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SUMMARY OF CHANGES

For Protocol Revision #6 to GOG-0186J

NCI Protocol #: GOG-0186J
Local Protocol #: GOG-0186J

NCI Version Date: 03/09/2015
Protocol Date:

This amendment is being submitted in response to an RRA from Dr. Pamela Harris (**harrispj@mail.nih.gov**).

#	Section	Page(s)	Change
1	Title Page	1	• NCI Version Date is now 03/09/2015. • Includes Revisions 1-6.
2	4.216		• The Pazopanib CAEPR has been updated; version 2.6 has been inserted: Added New Risk: ○ Rare but Serious: Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease)
3	IC		Additional changes have been made to the IC document.

PROTOCOL GOG-0186J

A RANDOMIZED PHASE IIB EVALUATION OF WEEKLY PACLITAXEL (NSC #673089) PLUS PAZOPANIB (NSC #737754) (IND #75648) VERSUS WEEKLY PACLITAXEL PLUS PLACEBO IN THE TREATMENT OF PERSISTENT OR RECURRENT EPITHELIAL OVARIAN, FALLOPIAN TUBE OR PRIMARY PERITONEAL CARCINOMA **(02/06/2012)**

NCT #01468909 **(01/12/2015)**

NCI Version Date: 03/09/2015
Includes Revisions #1- 6
POINTS:
PER CAPITA – 20
MEMBERSHIP – 6 **(06/11/2012)**
TR PER CAPITA – Award based on specimen submission with 1.0 point for each whole blood and plasma specimen (TOTAL = 4.0 points).

Lead Organization: NRG/NRG Oncology **(01/12/2015)**

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SCHEMA

Regimen 1: Paclitaxel 80 mg/m^2 administered weekly on days 1, 8, and 15 (1-hr IV infusion) with Placebo PO daily

Regimen 2: Paclitaxel 80 mg/m^2 administered weekly on days 1, 8, and 15 (1-hr IV infusion) with Pazopanib 800 mg PO daily

Until disease progression or adverse effects prohibit further therapy
One cycle = 28 days

OPEN TO PATIENT ENTRY DECEMBER 12, 2011; REVISED FEBRUARY 6, 2012; REVISED JUNE 11, 2012; REVISED OCTOBER 9, 2012; CLOSED TO PATIENT ENTRY APRIL 22, 2013; REVISED JULY 12, 2013; REVISED JANUARY 12, 2015; REVISED

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1.0 OBJECTIVES

1.1 Primary Objectives:

1.11 To estimate the progression-free survival hazard ratio of the combination of weekly paclitaxel and pazopanib compared to weekly paclitaxel and placebo 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.

1.22 To estimate and compare the proportion of patients responding to therapy by RECIST, CA125 response, the overall survival (OS), and the duration of response in each arm.

1.3 Translational Research Objectives:

1.31 To explore the association between plasma cytokines and angiogenic markers and progression-free and overall survival.

1.32 To explore the association between single-nucleotide polymorphisms (SNPs) and progression-free and overall survival.

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 13,850 women will die of ovarian cancer in 2010.[1] Although about 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 recur. 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.

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, 2010). 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, 2010).[3,4]

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.[5,6] Reported data suggest that combined pharmacologic disruption of PDGFR-β and VEGFR-2 signaling results in profound antiangiogenic effects in tumors.[7] 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. Follow-up studies were done with pazopanib and docetaxel with an endpoint of time to reach two tumor doublings. Pazopanib was administered orally (PO) at 100 mg/kg daily and docetaxel was administered intraperitoneally (IP) at 50 mg/kg once weekly for 3 weeks. In two independent experiments, the median time to reach two tumor doublings was longest in mice treated with both pazopanib and docetaxel concomitantly. These results clearly show an advantage of combining pazopanib with docetaxel (and likely other chemotherapeutic agents) for better tumor control.

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.

<u>Nonclinical Pharmacology and Toxicology</u>
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

Approximately 3000 subjects with cancer have been enrolled in clinical studies of pazopanib as of September 2009. 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 .[8] In subjects with ovarian cancer, 31% of subjects experienced a CA-125 response to pazopanib, with a median time to response of 29 days and median duration of response of 113 days (Investigator's Brochure, 2010). 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.[9] 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.[10] 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%.[11] 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. [12] 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.[13] 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.[14] 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, 2010)

Safety

The randomized, phase 3 study in mRCC subjects provided a key comparison of safety with pazopanib compared to placebo.[8] 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, 2010). 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, 2010).[15] 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. [16] 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. [16]

Preliminary PK information on the combination of pazopanib and paclitaxel administered to subjects with advanced cancer has been reported.[17] 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%.[17]

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 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, 2010). 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.[18] 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, 2010). 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).[19] 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.[20-24] 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.[25] 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.[19] 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.[26] 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.[27] 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 to a more immature vascular phenotype devoid of pericytes.[28] 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.[27,29] 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. 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. 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. [37]

2.4 Weekly Paclitaxel and Safety of Combination Weekly Paclitaxel/Pazopanib

Weekly paclitaxel has been studied in recurrent ovarian cancer as a single agent in a number of clinical settings including in the GOG-0126 mechanism.[38-40] In each of these cases, real or suspected taxane-resistance has been a feature of enrolled patients. Activity, measured as objective response, from these studies is

approximately 20% and appears to be among the most active chemotherapeutics in the resistant phenotype. Dose-dense therapy of taxanes has recently proved to be a significant advance in primary ovarian cancer with the reporting of a Japanese phase III trial comparing weekly administration to bolus administration of paclitaxel, both in combination with bolus carboplatin. PFS was improved by 11 months in the dose-dense arm (17 mos vs 28 mos, P = 0.0014).[41] Unique to the infusion schedule was the absence of a "break" week, which is attributed to the low rate of completion of unaltered infusion. Compliance is improved with this recovery week but the impact on response remains to be tested. The theoretical advantage to lower dose, frequent administration of paclitaxel is its impact on local cytokines, which may provide an addition anti-angiogenic effect.[42-46] It has been shown pre-clinically that low dose paclitaxel is synergistic with anti-VEGF targeted therapies and has substantial clinical activity in uncontrolled study settings.[47] It also appears to impact the expression of thrombospondin-I, a natural inhibitor of neovascularization and angiogenesis. Phase I data support the safety of pazopanib at 800 mg po daily with paclitaxel 80 mg/m^2.[48] In this study 25 patients with advanced cancer were treated with escalating doses of pazopanib (400 mg – 800 mg) in combination with weekly paclitaxel (15 mg/m^2 – 80 mg/m^2) days 1, 8 ,15 on a 28 day cycle. One DLT was observed at this dose (Gr 3 groin abscess). Dose alterations for each agent at this dose over the course of therapy occurred in 7 patients for pazopanib (liver enzyme elevation) and in 11 patients for paclitaxel (dose delay) or dose reductions (5 patients). Pazopanib increases the bioavailability of paclitaxel by 40% (C_{max}) to 45% (AUC). The optimal treatment dose in this trial was determined to be pazopanib at 800 mg po daily with paclitaxel 80 mg/m^2 IV, days 1, 8, and 15 of a 28-day cycle.

2.5 Translational Research

Cytokine levels have been evaluated as potential diagnostic and prognostic markers in ovarian cancer. They function primarily to regulate immunity, hematopoiesis, and inflammation. Systemic cytokine levels differ in cancer patients, possibly due to an interaction between the disease and the immune system resulting in cytokine production.[49] Various cytokines, including IL-6, IL-7, and IL-8, have been associated with ovarian cancer and identified as potential therapeutic and diagnostic tools for the disease.[50-52] Additionally, levels of vascular endothelial growth factor (VEGF) have been found to correlate significantly with patient survival and to be an independent prognostic indicator in overall survival in patients with ovarian cancer.[53]

There is growing recognition that serum markers such as VEGF cannot predict the response to anti-VEGF treatment. As such, we have included plasma studies to evaluate the correlation between cytokine levels (e.g., IL-6, IL-8, IL 11, IL-1a, Il-3, IL-4, VEGF, TPO, G-CSF, GM-CSF, osteopontin, and sVEGFRs) with progression-free and overall survival in patients treated with pazopanib, which targets VEGFR 1,2, and 3. Previous studies indicate that the pre-treatment levels of VEGF in plasma, not serum, are associated with progression-free and overall survival in

patients with persistent or recurrent gynecologic malignancies, including ovarian, uterine, and uterine leiomyosarcoma.[54-56] Since platelets can upload cytokines and the actual level of cytokines/growth factors can be affected by thrombocytosis, plasma markers are preferable for identifying potential predictive markers to treatment. In addition, SNPs will be examined for associations with progression-free and overall survival.

2.6 Rationale for Clinical Trial Design

This is a double-blind, placebo-controlled phase II trial. All patients will receive IV paclitaxel days 1, 8, and 15 every 28 days in combination with either oral pazopanib or an oral placebo. Blinding will preserve the integrity of the progression-free survival and overall survival endpoints by eliminating biases in disease assessment monitoring, the declaration of disease progression and the institution/selection of future therapies. Therefore, it is understood that investigators, patients and research personnel will not know whether or not patients have received pazopanib or placebo. Because of the intent-to-treat analysis, this rule applies to patients who enter the study and then are later found to be ineligible. The only indication for un-blinding to treatment arm is a serious adverse event in which it is determined by the Study Chair that un-blinding would improve patient safety.

