNCI* 96:487-488, 2004]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria that are to be integrated with objective tumor assessment for use only in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

such as germ cell tumors, where known residual benign tumors can remain.

It is mandatory to obtain cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when measurable disease has met criteria for response or stable disease. This confirmation is necessary to differentiate response or stable disease versus progressive disease, as an effusion may be a side effect of the treatment.

8.13 Response Criteria

Determination of response should take into consideration all target (See 8.131) and non-target lesions (See 8.132) and, if appropriate, biomarkers (See 8.133).

8.131 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.

8.132 Evaluation of Non-Target Lesions

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

Note: If CA-125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

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

Not evaluable (NE): When at least one non-target lesion is not evaluated at a particular time point.

Although a clear progression of only "non-target" lesions 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).

8.133 Evaluation of Biomarkers

If serum CA-125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

Progression **cannot** be based upon biomarkers, such as serum CA-125, for this study.

8.134 Evaluation of Best Overall (unconfirmed) Response

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

Time Point Response for Patients with Measurable Disease at baseline (i.e., Target Disease)

Target Lesions	Non-Target Lesions	Biomarker CA-125	New Lesions*	Time Point Response
CR	CR	Within normal limits	No	CR
CR	Non-CR/Non-PD	Any value	No	PR
CR	NE	Any value	No	PR
PR	Non-PD or NE	Any value	No	PR
SD	Non-PD or NE	Any value	No	SD
NE	Non-PD	Any value	No	NE
PD	Any	Any value	Yes or No	PD
Any	PD**	Any value	Yes or No	PD
Any	Any	Any value	Yes	PD

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Time Point Response for Patients with only Non-Measurable Disease at baseline (i.e., Non-Target Disease)

Non-Target Lesions	Biomarker CA-125	New Lesions*	Time Point Response
CR	Within normal limits	No	CR
CR	Above normal limits	No	Non-CR/non-PD*
Non-CR/non-PD	Any value	No	Non-CR/non-PD*
NE	Any value	No	NE
Unequivocal PD	Any value	Yes or No	PD
Any	Any value	Yes	PD

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion
** 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

8.135 Best Overall Confirmed Response

Confirmation of CR and PR for determination of best overall response is required for studies with a primary endpoint that includes response.

Confirmed CR and PR for best overall confirmed response

Time Point Response First time point	Time Point Response Subsequent time point	BEST overall confirmed response
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

*If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR or SD, not CR at the first time point. Under these circumstances, the original CR should be changed to PR or SD and the best response is PR or SD.

In non-randomized trials where response is part of the primary endpoint, confirmation of CR or PR is needed to deem either one the "best overall response." **Responses (CR and PR) require confirmation at greater than or equal to 4 weeks from initial documentation.**

For this study, the minimum criteria for SD duration is 8 weeks.

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

8.14 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.

Patients who do not experience an event (recurrence/progression) will be censored at date of last contact.

8.15 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of recurrence/progression or death from any cause, whichever occurs first. Patients who do not experience an event (recurrence/progression or death) will be censored at date of last contact.

8.16 Survival

Survival is defined as the duration of time from study entry to time of death from any cause. Patients who do not experience an event (death) will be censored at date of last contact.

8.2 Recurrence-Free or Progression-Free Survival (non-measurable disease studies) is the period from study entry until disease recurrence, progression, death (regardless of the cause). Patients who do not experience an event (disease recurrence, progression, death) will be censored at date of last contact.

The defined date of disease progression will depend on the method of determination as follows:

8.21 For disease recurrence or progression defined by imaging, the appearance of one or more new lesions, or unequivocal progression of existing non-target lesions, the date of progression will be defined as the date such lesions were first found to be progressed by imaging.

8.22 For disease progression defined by development or worsening of ascites or pleural effusions, the date of progression will be defined as the date when a sample was taken for cytologic verification.

8.23 For disease progression defined by CA125 criteria alone, the date of progression will be defined as the first date of the initial CA125 of greater than or equal to two times the nadir value or upper limit of normal, whichever of these is applicable. Since radiographic imaging is required within 2 weeks of the confirmatory (second) CA125 value, then if the imaging criteria are met for recurrence, then the date of progression would be defined as the date of the imaging study (See 8.21).

8.24 If global deterioration in health status attributable to the disease is used to define progression, then a date indicating this event (e.g. transfer to hospice care) can be used to define the date of progression.

In cases where several events can determine a date of progression, the earliest event should be used to establish the date of progression (with the exception provided in section 8.23).

9.0 DURATION OF STUDY

Patients will receive therapy until disease progression or intolerable toxicity intervenes. The patient can refuse the study treatment at any time.