2.7 Inclusion of Women and Minorities

The Gynecologic Oncology Group and GOG participating institutions 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 by participating institutions.

3.0 PATIENT ELIGIBILITY

3.1 Eligibility 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 non-measurable (detectable) 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
Non-measurable (detectable) disease in a patient is defined in this protocol as one who does not have measurable disease but has at least one of the following conditions:

- Ascites and/or pleural effusion attributed to tumor;
- Solid and/or cystic abnormalities on radiographic imaging that do not meet RECIST 1.1 (see Section 8.1) definitions for target lesions.

3.13
Patients with measurable disease must have at least one "target lesion" to be used to assess response on this protocol as defined by RECIST 1.1 (Section 8.1). 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.

3.14
Patients must <u>not</u> be eligible for a higher priority GOG protocol, if one exists. In general, this would refer to any active GOG phase III or Rare Tumor protocol for the same patient population. In addition, patients must not be eligible for the currently active phase II cytotoxic protocol in platinum resistant disease.

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

Patients who have received two or three prior regimens must have a GOG 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 (non-cytotoxic) agents and immunologic agents, 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 12 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). There is no restriction on minor procedures (e.g., minor: central venous access catheter placement, ureteral stent placement or exchange, paracentesis, thoracentesis). **(02/06/2012)**

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, biologic/targeted (non-cytotoxic) agents (e.g., 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, with no more than 1 non-platinum, non-taxane regimen. **Treatment with weekly paclitaxel for recurrent or persistent disease is NOT allowed.**

3.173 Patients are allowed to receive, but are not required to receive, biologic/targeted (non-cytotoxic) therapy as part of their primary treatment regimen.

Patients must have NOT received any biologic/targeted (non-cytotoxic) therapy targeting the VEGF and/or PDGF pathways for management of recurrent or persistent disease.

For the purposes of this study, Poly (ADP-ribose) polymerase (PARP) inhibitors will be considered "cytotoxic". 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 will 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.

3.182 Blood coagulation parameters: PT such that international normalized ratio (INR) is less than or equal to 1.5 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 1.5 x ULN.

3.183 Renal function: Creatinine less than or equal to 1.5 x institutional upper limit normal (ULN).

3.184 Urine Protein: Urine protein should be screened by urinalysis. If protein is 2+ or higher, 24-hour urine protein should be obtained and the level must be <1000 mg (<1.0 g/24hrs) for patient enrollment.

3.185 Hepatic function:
- Bilirubin less than or equal to 1.5 x ULN.
- AST *and* ALT less than or equal to 2.5 x ULN *and* alkaline phosphatase less than or equal to 2.5 x ULN.
- Subjects who have **BOTH** bilirubin greater than ULN *and* AST/ALT greater than ULN are not eligible

3.186 Thyroid function: Patients must have normal baseline thyroid function tests (TSH, T3, T4). 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.

3.187 Neurologic function: Neuropathy (sensory and motor) less than or equal to grade 1.

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 III for a list of concomitant medications associated with QTc and Torsades de Pointes.*

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

3.2 Ineligibility Criteria

3.21 Patient who have had previous treatment with pazopanib. Patients who have had previous treatment with weekly paclitaxel 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 three 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 radiation for localized cancer of the breast, head and neck, or skin is permitted, provided that it was completed more than three 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 140 mm Hg or diastolic greater than 90 mm Hg despite antihypertensive medications.

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 II 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 and/or liposomal doxorubicin) must have an echocardiogram assessment and are excluded if they have an ejection fraction less than 50%.

3.257 CTCAE 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.

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 Patients with history or evidence upon physical examination of CNS disease, including primary brain tumor, seizures which are not controlled with non-enzyme inducing anticonvulsants, any brain metastases, or history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) or subarachnoid hemorrhage within six months prior to the first date of study treatment.

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)

- patients with clinical symptoms or signs of gastrointestinal obstruction and patients who require parenteral hydration and/or nutrition.

3.212 Patients who are pregnant or nursing.

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

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

4.0 STUDY MODALITIES

4.1 Paclitaxel (NSC #673089)

4.11 Formulation: Paclitaxel is supplied as a 6mg/mL non-aqueous solution in multi dose vials containing 30mg/5mL, 100mg/16.7mL, or 300mg/50mL of paclitaxel. In addition to 6mg of paclitaxel, each mL of sterile non-pyrogenic solution contains 527mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

4.12 Storage: Unopened vials of paclitaxel are stable to the date indicated on the package when stored between 20 to 25°C (68 to 77°F). Protect from light.

4.13 Stability: Commercially available paclitaxel will be labeled with an expiration date. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described below, solutions of paclitaxel (0.3-1.2mg/ml) are physically and chemically stable for 27 hours.

4.14 Preparation: Paclitaxel must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride for Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C / 77°F) and room lighting conditions.

NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.

Paclitaxel should be administered through an inline filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® or IVEX-HP®, which incorporate short inlet and outlet PVC-coated tubing, has not resulted in significant leaching of DEHP.

All patients should be premedicated with corticosteroids, diphenhydramine, and H_2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Patients who experience severe hypersensitivity reactions to drug may need to repeat the premedication and to be re-challenged with a dilute solution and slow

infusion. Severe hypersensitivity reactions to paclitaxel do not have to proceed with a re-challenge.

4.15 Adverse Effects: Consult the package insert for the most current and complete information.

4.16 Supplier: Commercially available both from Bristol-Myers Squibb Oncology as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

4.2 Pazopanib (CTEP IND#75648, NSC#737754) or placebo

All investigators who receive a copy of the protocol should also obtain a copy of the Investigator's Brochure (IB). IB's are available from the Pharmaceutical Management Branch, CTEP, DCTD, NCI and may be obtained by emailing the IB Coordinator (ibcoordinator@mail.nih.gov) or by calling the IB Coordinator at 301-496-5725.

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 and matching placebo are supplied as aqueous film-coated tablets.

Each tablet contains 200 mg or 0 mg of the free base. Tablets are oval-shaped, white and packaged in white high density polyethylene (HDPE) induction-sealed bottles with white, plastic child-resistant caps.

Each bottle contains 34 tablets. Tablet excipients in all tablets include microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate. The film-coat consists of titanium dioxide, hypromellose, polyethylene glycol 400, and polysorbate 80. **(01/12/2015)**

4.28 Storage: Store tablets at USP controlled room temperature (20° to 25° C or 68° to 77° F). **(01/12/2015)**

4.29 Stability: Stability studies are ongoing. An opened original container of tablets is stable for 3 months. If exact quantity must be dispensed, then extra tablets must be removed, documented and destroyed immediately. Alternatively, if exact quantity is dispensed in a pharmacy bottle, the supply should be assigned a 30-day expiration. **If tablets of patient-specific/blinded supply are dispensed in a pharmacy bottle, all of the information of the CTEP applied label (including the Julian Date) MUST be on the bottle dispensed to the patient. (01/12/2015)**

4.210 Administration**:** Oral. Take on an empty stomach either 1 hour before or 2 hours after food. The tablets should be swallowed whole and cannot be crushed or broken. **(01/12/2015)**

4.211 Potential Drug Interactions: *In vitro* data indicate that pazopanib is primarily metabolized by CYP3A4 isoenzyme. Potent CYP3A4 inducers and inhibitors are prohibited on pazopanib trials. Pazopanib is also a substrate for p-glycoprotein and breast cancer resistance protein (BCRP) transporters and concomitant administration of inhibitors such as lapatinib will result in increased plasma pazopanib concentrations.

Clinical studies indicate that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6. Use caution when combining pazopanib with CYP3A4, CYP2C8, and CYP2D6 substrates known to have a narrow therapeutic window.

In vitro studies also showed that pazopanib is a potent inhibitor of UGT1A1 and OATP1B1. Pazopanib may increase concentrations of drugs primarily eliminated through these systems.

Avoid co-administration of pazopanib with medicines that increase gastric pH. If the concomitant use of a proton pump inhibitor (PPI) is medically necessary, pazopanib should be taken without food once daily in the evening with the PPI. If the concomitant administration of an H_2-receptor antagonist is medically necessary, pazopanib should be taken without food at least 2 hours before or at least 10 hours after a dose of an H_2-receptor antagonist. Administer pazopanib at least 1 hour before or 2 hours after administration of short-acting antacids.

Avoid co-administration of pazopanib with simvastatin. Concomitant use of pazopanib and simvastatin increases the risk of ALT elevation. Data are not sufficient to assess the risk of concomitant administration of other statins and pazopanib.

Precautions: Pazopanib/placebo should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. Monitor ECGs and serum electrolytes (e.g., calcium, magnesium, potassium) at baseline and periodically and maintain within the normal range.

For patients who develop hepatic impairment, refer to the protocol document for appropriate dose modification or dose delay. **(01/12/2015)**

4.212 Availability: Pazopanib is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Pazopanib is provided to the NCI under a Collaborative Agreement between Novartis Pharmaceuticals Corporation and the DCTD, NCI (see Appendix VI).

4.213 Clinical Supplies / Drug Ordering

Clinical Supplies**:** Pazopanib (IND#75648, NSC 737754) and matching Placebo will be provided free of charge by Novartis Pharmaceuticals Corporation and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Each blinded, patient-specific bottle will be labeled with …

- the protocol number (i.e., "GOG-0186J")
- the bottle number (i.e., "Bottle 1 of 2" and "Bottle 2 of 2")
- the number of capsules (i.e., "34 tablets")
- the patient ID number (e.g.,"0186J-YYY", where "0186J-YYY" represents the protocol number and sequence number which represents the unique patient ID number assigned by GOG at the time of patient registration)
- the patient initials (i.e., **F**irst initial, **M**iddle initial, **L**ast initial [e.g., "FML"])
- the agent identification (i.e., "Pazopanib 200 mg or Placebo")
- a blank line for the pharmacist to enter the patient's name

- administration instructions (i.e., "Take __ tablets every day for 28 days.")
- storage instructions (i.e., "Store at controlled room temperature between 20° and 25° C)."
- emergency contact instructions
- a Julian date

The Julian date indicates the day the bottle was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2009 = 09, 2010 = 10) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2009 would have a Julian date of '09001' and a bottle labeled and shipped on December 31, 2009 would have a Julian date of '09365'. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all bottles (i.e., both pazopanib and Placebo) shipped on or before that date thus eliminating any chance of breaking the blind.

Drug Ordering:

BLINDED (pazopanib or placebo) THERAPY

No blinded starter supplies will be available for this study. Blinded, patient-specific clinical supplies will be sent to the registering investigator at the time of randomization. This randomization will be performed by the GOG Statistical and Data Center (SDC) in Buffalo, NY. The patient ID number assigned by the GOG SDC must be recorded by the registering institution for proper study medication dispersion. Once a patient has been registered with the GOG SDC, the GOG SDC will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the GOG SDC the day the patient is registered and will be processed by the PMB the next business day and shipped the following business day. Shipments within the United States will be sent by US Priority Mail (generally two to three day delivery). Thus, if a patient is registered on Monday, the GOG SDC would enter a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. Sites could expect to receive their order approximately Friday or Monday. Shipments to United States sites can be expedited (i.e., receipt on Thursday in example above) by the provision of an express courier account name and number to the GOG SDC at the time the patient is registered/randomized.

The initial shipment will be for 8 **– 34 tablet bottles** (a 2-cycle / 8-week supply at a dose of 4 tablets per day) of pazopanib or matching Placebo. Six weeks after the initial shipment, sites may reorder an additional 8 **– 34 tablet bottles** (a 2-cycle / 8-week supply at a dose of 4 tablets per day) by

completing an NCI Clinical Drug Request form and faxing it to the PMB at 301-480-4612 or by using the Online Agent Ordering Processing system (OAOP). The assigned patient ID number (e.g., "0186J-YYY") and the patient initials (e.g., "FML") should be entered in the "Patient or Special Code" field. The agent name for the pazopanib must be written on the order form as "Pazopanib or Placebo". All drug orders should be shipped directly to the physician responsible for treating the patient.

4.214 Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov). A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "0816J-YYY") on this protocol.

The Julian Date-Order number (e.g., 2014352-003) from the patients-specific label must be used as the Lot number on the NCI DARF. **(01/12/2015)**

4.215 Drug Returns**: Only undispensed clinical supplies should be returned to the PMB**. When it is necessary to return study drug (e.g., sealed bottles remaining when a patient permanently discontinues protocol treatment, expired bottles recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov). The patient ID number (e.g., "0816J-YYY") and the patient initials (e.g., "FML") should be entered in the "Lot Number" field. Opened bottles with remaining capsules should be documented in the patient-specific NCI Investigational Agent Accountability Record (i.e., logged in as "returned by patient" and logged out as "destroyed on site") and destroyed on-site in accordance with institutional policy.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (301) 496-5725 Monday through Friday between 8:30am and 4:30pm Eastern Time. You may also contact PMB via e-mail at PMBAfterHours@mail.nih.gov.

Drug Transfers: Bottles **MAY NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the principal investigator at a given clinical site changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 301-480-4612) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov). The patient ID

number (e.g., "0816J-YYY") and the patient initials (e.g., "FML") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "GOG-0186J").

4.216 Comprehensive Adverse Events and Potential Risks list (CAEPR) for GW786034 (Pazopanib, GW786034, NSC 737754) **(06/11/2012) (07/12/2013) ( )**

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 Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2383 patients.* Below is the CAEPR for GW786034 (pazopanib, GW786034).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6[1], January 21, 2015

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 4.0 Term) [n= 2383]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Hemolytic uremic syndrome[2]	
		Thrombotic thrombocytopenic purpura[2]	
CARDIAC DISORDERS			
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Sinus bradycardia		
ENDOCRINE DISORDERS			

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 4.0 Term) [n= 2383]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypothyroidism		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		
		Gastrointestinal fistula[3]	***Gastrointestinal fistula[3] (Gr 2)***
		Gastrointestinal hemorrhage[4]	
		Gastrointestinal perforation[5]	***Gastrointestinal perforation[5] (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INVESTIGATIONS			
	Activated partial thromboplastin time prolonged		
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 3)***
Blood bilirubin increased			***Blood bilirubin increased (Gr 3)***
	Creatinine increased		***Creatinine increased (Gr 2)***
		Electrocardiogram QT corrected interval prolonged	
Lymphocyte count decreased			***Lymphocyte count decreased (Gr 3)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hypercalcemia		

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 4.0 Term) [n= 2383]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Hyperglycemia			***Hyperglycemia (Gr 2)***
	Hyperkalemia		***Hyperkalemia (Gr 2)***
	Hypermagnesemia		
	Hypernatremia		
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypocalcemia		***Hypocalcemia (Gr 2)***
	Hypoglycemia		***Hypoglycemia (Gr 2)***
	Hypokalemia		
	Hypomagnesemia		
Hyponatremia			***Hyponatremia (Gr 2)***
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Tumor pain		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 3)***
	Headache		***Headache (Gr 2)***
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Proteinuria		***Proteinuria (Gr 2)***
		Urinary fistula	***Urinary fistula (Gr 2)***
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
		Female genital tract fistula	***Female genital tract fistula (Gr 2)***
		Uterine fistula	***Uterine fistula (Gr 2)***
		Vaginal fistula	***Vaginal fistula (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
	Respiratory hemorrhage[6]		***Respiratory hemorrhage[6] (Gr 2)***
		Respiratory, thoracic and mediastinal disorders – Other (interstitial lung disease)[7]	

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 4.0 Term) [n= 2383]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Palmar-plantar erythrodysesthesia syndrome		
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
Skin and subcutaneous tissue disorders - Other (hair color change/hair depigmentation)			***Skin and subcutaneous tissue disorders - Other (hair color change/hair depigmentation) (Gr 2)***
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (Gr 3)***
		Thromboembolic event[8]	
		Vascular disorders - Other (arterial thromboembolic event)[8]	

[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]Thrombotic microangiopathy (TMA) which includes both Hemolytic uremic syndrome (HUS) and Thrombotic thrombocytopenic purpura (TTP) has been reported in clinical trials of GW786034.

[3]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Enterovesical 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.

[4]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.

[5]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.

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

[7]Interstitial lung disease may include, Adult respiratory distress syndrome, Pneumonitis, Pulmonary fibrosis, Respiratory, thoracic and mediastinal disorders - Other (Acute respiratory distress syndrome), Respiratory, thoracic and mediastinal disorders - Other (Aveolitis), Respiratory, thoracic and mediastinal disorders - Other (Bronchiolitis obliterans), Respiratory, thoracic and mediastinal disorders - Other (Interstitial fibrosis), Respiratory, thoracic and mediastinal disorders - Other (Interstitial pneumonia), Respiratory, thoracic and mediastinal disorders - Other (Interstitial pneumonitis), Respiratory, thoracic and mediastinal disorders - Other (Organizing pneumonia), Respiratory, thoracic and mediastinal disorders - Other (Pulmonary infiltrates), Respiratory, thoracic and mediastinal disorders - Other (Toxic pneumonitis).

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

[9]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events also reported on Pazopanib (GW786034) trials but with the relationship to Pazopanib (GW786034) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia; Hemolysis
CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Cardiac disorders - Other (sinus arrest); Cardiac disorders - Other (supraventricular extrasystoles); Cardiac disorders - Other (Takotsubo [Broken Heart Syndrome]); Cardiac disorders - Other (Torsades de Pointes); Chest pain - cardiac; Pericardial effusion; Supraventricular tachycardia
ENDOCRINE DISORDERS - Adrenal insufficiency
EYE DISORDERS - Blurred vision; Dry eye; Eye disorders - Other (asthenopia); Eye disorders – Other (eye/retinal hemorrhage); Eye disorders - Other (foreign body sensation in eyes); Eye pain; Floaters; Glaucoma; Photophobia; Retinal tear
GASTROINTESTINAL DISORDERS - Abdominal distension; Dry mouth; Duodenal obstruction; Dysphagia; Esophagitis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (hyperactive bowel); Gastrointestinal disorders - Other (oropharyngeal pain); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal pain; Oral pain; Pancreatitis; Periodontal disease; Proctitis; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Malaise; Non-cardiac chest pain; Pain
INFECTIONS AND INFESTATIONS - Infection[9]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Cardiac troponin T increased; Cholesterol high; Ejection fraction decreased; GGT increased; INR increased; Investigations - Other (blood lactate dehydrogenase increased); Investigations - Other (blood TSH increased); Lipase increased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Hypertriglyceridemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Chest wall pain; Generalized muscle weakness; Head soft tissue necrosis; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Neck pain
NERVOUS SYSTEM DISORDERS - Extrapyramidal disorder; Intracranial hemorrhage; Ischemia cerebrovascular; Memory impairment; Paresthesia; Peripheral sensory neuropathy; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Suicide attempt
RENAL AND URINARY DISORDERS - Hematuria; Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Reproductive system and breast disorders - Other (vaginal necrosis); Vaginal discharge; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Laryngeal edema; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumothorax; Postnasal drip; Sore throat; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Pruritus; Purpura; Skin hyperpigmentation; Skin ulceration
VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Vasculitis

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.