All patients will be treated until disease progression or treatment withdrawal. Patients will then be followed (with physical exams and histories) every three months for the first two years and then every six months for 1 year and then yearly for 2 years. The maximum follow-up period is 5 years. Off study tumor measurements should be continued for those patients who did not progress on therapy according to the schedule listed in Section 7. Patients will be monitored for delayed toxicity and survival for the 5-year period unless consent is withdrawn.

10.0 STUDY MONITORING & REPORTING PROCEDURE

10.1 Definitions

10.1.1 Adverse Events

An adverse event is any undesirable medical experience occurring to a subject who has been given an investigational product, whether or not related to the study drug(s). Medical conditions present before starting the investigational drug/intervention will be considered adverse events only if they worsen after starting study treatment. The following are adverse events:

- All unfavorable, harmful or pathological changes in the general condition of a patient.
- Subjective or objective symptoms (spontaneously offered by the patient and/or observed by the Investigator or the study nurse).
- All intercurrent events or exacerbation of pre-existing diseases which occurred after the administration of the study drug.
- All clinically significant changes in laboratory abnormalities.

- Any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable private information under the research.

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

AEs should be followed to resolution or stabilization, and reported as SAEs if they become serious (see below, definition of SAE). This also applies to patients experiencing AEs that cause interruption or discontinuation of investigational product, or those experiencing AEs that are present at the end of their participation in the study. Such patients should receive post-treatment follow-up as appropriate. AEs will be collected up to 30 days post last dose of study drug in all cases including early study termination. If an ongoing AE changes in its severity or in its perceived relationship to study drug, a new AE entry for the event should be completed.

10.1.2 Unexpected Adverse Event

Expected are those Adverse Events (AEs) that are bold and italicized in the CAEPR (see above). Any AE that is higher than grade 2 or not included in the CAEPR is considered an unexpected AE.

10.1.3 Serious Adverse Event

A serious adverse event or experience (SAE) or serious adverse drug reaction (ADR) is any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant disability/incapacity;
- Important medical events that may not result in death, be 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 in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

For the purposes of this study, the following must also be considered as an SAE:

1. ALT >3.0 x ULN with concomitant elevation in bilirubin (defined as total bilirubin ≥2.0 x ULN, with direct bilirubin >35%) or with hypersensitivity symptoms (e.g., fever, rash). Note: bilirubin fractionation should be performed if testing available.
2. 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). Note: bilirubin fractionation should be performed if testing available.

10.1.4 Attribution Assessment.

The Principal Investigator will evaluate all AEs and assess their toxicity and attribution, if any, to study drug. The following criteria will define the attribution:

Definite: The AE is clearly relation to the investigational agent.
Probable: The AE is likely related to the investigational agent.
Possible: The AE may be related to the investigational agent.
Unlikely: The AE is doubtfully related to the investigational agent.
Unrelated: The AE is NOT related to the investigational agent.

10.1.5 Hospitalization

Hospitalization or prolongation of hospitalization associated with Grade 3, 4, or 5 events, unexpected and expected, and regardless of attribution. Hospitalization for expedited AE reporting purposes is defined as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should be reserved for situations where the adverse event truly fits this definition and not for hospitalizations associated with less serious events. For example, a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours.

10.1.6 Pregnancy

Patients who become pregnant during the study should discontinue the study immediately. Patients should be instructed to notify the investigator if it is determined after completion of the study that they become pregnant either during the treatment phase of the study or within five days after the treatment period. Whenever possible a pregnancy should be followed to term, any premature termination reported, and the status of the mother and child should be reported to the Sponsor-Investigator after delivery.

10.2 Protocol violation

A protocol violation is defined as any change, deviation, or departure from the study design or procedures of a research project that is NOT approved by the IRB prior to its initiation or implementation, OR deviation from standard operating procedures, Good

Clinical Practices (GCPs), federal, state or local regulations. Protocol violations may or may not be under the control of the study team or staff. These protocol violations may be major or minor violations.

10.3 Data collection

Data will be collected using a centralized electronic case report form called **ON**-line **C**linical **O**ncology **R**esearch Environment = **Oncore**. Oncore is a highly secure, web based, cancer specific, and customizable system that provides fully integrative clinical data management and study administration capabilities developed in an ongoing collaborative effort with NCI designated Comprehensive Cancer Centers.

10.4 Reporting Requirements

10.4.1 Expedited Reporting of Adverse Events

Reporting of AEs will begin when the subject is administered the study drug or has a study related procedure. Events occurring in each subject will be recorded until 30 days post administration of the last treatment regardless of attribution. Adverse events that are possibly, probably, or definitely related to the study drug will be recorded until the subject completes treatment follow-up.