4.217 Emergency Unblinding

In the event of an emergency during normal business hours (Monday through Friday 9:00 am to 5:00 pm Eastern Time), contact the GOG Statistical and Data Center by phone at 1-800-523-2917. At all other times, call: 716-901-2853. If there is no answer, leave a message including a telephone number for a return call. A staff member from the GOG Statistical and Data Center will return your call. **Remember, this is only in the event of an emergency!** This procedure is to be used by the physician when the physician needs to know whether the patient is taking pazopanib or a placebo to manage the acute illness. Patients should be instructed that if they have any questions or symptoms they should contact the treating physician's office. The GOG Statistical and Data Center will require the protocol number (i.e., "GOG-0186J"), the patient ID number (e.g., "999-0186J-001"), and the patient initials (e.g., "FML") to unblind the patient.

5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

Sites must submit all IRB approvals (initial and continuing) on NCI-sponsored adult Cooperative Group phase I, II & III prevention and treatment studies to the CTSU Regulatory Office, at the Coalition of Cancer Cooperative Groups in Philadelphia. A CTSU IRB/Regulatory Approval Transmittal Sheet should be submitted along with the CTSU IRB Certification Form or its equivalent. (CTSU forms can be downloaded at https://www.ctsu.org/public/rss2_page.aspx). IRB submissions can be faxed or e-mailed (preferred methods) or mailed to:

Cancer Trials Support Unit (CTSU)
ATTN: Coalition of Cancer Cooperative Groups (CCCG)
Suite 1100
1818 Market Street
Philadelphia, PA 19103
FAX: 1-215-569-0206
CTSURegulatory@ctsu.coccg.org

5.1 Patient Entry and Registration **(10/09/2012)**

When a suitable candidate has been identified for protocol entry, the following steps should be taken:

OPEN (Oncology Patient Enrollment Network) Registration: All site staff will use OPEN to enroll patients to this study. OPEN can be accessed on the GOG web menu page by clicking on the OPEN link.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the GOG or CTSU roster.
- To perform registrations you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

5.2 Treatment Plan

5.21 Patients will be stratified according to their platinum-free interval PFI (those with a PFI less than or equal to 182 days versus those with PFI greater than 182 days), measurable disease status (measurable versus non-measurable or "detectable" disease), and prior use of bevacizumab therapy (no use versus prior use).

Regimen 1: Paclitaxel 80 mg/m^2 administered weekly on days 1, 8, and 15 (1-hr IV infusion) with placebo PO daily.

Regimen 2: Paclitaxel 80 mg/m^2 administered weekly on days 1, 8, and 15 (1-hr IV infusion) with pazopanib 800mg PO daily.

One cycle equals 28 days.

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 (Appendix II). 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/placebo should be reviewed for potential drug-drug interactions (see Section 4.211, 5.33 and Appendices III).

5.211 Recommended preparative regimen for paclitaxel (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 H1 blocker such as loratadine or fexofenadine), and a standard dose of antihistamine H2 IV (such as cimetidine, ranitidine, or famotidine). The

preparative regimen can be altered at the discretion of the treating investigator.

5.22 See the GOG General Chemotherapy Guidelines (Appendix V).

5.23 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 III 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 III)

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** EKG **is required prior to study registration, and subjects with QTc > 480 msec are excluded**. Repeat EKG must be performed during the week 4, cycle 1 visit. If the QTc interval at 4 weeks is ≥ 500 msec, the EKG should be repeated within 7 days and, if the QTc interval remains ≥ 500 msec, the subject should be removed from the study. Additionally, if the QTc interval is increased by 60 msec or more from baseline but the QTc interval remains at < 500 msec, an EKG should be repeated within 7 days. If the repeat EKG again shows a ≥ 60 msec increase in the QTc interval from baseline, consideration should be given to removing the subject from the study or increasing monitoring, after discussion with the study chair.

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/placebo. A comprehensive list of agents that are associated with a risk of prolonging the QTc interval is provided in Appendix III. Subjects who begin any drugs with a high risk for QTc prolongation while receiving pazopanib/placebo should be monitored carefully for signs of potential problems with QTc prolongation (syncope, *etc*.). An EKG is not mandated in this circumstance; however, it should be performed at the treating physician's discretion.

5.414 Potassium, calcium, phosphate, and magnesium levels must be obtained before administration of the first dose of pazopanib/placebo and frequently thereafter (as described in Section 7.1).

Abnormalities in potassium, calcium, phosphate, and magnesium levels should be managed as detailed in Section 6.26.

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 IV**.

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 Section 6.273.

5.44 Hepatotoxicity **(07/12/2013)**

Cases of hepatic failure, including fatalities, have been reported during the use of GW786034. Two of 977 patients (0.2%) died with disease progression and hepatic failure in trials that supported the renal cell carcinoma (RCC) indication. One of 240 patients (0.4%) died of hepatic failure in the randomized soft tissue sarcoma (STS) trial. In RCC monotherapy trials using GW786034, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been reported as very common (≥10%), and abnormal hepatic function and hyperbilirubinemia have been reported as common (≥1% to <10%) adverse reactions. In STS monotherapy trials using GW786034, increased ALT and AST have been reported as common (≥1% to <10%) adverse reactions.

Elevated ALT (>3X ULN) and concurrent elevated ALT (>3X ULN) and bilirubin (>2X ULN) have been observed primarily between weeks 3 and 9 of therapy in GW786034 clinical trials. A comparison across trials with GW786034 indicates ALT >3X ULN in 1% and approximately 5% of patients treated with GW786034 at weeks 2 and 3, respectively. Most new cases of ALT >3X ULN occurred by week 9. More frequent monitoring between weeks 3 and 9 may lead to earlier detection of elevated serum liver tests and hepatotoxicity in patients taking GW786034.

See Section 7.1 for the **Risk Mitigation Plan** where serum liver function tests should be monitored before initiation of treatment with GW786034 and at weeks 3, 5, 7, and 9. Thereafter, monitoring should occur at months 3 and 4, and as clinically indicated. Periodic monitoring should continue after month 4.

5.5 Criteria for removal from treatment

5.51 Inability to tolerate the lowest doses of paclitaxel 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.

6.0 TREATMENT MODIFICATIONS

Study Drug	Initial dose level	1 level reduction	2 level reduction
Paclitaxel	80 mg/m^2	60 mg/m^2	40 mg/m^2
Pazopanib/Placebo	800 mg PO	600 mg PO	400 mg PO

Please note all CTCAE grading below refers to version 4.0.

A maximum of two dose reductions is allowed for each patient. Patients experiencing toxicity (hematologic or non-hematologic) that meets criteria for further dose reduction, after this maximum, will be removed from study therapy.

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

6.12 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 therapy.

Day 8 and Day 15 paclitaxel treatment will not be given unless ANC is ≥ 1000 cells/mcl and the platelet count is ≥ 75,000/mcl. If Day 8 or Day 15 paclitaxel is held, it should not be made up.

6.14 Patients requiring greater than two dose reductions of paclitaxel for any cause will result in discontinuation of study treatment. Patients requiring greater than two dose reductions of pazopanib/placebo for any cause will result in discontinuation of pazopanib/placebo (with continuation of paclitaxel, if appropriate, until unacceptable toxicity or progression of disease).

6.15 Dose modification for paclitaxel:

	ANC[1]	**PLT**	**ACTION**
Day 1	<1500	< 100,000	Delay. Monitor counts weekly until adequate for treatment. Restart when counts are adequate for treatment; reduce one dose level. If counts do not recover after 2 weeks delay, remove from study.
Day 8	< 1000	< 75,000	Hold dose
Day 15	< 1000	< 75,000	Hold dose
[1]For febrile neutropenia, and/or documented grade 4 neutropenia persisting greater than or equal to 7 days, reduce paclitaxel by one dose level on subsequent cycles.			

6.16 Dose interruption and modification of pazopanib/placebo:

Thrombo-cytopenia/ Neutropenia/ Anemia [1]	Grades 1 or 2	No interruption in treatment; maintain current dose.
	Grade 3 or 4	Interrupt treatment until toxicity is ≤grade 2; reduce one dose level. If no recovery to ≤grade 2 or recurrent grade 3 or 4, discontinue pazopanib/placebo. Maximal interruption is 2 weeks.
[1] The dose delays and modifications for anemia apply only to anemia which is due to hemorrhage or bleeding. No specific dose delays or dose reductions are required for anemia due to other causes, but the investigator should dose delay and dose-decrease, if he/she feels it is necessary, in a manner consistent with good medical practice.		

6.2 Dose and Treatment Modifications for Pazopanib/Placebo

6.21 Management of Hypertension: See Appendix IV

Increases in blood pressure (BP) and cases of hypertension have been associated with many drugs acting on the VEGF pathway. The proposed mechanism for this increase is through inhibition of VEGF-induced peripheral vasodilation. Hypertension following pazopanib treatment has been seen in animal studies as well as clinical trials. Specific guidelines for monitoring and management of this AE are provided below and in Appendix IV.

- While subjects are receiving treatment with pazopanib/placebo, the early initiation of antihypertensive treatment for grade 1 or 2 hypertension to minimize more severe or persistent hypertension is not considered a grade 3 AE.

- Decisions to hold or decrease the pazopanib/placebo dose during treatment must be based on BP readings taken in the clinic by a medical professional.

Recommended Hypertension Monitoring and Management
(BP in mmHg)

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Pazopanib/Placebo Dose Modification
Persistent Grade 1 Pre-hypertension Systolic 120-139 Diastolic 80-89		Standard	No change
Grade 2 Systolic 140-159 or Diastolic 90-99; medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mmHg (diastolic) or to >140/90 mm Hg if previously WNL;	Step 1) Initiate BP treatment and if needed, after 24-48 hr Rx, increase dose in stepwise fashion every 24-48 hours until BP is controlled or at max dose of Rx Step 2) If BP still not controlled, add another anti-hypertensive Rx, a LA DHP-CCB, ACE1,	BP should be monitored as recommended by the treating physician	No change except as described in step 4

monotherapy indicated	ARB, or ABB; increase dose of this drug as described in step 1 Step 3) If BP still not controlled, add 3rd drug from the list of antihypertensives in step 2; increase dose of this drug as described in step 1 Step 4) If BP still not controlled, consider either 1 dose reduction of Pazopanib/placebo or stopping Pazopanib/placebo *NOTE: Stopping or reducing the dose of pazopanib/placebo is expected to cause a decrease in BP.* *The treating physician should monitor the subject for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly* BP should be monitored as recommended by the treating physician No change except as described in step 4		

Grade 3 Systolic ≥160 or Diastolic ≥100; medical intervention indicated; more than one drug or more intensive therapy than previously indicated	HOLD pazopanib/placebo until systolic BP ≤159 and diastolic BP ≤99. BP management is identical to that for Grade 2 (see steps 1-4 above) **with 2 major exceptions:** **1) If systolic BP >180 or diastolic BP >110 and the subject is symptomatic: optimal management with intensive IV support in ICU; STOP pazopanib/placebo and notify hospital staff that stopping pazopanib/placebo may result in a decrease in BP** **and** **2) If systolic BP >180 or diastolic BP >110 and the subject is asymptomatic, 2 new antihypertensives must be given together in step 1 (and dose escalated appropriately as in step 1).** *NOTE: Stopping or reducing the dose of*	BP should be monitored as recommended by the treating physician **unless the subject is symptomatic with systolic BP >180 or diastolic BP >110 in which case, monitoring should be intensive.**	HOLD pazopanib/placebo until systolic BP ≤159 and diastolic BP ≤99. After this, Pazopanib/placebo may be readministered. If BP is still grade 2, manage as described above for grade 2 hypertension. In most circumstances, if BP cannot be controlled after an optimal trial of antihypertensive medications, consider either 1 dose reduction of pazopanib/placebo when systolic BP ≤159 and diastolic BP ≤99 or stopping pazopanib/placebo. **HOWEVER, If the subject requires hospitalization for management of symptomatic systolic BP >180 or diastolic BP >110,** permanently discontinue pazopanib/placebo or if BP is

	pazopanib/placebo is expected to cause a decrease in BP. *The treating physician should monitor the subject for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly*		controlled to systolic BP ≤159 and diastolic BP ≤99, consider re-starting pazopanib/placebo at 1 lower dose level after consultation with the Study Chair
Grade 4 Life-threatening Consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	**Optimal management with intensive IV support in ICU; STOP pazopanib/placebo and notify hospital staff that stopping pazopanib/placebo may result in a decrease in BP**	Intensive	Permanently discontinue pazopanib/placebo or if systolic BP ≤159 and diastolic BP ≤99, consider re-starting pazopanib/placebo at 1 lower dose level after consultation with the Study Chair

Abbreviations: LA (long acting), Dihydropyridine calcium-channel blockers (DHP-CCB), selective beta blockers (BB), Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin II Receptor Blockers (ARB), alpha beta blocker (ABB)

- *See table below for suggested antihypertensive medications by class
- If subjects require a delay of >2 weeks for management of hypertension, discontinue protocol therapy
- If subjects require >2 dose reductions, discontinue protocol therapy
- Subjects may have up to 2 drugs for management of hypertension prior to any dose reduction in pazopanib/placebo
- 24-48 hours should elapse between modifications of antihypertensive therapy
- Hypertension should be graded using CTCAE v4

In some instances of treatment for hypertension, a lower dose of the medication may be sufficient to provide the required antihypertensive control. In other instances, the standard dose of such a medication may be associated with AEs because of increased exposure. Alternatively, the investigator may choose to replace the medication with another in the same pharmacologic class that is less likely to interact with pazopanib/placebo. If such a medication is discontinued

and replaced, the transition period should occur no less than 7 days prior to the first dose of pazopanib/placebo. Based on prior clinical experience with pazopanib, the use of calcium channel blockers (dihydropyridine category) and ACE inhibitors as first-line and second-line therapy is recommended.

Oral Antihypertensive Medications

Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug-interactions with pazopanib/placebo through CYP450.

Agent Class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic Metabolism
Dihydropyridine Calcium-Channel Blockers (DHP-CCB)	**Nifedipine XL**	**30 mg daily**	**60 mg daily**	**90 mg daily**	**CYP 3A4 substrate**
	amlodipine	**2.5 mg daily**	**5 mg daily**	**10 mg daily**	**CYP 3A4 substrate**
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate and inhibitor
Selective β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	atenolol	**25 mg twice daily**	**50 mg twice daily**	**100 mg twice daily**	**No**
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5mg twice daily	5-10 mg twice daily	20 mg twice daily	Yes (CYP450 unknown)
Angiotensin Converting Enzyme Inhibitors (ACEIs)	captopril	12.5mg 3x daily	25mg 3x daily	50mg 3x daily	CYP 2D6 substrate
	enalapril	5 mg daily	10-20 mg daily	40 mg daily	CYP 3A4 substrate
	ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	lisinopril	**5 mg daily**	**10-20 mg daily**	**40 mg daily**	**No**
	fosinopril	10 mg daily	20 mg daily	40 mg daily	Yes (CYP450 unknown)
	Rarely used: **perindopril**	**4 mg daily**	**None**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
	losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 substrate

Angiotensin II Receptor Blockers (ARBs)	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	telmisartan	**40 mg daily**	**None**	**80 mg daily**	**Yes, but not CYP450**
	valsartan	**80 mg daily**	**None**	**160 mg daily**	**Yes, but not CYP450**
α and β Blocker	labetalol	100 mg twice daily	200 mg twice daily	400 mg twice daily	CYP 2D6 substrate and inhibitor

6.22 Pazopanib/placebo should be held for:

- hypokalemia or hyperkalemia ≥ grade 2;
- hypocalcemia or hypercalcemia ≥ grade 3*;
- hypophosphatemia ≥ grade 3;
- hypomagnesemia or hypermagnesemia ≥ grade 3

*Formula: Corrected Calcium = (0.8 x (Normal Albumin - Pt's Albumin)) + Serum Ca
Normal Albumin is 4.0 g/dL in most laboratories

Management of Abnormal Laboratory	**Assessments**

Hypokalemia or hyperkalemia ≥ grade 2,
Hypocalcemia or hypercalcemia* ≥ grade 3,
Hypophosphatemia ≥ grade 3, or
Hypomagnesemia or hypermagnesemia ≥ grade 3
	• EKG must be performed.
	• Laboratory values should be corrected as soon as possible in a manner consistent with good medical judgment.
	  • Pazopanib/placebo may be re-administered when
	  - hypokalemia or hyperkalemia is ≤grade 1;
	  - hypocalcemia or hypercalcemia* is ≤grade 2;
	  - hypophosphatemia is ≤grade 2; and
	  - hypomagnesemia or hypermagnesemia is ≤grade 2
	  • Even though pazopanib/placebo administration is allowed at these lower grades, every effort should be made to correct the abnormal lab values to normal if possible.

*Calcium should be corrected for albumin

6.23 Management of QTc Prolongation: Management of QTc prolongation of >500 msec *and* management of QTc prolongation of >60 msec from baseline.

Management of QTc Prolongation	
If EKG reveals an increase in the QTc to >500 msec or an increase in the QTc >60 msec from baseline	Repeat EKG before re-administration of Pazopanib/placebo.
If repeat EKG shows QTc interval is >500 msec	Remove patient from study treatment.
If on repeat EKG, QTc remains >60 msec longer than baseline but is less than 500 msec	Consider removing patient from study treatment.

6.24 Management of Proteinuria:

Proteinuria will be monitored by urine analysis dipstick.