All adverse events occurring at all participating sites must be recorded into the University of Virginia Cancer Center OnCore database within the time frame specified below:

Table B: Therapeutic Medium Risk Phase II Studies
Reporting requirements for AEs that occur within 30 days of the last dose of protocol specified treatment

	Grade 1	Grade 2		Grade 3				Grade 4 & 5	
	Expected and unexpected	Expected	Unexpected	Expected		Unexpected		Expected	Unexpected
				Without hospitalization	With hospitalization	Without hospitalization	With hospitalization		
Unrelated Unlikely	Not required	Not required	Not required	ONCORE 30 days	ONCORE 15 days	ONCORE 30 days	ONCORE 15 days	ONCORE 15 days	ONCORE 15 days
Possible Probable Definite	ONCORE 30 days	ONCORE 30 days	ONCORE 15 days	ONCORE 30 days	ONCORE 15 days	ONCORE 15 days	ONCORE 15 days	ONCORE 15 days	ONCORE (24-hrs)* 7 days

*Enter into Oncore within 24 hours if unexpected and definitely related to protocol specified treatment
Hospitalization defined as an inpatient hospital stay or prolongation of a hospital stay equal to or greater than 24 hours

* For Hospitalization Only — Any medical event equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of requirements for Phase of study, expected or unexpected and attribution.

IRB Reporting Requirements

Serious and unexpected adverse events must be submitted to the site Institutional Review Board according to the participating site institutional policies.

For the University of Virginia clinical site, the Principal Investigator (PI) or designee is responsible for reporting AEs and unanticipated problems to the UVA HSR-IRB according to the following guidelines.

Type of Event	**To whom will it be reported:**	Time Frame for Reporting	How reported?
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation *An internal event is one that occurs in a subject enrolled in a UVa protocol*	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, Unexpected adverse event *See Oncore reporting requirement (sponsor's protocol section 10.5).*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not adverse events or protocol violations This would include a Data Breach.	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. *http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc)*
Protocol Violations (*The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by your sponsor, if applicable.)* Or Enrollment Exceptions	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html* *Go to 3rd bullet from the bottom.*
Data Breach	The UVa Corporate Compliance and Privacy Office, a ITC: if breach involves electronic data- UVa Police if breach includes such things as stolen computers.	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible and no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office- Phone 924-9741 **ITC:** Information Security Incident Reporting procedure, http://www.itc.virginia.edu/security/reporting.html Phone- (434) 924-7166

INDEPENDENT DSMB/DSMC			
DSMB/DSMC Reports	IRB	15 calendar days of the study team receiving the report	Copy of DSMB/ DSMC report

Major Protocol Violations OR enrollment Exceptions will be reported within 7 calendar days from the time the study team received knowledge of the event.

10.4.2 Additional Reporting Requirements for Participating Clinical Sites

In addition to the OnCore and IRB reporting requirements described above, all participating sites are required to report specific events to the Sponsor (UVa) to comply with GSK reporting requirements. These additional reporting requirements are as follows:

Serious Adverse Events:
SAEs should be initially reported to the Sponsor (UVA) using the Safety Reporting Cover Sheet within 24 hours of awareness. Complete SAE information should be reported to the Sponsor (UVa) via Oncore within 3 calendar days for deaths or life-threatening events and 5 calendar days for other serious adverse events. Relevant hospital case records and autopsy reports *(where applicable)* should be sent to the Sponsor (UVA) at the time of Oncore data entry.

The Safety Reporting Cover Sheet and supporting information should be sent to:

Linda Duska, MD
UVaPAZ@Virginia.edu

Pregnancy:
Pregnancy must be reported within 7 days of when the site is aware of the pregnancy to the Sponsor (UVa). Each pregnancy should be reported to the Sponsor (UVa) using the Safety Reporting Cover Sheet.

All pregnancy information should be sent to:

Linda Duska, MD
UVaPAZ@Virginia.edu

Reporting to the Participating Sites:

Because UVA PI is the Sponsor for the study, the UVA PI or designee is responsible for providing safety updates to all participating sites per the following guidelines:

UVA PI of MULTI-SITE TRIAL			
Type of Event	**To whom will it be reported:**	Time Frame for Reporting	How reported?
Serious, unexpected and related or possibly related adverse events	All Research Sites	Within 15 days after the Overall PI receives knowledge of the event.	IND/IDE Safety Report (Cover letter, copy of MedWatch/narrative)
Unanticipated Problem	All Research Sites	Within 15 calendar days from the time the Overall PI receives knowledge of the event.	Letter to Participating PIs, Copy of MedWatch or narrative

11.0 DATA SAFETY AND MONITORING PLAN

11.1 Data Safety Monitoring

The University of Virginia Cancer Center Data and Safety Monitoring Committee (DSMC) will provide oversight of the conduct of this study. The CC DSMC reports to the UVA Protocol Review Committee (PRC).