Increases in proteinuria may occur during treatment and should be managed as follows:

Management of Proteinuria	
Dipstick 2+ or greater	Hold pazopanib/placebo and obtain 24 hour urine
If 24-hour urine protein <3 grams	Continue pazopanib/placebo
If 24-hour urine protein is greater than or equal to 3 grams	Step 1: Interrupt pazopanib/placebo treatment Step 2: Monitor 24-hour urine protein (weekly) until 24 hour urine protein is < 3 grams, then restart pazopanib/placebo dose-reduced by one dose level. Discontinue pazopanib/placebo if urine protein does not recover to < 3 grams after 8 weeks of pazopanib/placebo interruption
Nephrotic syndrome	Permanently discontinue pazopanib/placebo

6.25 **Management of Subjects with Elevations in AST, ALT and/or Bilirubin (01/12/2015)**

Management of Subjects with Elevations in AST, ALT and/or Bilirubin	
Event	**Dose Modification Algorithms**
ALT ≤3.0 x ULN	Continue at current dose. Discontinue simvastatin if patient has been receiving simvastatin and has ALT >ULN.
ALT >3.0 x ULN to ≤8.0 x ULN **without** bilirubin elevation (defined as total bilirubin <2.0 x ULN or direct bilirubin ≤35%)[a] and **without** hypersensitivity symptoms (e.g., fever, rash)	(1) Continue pazopanib at current dose levels. Discontinue simvastatin if patient has been receiving simvastatin. (2) Monitor patient closely for clinical signs and symptoms; perform full panel LFTs[b] at least weekly until ALT/AST is reduced to Grade 1.
ALT >8.0 x ULN **without** bilirubin elevation (defined as total bilirubin <2.0 x ULN or direct bilirubin ≤35%)[a] and **without** hypersensitivity symptoms (e.g., fever, rash)	**1st occurrence** (1) Interrupt pazopanib until toxicity resolves to ≤Grade 1 or baseline. Discontinue simvastatin if patient has been receiving simvastatin. Repeat full panel LFTs and clinical liver assessment within 24-72 hours, then full panel LFTs at least weekly until ALT/AST is reduced to Grade 1. Follow patient clinically as appropriate. (2) If the potential benefit for reinitiating pazopanib treatment is considered to outweigh the risk for hepatotoxicity, then consult a CTEP medical monitor before reintroducing pazopanib at a reduced dose (usually 400 mg daily.) Re-challenge 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 - Patient is benefiting from therapy. If approval for re-treatment is granted, the patient must be re-consented (ensuring documentation that patient is aware of all associated hepatotoxicity risks). Measure full panel LFTs at least weekly for 8 weeks at the reduced dose. **Recurrence** Discontinue pazopanib permanently and monitor patient closely for clinical signs and symptoms; perform full panel LFTs at least weekly until ALT/AST is reduced to Grade 1.
ALT >3.0 x ULN **with** concomitant elevation in bilirubin (defined as total bilirubin <2.0 x ULN; with direct bilirubin >35%)[a] or **with** hypersensitivity symptoms (e.g., fever, rash).	(1) Permanently discontinue pazopanib (and simvastatin, if patient is receiving simvastatin) and report the event to the CTEP medical monitor within 24 hours**.** Have patients return to the clinic within 24 hours, if possible, for repeat full panel LFTs and liver event follow up assessments. (2) Consult a gastroenterologist / hepatologist to identify potential co-factors. (3) Monitor patient closely for clinical signs and symptoms. Perform full panel LFTs at least weekly until LFTs are reduced to Grade 1.

Management of Subjects with Elevations in AST, ALT and/or Bilirubin	
Event	**Dose Modification Algorithms**
For isolated total bilirubin elevation **without** concurrent ALT increases (defined as ALT <3 X ULN).	Continue at current dose. Discontinue simvastatin if patient has been receiving simvastatin and has ALT > ULN.
a. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable and a patient meets the criterion of total bilirubin >1.5 x ULN, then the event should be promptly reported as an SAE. b. Full panel LFTs include: AST, ALT, alkaline phosphatase, GGT, and total bilirubin. Coagulation tests should be performed as clinically indicated. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver function test; SAE, serious adverse event; ULN, upper limit of normal	

AST, ALT and/or Bilirubin	
AST/ALT elevations between >3X ULN and 8X ULN	Continue pazopanib, but monitor weekly until AST/ALT returns to ≤ 2.5 or baseline
AST/ALT >8 X ULN	Hold pazopanib/placebo until AST/ALT returns to ≤ 2.5 X ULN or baseline. If the potential benefit of reinitiating pazopanib/placebo treatment is considered to outweigh the risk for hepatotoxicity, then consider reintroducing pazopanib/placebo at a reduced dose of 400 mg once daily (2 level dose reduction) and measure serum liver tests weekly for 8 weeks only after discussion with the Study Chair and CTEP. If AST/ALT elevations >3 X ULN recur, then pazopanib/placebo should be permanently discontinued.
AST/ALT >3 X ULN and concurrent bilirubin elevations >2 X ULN	Permanently discontinue pazopanib/placebo.

6.26 **Management of Other Adverse Events**

Adverse Event	**Grade**	**Treatment Modification**
Hemorrhage/ Bleeding/	Grade 1	No interruption in treatment unless hemoptysis. If hemoptysis, contact PI to determine if it is appropriate to continue pazopanib/placebo.

		Maintain current dose.
	Grade 2	For non-pulmonary bleeding, hold pazopanib/placebo unless resolved to ≤grade 1; reduce dose to next lower dose level, and continue treatment. For pulmonary bleeding, permanently discontinue pazopanib/placebo and remove subject from study. If grade 2 or greater hemorrhage/ bleeding recurs following dose reduction, stop pazopanib/placebo and remove subject from study.
	Grades 3 or 4	Discontinue treatment and withdraw subject from study.
Vascular/ Thrombosis	Grade 1	No interruption in treatment; maintain current dose.
	Grade 2, 3	Hold pazopanib/placebo until subject is receiving a stable dose of Low Molecular Weight Heparin (LMWH). Treatment may resume during the period of full-dose anticoagulation if all of the following criteria are met: • The subject must be have been treated with an anticoagulant at the desired level for at least one week. • The subject must not have had a grade 3 or 4 or significant grade 2 hemorrhagic event while on anticoagulant. Subject should be monitored as clinically indicated during anticoagulation treatment and after resuming study treatment. When treating with warfarin, international normalized ratio (INR) should be monitored within three to five days after any change in pazopanib/placebo dosing (*e.g.*, re-initiating, escalating/de-escalating, or discontinuing pazopanib), and then at least weekly until the INR is stable. The dose of warfarin (or its derivatives) may need to be adjusted to maintain the desired level of anticoagulation.
	Grade 4 or pulmonary embolus	Discontinue treatment and remove subject from study.
Arterial Thrombosis/ ischemia	All grades	Discontinue pazopanib/placebo and remove subject from study.
Thrombo-cytopenia/ Neutropenia/ Anemia [1]	Grades 1 or 2	No interruption in treatment; maintain current dose.
	Grade 3 or 4	Interrupt treatment until toxicity is ≤grade 2; reduce one dose level. If no recovery to ≤grade 2 or recurrent grade 3 or 4, discontinue pazopanib/placebo and remove subject from study. However, if the subject is benefiting from therapy, contact the sponsor (DCTD, NCI) to discuss course of action.

[1] The dose delays and modifications for anemia apply only to anemia which is due to hemorrhage or bleeding. No specific dose delays or dose reductions are required for anemia due to other causes, but the investigator should dose delay and dose-decrease, if he/she feels it is necessary, in a manner consistent with good medical practice.

6.27 Management of Other Clinically Significant Toxicities which are not Specifically Addressed Above

Observation	Action
AE resolves promptly with supportive care	Maintain dose level
1. Lower grade but related AEs (*e.g.*, abdominal pain)	Reduce one dose level*
AE does not resolve to grade 2 or below after treating subject at the lowest (*i.e.*, 400 mg daily) reduced dose level.	In general, remove subject from study **
* Alternatively and if medically appropriate, investigators may choose to hold dose for up to 14 days or withdraw subject from study. ** After consultation with study sponsor (DCTD, NCI), a dose of 400 mg daily may be considered for subjects on study ≥3 months who are benefiting from the agent.	

6.3 Dose and Treatment Modifications for Paclitaxel Non-Hematologic Toxicity

6.31 Grade 2 (or greater) peripheral neuropathy requires reduction of one dose level of paclitaxel and delay in subsequent therapy for a maximum of 2 weeks until recovered to grade 1. If no recovery after 2 weeks, patient should be removed from study.

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 paclitaxel and delay in subsequent therapy for a maximum of 2 weeks until recovered to grade 1.

6.34 Other non-hematologic toxicities with an impact on organ function of grade 2 (or greater) require reduction of one dose level of paclitaxel 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

7.1 Tests and Observations

The following observations and tests are to be performed and recorded on the appropriate form(s):

Parameter	Pre-Therapy **(02/06/2012)**	Weekly	Prior to Each cycle	Every other cycle	Off of all study therapy
History & Physical	1		X		
Vital Status					2
Vital signs (Blood Pressure, Heart Rate and Temperature)	1	3	X		
Performance Status	1				
Toxicity Assessment	4	3	X		2, 5
CBC/Differential/Platelets	4	6	7		
PT/INR and PTT	4, 8				
Electrolytes, BUN, creatinine, Ca, Mg, PO_4	4, 9	3, 9	X		
Bilirubin, AST, ALT, Alkaline Phosphatase	4	3	X§ **(07/12/2013)**		
Thyroid Function tests (TSH, T3, T4)	4				
Pregnancy Test (if childbearing potential exists)	4				
Chest imaging (x-ray or CT of chest)	1			10	10†
Radiographic tumor measurement	1, 11			11	11†
CA-125	4		X		
Electrocardiogram (ECG)	1	12			

LVEF Testing (Required for subjects who have received prior anthracycline – including doxorubicin and/or liposomal doxorubicin)	1				
Urinalysis (Dipstick) to evaluate for proteinuria	13			14	
Patient Tablet Calendar			15		

One cycle = 28 days

† **Until disease progression or until patient initiates a subsequent cancer therapy**

§ **Serum liver tests should be monitored before initiation of treatment with GW786034 and at weeks 3, 5, 7 and 9. Thereafter, monitoring should occur at months 3 and 4, and as clinically indicated. Periodic monitoring should continue after month 4. (07/12/2013)**

Notes:

1. Must be obtained within 28 days prior to initiating protocol therapy.
2. Follow-up every 3 months for 2 years and then every 6 months for 3 years. Follow-up forms (Form Q) are collected for the 5-year follow-up period or until study termination.
3. During the first cycle of therapy patients should be seen every week; thereafter the patient can be seen prior to each cycle.
4. Must be obtained within 14 days prior to initiating protocol therapy.
5. Report all adverse events that occur within 30 days of last protocol treatment on the T form for the last cycle of therapy administered. For reporting of delayed toxicity, see Section 10.1.
6. If grade 4 neutropenia is documented (ANC <500/mcl), obtain twice per week until resolved to grade 3.
7. CBC/Differential/Platelets must be obtained within 4 days of re-treatment with protocol therapy.
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, according to CTCAE version 4 criteria, the potassium level is grade 2 or greater and/or if the calcium, magnesium and/or phosphorous are grade 3 or higher, an EKG must be performed and appropriate action taken based on the results in Section 6.24.
10. Repeat chest imaging every other cycle (or equivalent time frame for patients off treatment prior to disease progression) for the first 6 months if initially abnormal or if required to monitor tumor response.
11. CT scan or MRI if used to follow lesion for measurable disease every other cycle (or equivalent time frame for patients off treatment prior to disease progression) for the first 6 months; 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. Responses (CR and PR) require confirmation at greater than or equal to 4 weeks from initial documentation (see section 8).
12. Repeat EKG must be performed during the week 4, cycle 1 visit. If the QTc interval at 4 weeks is

>500msec, the EKG should be repeated within 7 days and, if the QTc interval remains >500 msec the patient should be removed from the study. Additionally, if the QTc interval is increased by >60 msec from baseline but the QTc interval remains at <= 500 msec, an EKG should be repeated within 7 days. If the repeat EKG again shows a >60 msec increase in the QTc interval from baseline, consideration should be given to removing the patient from the study or increasing monitoring, after discussion with the study chair.

13. Urinalysis (dipstick) to evaluate for proteinuria must be obtained 14 days prior to initiating protocol therapy. If protein is 2+ or higher, 24-hour urine protein should be obtained and the level must be <1000 mg (<1 g/24hrs) for patient enrollment (see section 3.184). Please record value on the D2R form.
14. Urinalysis (dipstick) to evaluate for proteinuria should be performed prior to every other cycle (for example, prior to cycles 1, 3, 5, 7, ETC). See the guidelines provided in Section 6.0 regarding treatment with pazopanib and proteinuria. Each value should be recorded on the D2R form, for the appropriate cycle.
15. See Appendix II.

7.2 Pathology Requirements

Stained slides to confirm eligibility by Central Pathology Committee Review are not required for this protocol.

7.3 Translational Research

7.31 Specimen Requirements

If the patient gives permission for her specimens to be collected for this optional translational research study component, then the participating Institution is required to submit the patient's specimens as outlined below (unless otherwise specified).

A detailed description of the specimen requirements and procedures can be found in Appendix VII.

Required Specimens (Specimen Codes)	**Form SP**	**Collection Time Points**	**Deadlines and Recommendations**
Whole Blood (WB01) 7-10mL drawn into a purple-top (EDTA) tube	SP-WB01-186J	Collect prior to or after starting therapy	Ship to the GOG Tissue Bank the day the blood is collected[1] Submit Form SP online within 26 weeks of registration
Pre-Cycle 1 Plasma (PB01) prepared from 7-10mL of blood drawn into a purple top (EDTA) tube	SP-PB01-186J	Collect within 14 days of starting cycle 1 of therapy	Ship to the GOG Tissue Bank within 26 weeks of registration[1] Submit Form SP online within 26 weeks of registration
Pre-Cycle 2 Plasma (PB02) prepared from 7-10mL of blood drawn into a purple top (EDTA) tube	SP-PB02-186J	Collect prior to starting cycle 2 of therapy or at the time the patient goes off-study due to disease progression or toxicity	
Pre-Cycle 6 Plasma (PB03) prepared from 7-10mL of blood drawn into a purple top (EDTA) tube	SP-PB03-186J	Collect prior to starting cycle 6 of therapy or at the time the patient goes off-study due to disease progression or toxicity	

[1] Ship specimens to: GOG Tissue Bank / Protocol GOG-186J, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, E-mail: gogbank@nationwidechildrens.org.

7.32 Laboratory Testing

7.321 Analysis of Plasma Cytokines and Angiogenic Markers

Plasma will be used to detect various cytokines and angiogenic markers (e.g., IL-6, IL-8, IL 11, IL-1a, Il-3, IL-4, VEGF, TPO, G-CSF, GM-CSF, osteopontin, and sVEGFRs) using the Luminex MILLIPLEX MAG Human Cytokin/Chemokine panel (Millipore Corp, Billerica, MA).

7.322 SNP Anlaysis

DNA will be isolated from whole blood specimens. SNPs will be assessed using the iPLEX assay on the Sequenome MassARRAY platform (Sequenom Inc, San Diego, CA).

7.33 Future Research

Details regarding the banking and use of specimens for future research can be found in Appendix VII.

7.4 Quality of Life

Not applicable.

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, the GOG 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 cannot be used to assess response or progression in this study**. 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 date of study entry, including the baseline measurements.

8.15 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of progression or death, whichever occurs first.

8.16 Survival

Survival is defined as the duration of time from study entry to time of death or the date of last contact.

9.0 DURATION OF STUDY

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

9.2 All patients will be treated (with completion of all required case report forms) until disease progression, initiation of a subsequent cancer treatment, or study withdrawal. Patients will then be followed every three months for the first two years and then every six months for the next three years. Patients will be monitored for delayed toxicity and survival for this 5-year period with Q forms submitted to the GOG Statistical and Data Center, unless consent is withdrawn. Q forms will no longer be required if the study is terminated prior to the completion of the 5-year follow-up period.

9.3 A patient is considered off study therapy when the patients has progressed or died, a subsequent drug or therapy (directed at the disease) is initiated or ***all*** study therapy is discontinued. Report all treatment received on From D2R and adverse events on Form T until the patient qualifies as being off study therapy.

10.0 STUDY MONITORING AND REPORTING PROCEDURE

10.1 ADVERSE EVENT REPORTING FOR AN INVESTIGATIONAL AGENT (CTEP IND)

10.11 Definition of Adverse Events (AE)

Adverse event (21 CFR 312.32(a)): Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

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). The CTCAE v4.0 Manual is also available on the GOG member web site (http://www.gog.org under MANUALS).

10.12 Reporting Expedited Adverse Events

Depending on the phase of the study, use of investigational agents, and role of the pharmaceutical sponsor, an expedited AE report may need to reach multiple destinations. For patients participating on a GOG trial, all expedited AE reports should be submitted by using the CTEP automated system for expedited reporting (AdEERS). All AdEERS submissions are reviewed by GOG before final submission to CTEP. Submitting a report through AdEERS serves as notification to GOG, and satisfies the GOG requirements for expedited AE reporting. All AdEERS reports will be immediately directed to the Study Chair for further action.

The requirement for timely reporting of AEs to the study sponsor is specified in the Statement of Investigator, Form FDA-1572. In signing the FDA-1572, the investigator assumes the responsibility for reporting AEs to the NCI. In compliance with FDA regulations, as contained in 21 CFR 312.64, AEs should be reported by the investigator.

10.13 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements:

- All Grades 2 and 3 myelosuppression (including neutropenia, anemia, and thrombocytopenia) that does not require hospitalization is exempt from expedited reporting.

10.14 Procedures for Expedited Adverse Event Reporting:

10.141 AdEERS Expedited Reports: Expedited reports are to be submitted using AdEERS available at http://ctep.cancer.gov. The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.

AML/MDS events must be reported via AdEERS (in addition to routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplatic syndrome, or 3) Treatment-related secondary malignancy.

For the purposes of expedited reporting of adverse events to CTEP, unexpected events are those not listed in the Agent Specific Adverse Event List (ASAEL). The ASAEL is a subset of AE's within the Comprehensive Adverse Event and Potential Risks List (CAEPR). This list of events is based on CTEP's clinical experience with this agent and defines "expected" Grade 2 and 3 AE's not requiring hospitalization as exempt from expedited reporting. The CAEPR is a complete list of reported and/or potential AE's associated with an agent under a CTEP IND. For questions or comments regarding the ASAEL or CAEPR, please contact the AdEERS MD Help Desk at adeersmd@tech-res.com.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted.

10.15 Regular adverse events reporting

For studies using investigational agents, the GOG Statistical and Data Center (SDC) routinely reports adverse events electronically to the CTEP Clinical Data Update System (CDUS Version 3.0). The SDC submits this data quarterly. The AEs reported through AdEERS will also be included with the quarterly CDUS data submissions.