The DSMC will review the following:

- All adverse events
- Audit results
- Application of study designed stopping/decision rules
- Whether the study accrual pattern warrants continuation/action
- Protocol violations
- Endpoint data

The CC DSMC will meet every month for aggregate review of data. Issues of immediate concern by the DSMC are brought to the attention of the PI (and if appropriate to the PRC and IRB) and a formal response from the PI is requested. Auditing will occur according to the UVa Cancer Center Institutional Data & Safety Monitoring Plan.

DSMC reports will be sent to participating sites every 6 months.

12.0 STUDY MANAGEMENT

12.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

12.2 Registration Procedures
Registration procedures are outlined in Section 5.0.

12.3 Adherence to the Protocol
Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

12.4 Emergency Modifications
Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB-HSR approval/favorable opinion.

For any such emergency modification implemented, a UVA IRB modification form must be completed by study Personnel within five (5) business days of making the change.

12.5 Single Patient/Subject Exceptions
Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the Principal Investigator

12.6 Other Protocol Deviations/Violations
All other planned deviations from the protocol must have prior approval by the Principal Investigator

12.7 Protocol Deviations: A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants

- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

The clinical research team will record the deviation, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

12.7.1 Protocol Violations: An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

12.8 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

12.9 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

13.0 STATISTICAL CONSIDERATIONS

This is a multi-center, stratified, randomized phase II trial to evaluate the potential activity of the combination of weekly gemcitabine and pazopanib (experimental) compared to weekly gemcitabine alone (control) in patients with persistent or recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma. Specifically, the study is designed to estimate the progression-free survival hazard ratio of the combination compared to gemcitabine alone, and determine if the data support further research. Secondary objectives include determination, by arm, of the adverse event profile; preliminary estimates of response, duration of response, and overall survival; and relevant hazard ratios of the combination to gemcitabine alone.

13.1 Study Design/Endpoints

The primary endpoint is progression-free survival (PFS). In order to consider the combination worthy of further study the data need to support an improvement in median

PFS of approximately 60% (or a reduction in the hazard rate by 37.5%). The treatment arms/regimens will be:

Regimen 1. Gemcitabine 1000 mg/m^2 administered weekly on days 1 and 8 (30-60 minutes IV infusion)

Regimen 2. Gemcitabine 1000 mg/m^2 administered weekly on days 1 and 8 (30-60 minutes IV infusion) with Pazopanib 800mg PO daily days 1-21

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of recurrence/progression or death from any cause, whichever occurs first. Patients who do not experience an event (recurrence/progression or death) will be censored at date of last contact (Section 8.15). Secondary endpoints include the adverse event profile, tumor response (Section 8.13) and duration (Section 8.14), and overall survival (Section 8.16) by arm.

13.2 Sample Size/Accrual Rate

There are no published data estimating PFS using gemcitabine alone in a stratified analysis of patients who are platinum sensitive and those who are resistant in the target population, although Safra (2006)[51] provides an overall estimate where the patient population was equally divided between platinum sensitive and platinum resistant patients. Specifically, data[51,56] for treatment with gemcitabine alone indicate an approximate PFS of 2.4 – 2.8 months for platinum resistant and 5 months for platinum sensitive patients. The combined sample in Safra (2006) [51] indicates an overall median PFI of 3.73 months which is consistent with a linear relationship of median PFS between the two cohorts. If our patient population of platinum resistant to platinum sensitive is 1:1 then based upon a simple average the median PFS for the control regimen of gemcitabine alone would be approximately 3.8 months.

If we assume type I and type II error rates of 10% for a one-sided logrank test; the ability to detect a relative reduction in the hazard for PFS of 37.5% (HR of 0.625) requires approximately 122 observed events (recurrences/progressions or deaths). Uniform accrual will not be assumed since the study will be opened at the PIs institution (UVA) approximately 6 months earlier than for other participating sites. Therefore, sample size was estimated for this accrual pattern in 6 months blocks for a total accrual period of 2½ years and minimum follow-up of 6 additional months using the methods of Lakatos (1988, 2002).[57-58]

With the target population expected to be 1:1 for platinum resistant to platinum sensitive with a yearly dropout/loss rate of 10% then approximately 148 patients are required if 1-2 patients/month will be accrued at UVA in the 1st 6 month accrual period. Under this scenario, monthly accrual will need to increase to 4-5 patients per month in order to complete accrual in 2½ years.

13.3 Stratification Factors

Patients will be stratified according to their second line platinum-free interval PFI (resistant: those with a PFI less than or equal to 182 days versus sensitive: those with PFI greater than 182 days), and number of previous chemotherapy regimens (one versus two or more). PFI will be measured from the end of the most recent platinum induction

treatment. Patients will be randomized with equal allocation to each arm using a stratified block randomization scheme with varying block sizes (of size 4-6).

13.4 Futility Analysis

An interim analysis will be performed after approximately ½ of the expected events (61 recurrences/progressions or deaths) have been observed. The futility stopping bound was based upon the beta spending function where a quarter of the beta is spent at the interim analysis. The interim decision will indicate termination of the study and acceptance of the null if the stratified estimate of the hazard ratio has a p-value outside the futility boundary p-value which is estimated at 0.312. This estimate was generated under the assumptions specified for sample size determination and were based upon 10,000 simulations for a non-binding beta spending function where a quarter of the beta is spent at the interim analysis. The PASS 11 Power Analysis and Sample Size package was used to generate the futility bound and sample size estimate.

13.5 Analysis of Primary and Secondary Endpoints

The primary analysis for PFS will occur after 122 events have been observed or approximately 6 months after the last patient has been accrued to the study. PFS distributions will be estimated by the product limit method of Kaplan and Meier, and the Cox proportional hazards stratified maximum likelihood estimate will be used to estimate the hazard ratio of regimen 2 to regimen 1, and the stratified logrank statistic will be used to determine if the data support a 60% increase in median PFS of regimen 2 compared to regimen 1 with a one-sided 10% level test.

Adverse events will be tabulated by frequency and severity, overall and by arm. Differences in the level of adverse events by treatment regimen will be assessed by classifying them as severe or not severe and examining the relative proportion of severe toxicities.

Response as assessed by the proportion responding by RECIST and CA125 will be summarized. Association between measurable and non-measurable disease status on PFS and OS will be examined with plots of survival curves, estimates of quartiles and hazard ratios. The Cox proportional hazards stratified maximum likelihood estimate will be used to estimate the hazard ratio of regimen 2 to regimen 1 for the relevant time to event distributions. Formal tests for differences will be carried out with a Cox model or log-rank test if appropriate. The impact of additional, various prognostic factors or biological markers may be explored if sufficient data are obtained.

All analyses pertaining to OS will occur after all patients have been followed for a minimum of 3 years. This follow-up period with accrual of 148 patients (over a 2½ year accrual period) provides approximately 85% power to detect a relative reduction in the hazard for OS of 37.5% (HR of 0.625) from an estimated median survival of 13.1 months for the control regimen of gemcitabine alone. As with median PFS, median OS was approximated from reported data[51,56] for treatment with gemcitabine alone.

13.6 Reporting and Exclusions

The primary analysis will be based upon all eligible patients who received any protocol treatment, and will be based upon the arm they were randomized to regardless of treatment received (intent-to-treat).

13.6.1 Evaluation of toxicity

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

13.6.2 Evaluation of response and progression-free survival

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [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 received any protocol treatment 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).

Sub-analyses may be performed within resistant or sensitive subpopulations or on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis will be clearly reported.

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Appendix I: New York Heart Association (NYHA) classification

New York Heart Association Criteria

Class	Definition
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even with rest. With any physical activity, increased discomfort is experienced.

Source: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964: 114.

Appendix II: Medications That May Cause QTc Prolongation

The following table presents a list of drugs that prolong, may prolong or are unlikely to prolong the QTc. Please note that the list provided below has been prepared Feb 2012 and the full list is frequently updated. For the most current list of medications, users should be directed to the following website: *http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm*.

Drugs with a risk of Torsades de Pointes Drugs that are generally accepted to have a risk of causing Torsades de Pointes		*Drugs with a possible risk of Torsades de Pointes: Drugs that prolong the QT interval and/or in some reports have been associated with torsades de pointes but at this time lack substantial evidence for causing torsades de pointes*		*Drugs with a conditional risk of Torsades de Pointes: Drugs that carry a risk of torsades de pointes and/or QT prolongation under certain conditions, such as patients with congenital long QT syndrome, drug overdose or co-administration of interacting drugs*	
Generic	**Brand Name**	**Generic**	**Brand Name**	**Generic**	**Brand Name**
Amiodarone	Cordarone®	Alfuzosin	Uroxatral®	Amitriptyline	Elavil®
Amiodarone	Pacerone®	Amantadine	Symmetrel®	Ciprofloxacin	Cipro®
Arsenic trioxide	Trisenox®	Atazanavir	Reyataz®	Clomipramine	Anafranil®
Astemizole	Hismanal®	Azithromycin	Zithromax®	Desipramine	Pertofrane®
Bepridil	Vascor®	Chloral hydrate	Noctec®	Diphenhydramine	Benadryl®
Chloroquine	Aralen®	Clozapine	Clozaril®	Diphenhydramine	Nytol®
Chlorpromazine	Thorazine®	Dolasetron	Anzemet®	Doxepin	Sinequan®
Cisapride	Propulsid®	Dronedarone	Multaq®	Fluconazole	Diflucan®
Citalopram	Celexa®	Escitalopram	Lexapro®	Fluoxetine	Sarafem®
Clarithromycin	Biaxin®	Escitalopram	Cipralex®	Fluoxetine	Prozac®
Disopyramide	Norpace®	Famotidine	Pepcid®	Galantamine	Reminyl®
Dofetilide	Tikosyn®	Felbamate	Felbatrol®	Imipramine	Norfranil®
Domperidone	Motilium®	Fingolimod	Gilenya®	Itraconazole	Sporanox®
Droperidol	Inapsine®	Foscarnet	Foscavir®	Ketoconazole	Nizoral®
Erythromycin	Erythrocin®	Fosphenytoin	Cerebyx®	Nortriptyline	Pamelor®
Erythromycin	E.E.S.®	Gatifloxacin	Tequin®	Paroxetine	Paxil®
Flecainide	Tambocor®	Gemifloxacin	Factive®	Protriptyline	Vivactil®
Halofantrine	Halfan®	Granisetron	Kytril®	Ritonavir	Norvir®
Haloperidol	Haldol®	Indapamide	Lozol®	Sertraline	Zoloft®
Ibutilide	Corvert®	Isradipine	Dynacirc®	Solifenacin	VESIcare®
Levomethadyl	Orlaam®	Lapatinib	Tykerb®	Trazodone	Desyrel®
Mesoridazine	Serentil®	Lapatinib	Tyverb®	Trimethoprim-Sulfa	Sulfa®
Methadone	Methadose®	Levofloxacin	Levaquin®	Trimethoprim-Sulfa	Bactrim®
Methadone	Dolophine®	Lithium	Lithobid®	Trimipramine	Surmontil®
Moxifloxacin	Avelox®	Lithium	Eskalith®		
Pentamidine	Pentam®	Moexipril/HCTZ	Uniretic®		
Pentamidine	NebuPent®	Nicardipine	Cardene®		
Pimozide	Orap®	Nilotinib	Tasigna®		
Probucol	Lorelco®	Octreotide	Sandostatin®		
Procainamide	Pronestyl®	Ofloxacin	Floxin®		

Drugs with a risk of Torsades de Pointes Drugs that are generally accepted to have a risk of causing Torsades de Pointes		*Drugs with a <u>possible</u> risk of Torsades de Pointes: Drugs that prolong the QT interval and/or in some reports have been associated with torsades de pointes but at this time lack substantial evidence for causing torsades de pointes*		*Drugs with a <u>conditional</u> risk of Torsades de Pointes: Drugs that carry a risk of torsades de pointes and/or QT prolongation under certain conditions, such as patients with congenital long QT syndrome, drug overdose or co-administration of interacting drugs*	
Procainamide	Procan®	Ondansetron	Zofran®		
Quinidine	Cardioquin®	Oxytocin	Pitocin®		
Quinidine	Quinaglute®	Paliperidone	Invega®		
Sotalol	Betapace®	Perflutren lipid microspheres	Definity®		
Sparfloxacin	Zagam®	Quetiapine	Seroquel®		
Terfenadine	Seldane®	Ranolazine	Ranexa®		
Thioridazine	Mellaril®	Risperidone	Risperdal®		
Vandetanib	Caprelsa®	Roxithromycin*	Rulide®		
		Sertindole	Serdolect®		
		Sertindole	Serlect®		
		Sunitinib	Sutent®		
		Tacrolimus	Prograf®		
		Tamoxifen	Nolvadex®		
		Telithromycin	Ketek®		
		Tizanidine	Zanaflex®		
		Vardenafil	Levitra®		
		Venlafaxine	Effexor®		
		Voriconazole	VFend®		
		Ziprasidone	Geodon®		

Appendix III

Table A. Dose Modification Algorithms for Potential Pazopanib Treatment-related Adverse Events

AE Terms & Descriptions	Dose Modification Algorithms
Hypertension	
(A). Asymptomatic and persistent SBP of ≥140 and <170 mmHg, or DBP ≥90 and <110 mmHg, or a clinically significant increase in DBP of 20 mmHg (but still below 110 mmHg).	Step 1. Continue investigational product (IP) at the current dose. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled[a] blood pressure (BP). If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).
(B). Asymptomatic SBP ≥170 mmHg, or DBP ≥110 mmHg, or failure to achieve well-controlled BP within 2 weeks in scenario (A).	Step 1.Consider reducing or interrupting IP, as clinically indicated. Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Step 4. Once BP is well-controlled, restart IP dose-reduced by 200 mg if IP was interrupted.
(C). Symptomatic hypertension or recurring SBP ≥170 mmHg, or DBP ≥110 mmHg, despite modification of antihypertensive medication(s)	Step 1. Interrupt IP Step 2. Adjust current or initiate new antihypertensive medication(s). Step 3. Titrate antihypertensive medication(s) during next 2 weeks as indicated to achieve well-controlled BP. Referral to a specialist for further evaluation and follow-up is also recommended. Step 4. Once BP is well-controlled, restart IP dose-reduced by 200 mg.
(D). Refractory hypertension unresponsive to above interventions.	Discontinue IP and continue follow-up per protocol.
Prolongation of QTc Interval: If the QTc is prolonged, the ECG should be manually read to ensure accuracy of the reading. The values below refer to manually-read ECGs.	
QTc ≥ 480 < 500 msec	Continue IP; monitor as clinically indicated.
QTc ≥500 msec	Discontinue IP and continue follow-up per protocol.
Proteinuria	
UPC <3	Continue pazopanib at the current dose; monitor as clinically indicated
UPC ≥3 or 24-h urine protein ≥3g	Step 1. Interrupt IP. Step 2. Weekly UPC or 24-hr urine protein monitoring until UPC is <3 or 24-hr urine protein is <3 grams. Then restart pazopanib dose-reduced by 200 mg. Step 3. If UPC ≥3 or 24-h urine protein ≥3g recurs, repeat steps 1 and 2. Step 4. If UPC ≥3 or 24-hr urine protein ≥3 recurs and the pazopanib

AE Terms & Descriptions	Dose Modification Algorithms
	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 Sponsor 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 IP and continue follow-up per protocol. Otherwise, interrupt IP until the AE resolved to ≤ Grade 1. Step 2. Restart IP; consider reducing dose and monitor as clinically indicated.
Grade 3 or 4, or Recurrent ≥ Grade 2 event after dose interruption/reduction.	Discontinue IP and continue with follow-up per protocol.
Venous Thrombosis (DVT, PE)	
Grade 2	Continue IP at the current dose; monitor as clinically indicated
Grade 3	Step 1. Interrupt IP. Step 2. Initiate and monitor anticoagulation as clinically indicated. Step 3. Resume IP at reduced dose <*proposed: same dose*> only if all of the following criteria are met: • The subject must have been treated with anticoagulant at the desired level of anticoagulation for at least one week. • No Grade 3 or 4 or clinically significant Grade 2, hemorrhagic events have occurred while on anticoagulation treatment. Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment. When treating with warfarin, international normalized ratio (INR) should be monitored within three to five days after any change in IP dosing (eg, re-initiating, escalating/de-escalating, or discontinuing IP), and then at least weekly until the INR is stable. The dose of warfarin (or its derivatives) may need to be adjusted to maintain the desired level of anticoagulation
Grade 4 and/or PE	Discontinue IP and continue follow-up per protocol.
Arterial Thrombosis/Ischemia	
Any Grade	Discontinue IP and continue follow-up per protocol.

Thrombocytopenia/Neutropenia/Anemia: Investigate and document underlying cause	
Grade 1 or 2	Continue IP with current dose; monitor as clinically indicated.
Grade 3 or 4	Step 1. Interrupt IP until toxicity resolves to ≤ Grade 2. Step 2. Restart IP dose-reduced by 200 mg and monitor as clinically indicated. If no recovery to ≤ Grade 2 or recurrent Grade 3 or 4, discontinue IP and follow-up per protocol.
Palmar-plantar Erythrodysesthesia Syndrome	
Grade 1 Minimal skin changes or dermatitis without pain (erythema, oedema, hyperkeratosis)	1. Continue IP at present dose
Grade 2 Skin changes with pain; limiting instrumental activities of daily living (ADLs) (peeling, blisters, oedema, bleed, hyperkeratosis)	1. Hold IP 2. Treat as clinically appropriate 3. Upon resolution to Level 1 or better restart IP with a dose reduction to 400 mg 4. If recurrent consider a further dose reduction to 200mg or discontinuation
Grade 3 Severe skin changes with pain and limiting self care ADLs	1. Discontinue IP
Other Clinically Significant Adverse Events[b]	
Grade 1	Continue IP; monitor as clinically indicated.
Grade 2 or 3, if clinically significant	Step 1. Interrupt IP until toxicity resolves to ≤ Grade 1. Step 2. Restart IP dose-reduced by 200 mg and monitor as clinically indicated.
Grade 4	Discontinue IP and continue follow-up per protocol.

a. Well-controlled BP defined as SBP <140 mmHg and mean DBP <90 mmHg.
b. AEs are graded according to NCI Common Terminology Criteria for Adverse Events v4.0 (NCI CTCAE v4)
Abbreviations: BP, blood pressure; IP, investigational product.

Table B. Guidelines for Management of Treatment Emergent Hepatotoxicity

Event	Dose Modification Algorithms
(A). ALT of ≤ 3.0 x ULN	Continue pazopanib at current dose with full panel LFTs[a] monitored as per protocol.
(B). ALT >3.0 x ULN to ≤8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[b] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	**Liver Event Monitoring Criteria:** (1) Continue pazopanib at current dose levels. (2) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1.
(C). ALT >8.0 x ULN **without** bilirubin elevation (defined as total bilirubin[b] <2.0 x ULN or direct bilirubin ≤35%) and **without** hypersensitivity symptoms (e.g., fever, rash)	**1st occurrence – Liver Event Interruption Criteria:** (1) Interrupt pazopanib until toxicity resolves to ≤Grade 1 or baseline. Report the event to Sponsor as an SAE **within 24 hours** of learning of its occurrence. Make every reasonable attempt to have subjects return to the clinic within 24 to 72 hours for repeat liver chemistries and liver event follow up assessments. (2) Liver imaging and other laboratory investigations should be considered as clinically appropriate. (3) Monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1. (4) If the subject is benefiting from the study treatment, contact Sponsor for possible re-challenge. Re-treatment may be considered if ALL following criteria are met: - ALT/AST reduced to Grade 1 - Total bilirubin <1.5 x ULN or direct bilirubin ≤35% - No hypersensitivity signs or symptoms - Subject is benefiting from therapy. (5) Reintroduce pazopanib at a reduced dose of 400 mg once daily and measure serum liver tests weekly for 8 weeks. **Recurrence – Liver Event Stopping Criteria:** Discontinue pazopanib permanently and monitor subject closely for clinical signs and symptoms; perform full panel LFTs[a] weekly or more frequently if clinically indicated until ALT/AST is reduced to Grade 1.
(D). ALT >3.0 x ULN **with** concomitant elevation in bilirubin[b] (defined as total bilirubin ≥2.0 x ULN; with direct bilirubin >35%) or **with** hypersensitivity symptoms (e.g., fever, rash) or bilirubin is >3.0 x ULN regardless of ALT values.	**Liver Event Stopping Criteria:** (1) Discontinue pazopanib immediately, report the event to Sponsor as an SAE **within 24 hours** of learning of its occurrence. Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries and liver event follow up assessments. (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.

Event	Dose Modification Algorithms
For isolated total bilirubin[b] elevation (>1.5 x to 3x ULN) without concurrent ALT increases (defined as ALT <3 X ULN).	(1) Isolated hyperbilirubinemia (i.e., in the absence of elevated ALT or other signs/symptoms of liver injury) does not require dose modification. 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. **The dose of pazopanib should be reduced to 200 mg per day in patients with moderate hepatic impairment.**

a. Full panel LFTs include: AST, ALT, alkaline phosphatase, GGT, and total bilirubin. Coagulation tests should be performed as clinically indicated.

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

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

Appendix IV. General Chemotherapy Guidelines:

- For 21 day cycles, a patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.

- It will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window before and after the protocol-defined date" for "Day 1" treatment of 21 day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due).

- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window," for example; "Day 8 chemotherapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" can be given on Day 14, Day 15, or Day 16.

- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).

- Chemotherapy doses will be based on the subject's weight at baseline and will remain the same throughout the study. However, the doses will be recalculated if the patient has a weight change of greater than or equal to 10% from baseline.

- Maximum body surface area used for chemotherapy dose calculations will be 2.0 m^2. For chemotherapy dose calculations that use mg/kg, there will be no maximum kilogram amount used (doses will be calculated on actual weight in kg).