10.2 GOG DATA MANAGEMENT FORMS

The following forms must be completed and submitted to the GOG Statistical and Data Center (SDC) in accordance with the schedule below. All forms except the BDR Form and Pathology report **must** be submitted via the SDC Electronic Data Entry System (SEDES) which is available through the GOG website (www.gogstats.org). The BDR Form should be submitted via mail. The GOG Uploader Application in SEDES is an alternate method for submitting pathology reports and BDR to the GOG SDC.

Form	Due within		Copies*	Comments
	Weeks	Event		
Specimen Consent Application	1	Registration	N/A	Complete online
Form R (Registration Form)	2	Registration	1	Mandatory submission via SEDES
Form OHR (Recurrent Gynecologic Cancer-On Study History Form)	2	Registration	1	Mandatory submission via SEDES
Form DR (Pre-Treatment Summary Form)	4	Registration	1	Mandatory submission via SEDES
Form BDR (Pre-Treatment Body Diagram Form)	4	Registration	2	Submit to SDC via postal mail
Form D2M (Solid Tumor Evaluation Form)	4	Registration	1	Mandatory submission via SEDES
Primary disease:** Pathology Report Recurrent or Persistent Disease:** Pathology Report (only if histologically documented)	6 6	Registration Registration	1 1	Submit to SDC via postal mail or via report uploader
Form BMR (CA-125 reporting) (Biomarker Reporting Form)	2	Registration and completion of each cycle of therapy and disease assessment	1	Submit via SEDES
Form D2R (Cycle Dose Drug Form)	2	Completion of each cycle of therapy	1	Mandatory submission via SEDES
Form D2M (Solid Tumor Evaluation Form)	2	Clinical response assessment	1	Mandatory submission via SEDES
Form T (Common Toxicity Reporting Form)	2	Beginning of each subsequent cycle	1	Mandatory submission via SEDES
Form Q0 (Treatment Completion Form)	2	Completion of study Rx and change in Rx	1	Mandatory submission via SEDES
Form SP-WB01-186J for whole blood	26	Registration		Mandatory submission via SEDES †

Form SP-PB01-186J for pre-cycle 1 plasma	26	Registration		Mandatory submission via SEDES †
Form SP-PB02-186J for pre-cycle 2 plasma	26	Registration		Mandatory submission via SEDES †
Form SP-PB03-186J for pre-cycle 6 plasma	26	Registration		Mandatory submission via SEDES †
Form Q (Follow-up Form)	2	Disease progression; death; normal follow-up	1	Mandatory submission via SEDES quarterly for 2 years, semi-annually for 3 more years

* The number of required copies including the original form which must be sent to the Statistical and Data Center.

** **Pathology slides for Central Pathology Committee Review are not required on this study.**

† Form SP must be submitted online regardless of whether the specimen is submitted for research.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

11.0 STATISTICAL CONSIDERATIONS

The purpose of this study is to assess the relative activity of Arm 2 (the combination regimen) to Arm 1 (the control of paclitaxel) through the hazard ratio of disease progression or death (PFS endpoint) as a superiority study. The combination regimen must demonstrate a reduction in the hazard rate before it can be deemed interesting and worthy of further investigation. A reduction in the hazard rate by 37.5% is considered important to detect. If the combination regimen has a hazard rate roughly equal to the control, then there would be little benefit seen from adding the experimental drug to paclitaxel with a potential added risk through new drug toxicities. Therefore, a combination regimen yielding roughly equal hazard rates to the control should be rejected.

Patients will be stratified according to their platinum-free interval PFI (those with a PFI ≤ 182 day versus those with PFI > 182 days), measurable disease status (measurable versus non-measurable or "detectable" disease), and prior use of bevacizumab therapy (no use versus prior use).

11.1 Parameters employed to evaluate treatment efficacy and toxicity are:

11.11 Primary Endpoints

11.111 The Cox proportional hazards, (platinum-free interval, measurable disease status, prior use of bevacizumab) stratified, maximum likelihood estimate of the logarithm of the hazard ratio of Arm 2 to Arm 1 for disease progression or death (PFS endpoint).

11.12 Secondary Endpoints

11.121 Adverse events as assessed by CTCAE

11.122 Frequency and duration of tumor response by RECIST, CA-125 as well as overall survival.

11.13 Translational Research Endpoints

11.131 Plasma cytokines and angiogenic markers against PFS and OS.

11.132 Single-nucleotide polymorphisms (SNPs) against PFS and OS.

11.2 The anticipated annual accrual is approximately 50 patients.

11.21 The anticipated period of active accrual is expected to be 16 to 30 months, depending on the results of an interim analysis and rates of local IRB approval.

11.3 Study Plan:

Given that this is a Phase 2 study, the probabilities of type I and type II errors being equal to 10% and 20% respectively, are considered acceptable. Patients will be randomized equally to each arm. The level of reduction in the hazard ratio of Arm 2 to Arm 1 that is considered interesting to detect is 37.5%. The null hypothesis is therefore Ho: $\Delta \geq 1$ versus Ha: $\Delta \leq 0.625$ (or $H_0 : \theta \geq 0$ and $H_a : \theta \leq -0.4700$ where θ is the natural logarithm of the hazard ratio). This alternative hypothesis is comparable to the experimental therapy increasing the cumulative proportion of patients alive and progression-free at 5 months from 50% to 65%. Using Schoenfeld's equation to approximate the number of required events to achieve the study's desired operating characteristics, we obtain $D = (Z_\alpha + Z_\beta)^2 \times (R + 1)^2 / (R \times \ln \{\Delta\}^2) = 81.63$ when $Z_\alpha = 1.2816$, $Z_\beta = 0.8416$, and $R = 1$. $Z_\alpha = 1.28$ since the alternative hypothesis is one-sided. R is the ratio of patients assigned to the experimental therapy to the control therapy which equals one since patients will be assigned to the arms with equal probability. Based on these desired characteristics, it is necessary to observe approximately 82 events. To assure data maturation in a timely manner, up to 110 patients could be accrued to the clinical trial. Further justification for the final sample size when utilizing an interim analysis is provided below:

At approximately the 42nd event (taking events from both treatment arms), an interim futility analysis will be conducted using the method provided by Weiand's et al.[59] futility rule. More specifically, the interim decision rule will reject the combination therapy as being uninteresting if the stratified estimate of the hazard ratio is greater than 1. This decision rule will stop the study early 50% of the time when the hazard ratio is truly one. On the other hand, there could be a non-trivial probability of falsely declaring active regimens not interesting. To correct this problem, group sequential methods will be utilized that incorporate the futility rule as outlined by Jennison and Turnbull[60] (p49, eq. 3.1). The standardized test statistics, related to the log hazard ratio at the interim and final analyses will be designated by Z_1 and Z_2, respectively. Specifically, $Z_i = \left(\hat{\theta}_i - 0\right) / \hat{\sigma}_{\hat{\theta}_i}$ where $i = 1, 2$ according the stage of the study. According to Jennison and Turnbull, these statistics will be distributed as a multivariate normal distribution with the following parameters:

$$\begin{pmatrix} Z_1 \\ Z_2 \end{pmatrix} \sim MVN\left(\begin{pmatrix} \theta\sqrt{I_1} \\ \theta\sqrt{I_2} \end{pmatrix}, \Sigma = \begin{bmatrix} 1 & \sqrt{I_1 / I_2} \\ \sqrt{I_1 / I_2} & 1 \end{bmatrix} \right)$$

where I_k is the information obtained at the k[th] stage of the design with $I_k = d_k / 4$ and d_k being the total number of observed events at that time. Since the use of Weiand et al. plans on observing Z_1 at 50% information time, the covariance between Z_1 and Z_2 is about 0.707. The cumulative distribution function of Z_1 and

Z_2 is provided below by F(.):

$$P\left(Z_1 \le z_1, Z_2 \le z_2\right) = F\left(z_1, z_2 \mid \theta, I_1, I_2\right)$$

The design will reject the regimen if $Z_1 > 0$ in the first stage or $Z_1 < 0$ in the first stage, but $Z_2 > c_2$ in the second stage where c_2 is a critical value for rejecting H_0. This is expressed mathematically as:

$$\begin{aligned}
&P\left(Z_1 > 0 \cup \left\{Z_1 < 0 \cap Z_2 > c_2\right\}\right) = P\left(Z_1 > 0\right) + P\left(Z_1 < 0, Z_2 > c_2\right) \\
&= \left[1 - P\left(Z_1 < 0\right)\right] + \left[P\left(Z_1 < 0\right) - P\left(Z_1 < 0, Z_2 < c_2\right)\right] \\
&= 1 - F\left(0, \infty \mid \theta, I_1, I_2\right) + F\left(0, \infty \mid \theta, I_1, I_2\right) - F\left(0, c_2 \mid \theta, I_1, I_2\right) \\
&= 1 - F\left(0, c_2\right)
\end{aligned}$$

Under H_0, the desired probability of rejecting the regimen is 90% (when the null hypothesis is true, alpha = 1 – 90% = 10%). Searching algorithms can quickly find the value of $c_2 = -1.25$ which deviates slightly from the nominal value of -1.28 obtained with a single stage test.

The required number of events to obtain 80% power is 84 with the interim analysis. That is to say:

$$F\left(0, -1.25 \mid \theta = -0.47, I_1 = 10.5, I_2 = 21\right) = 0.8001$$

In addition to the calculations above, the operating characteristics of the procedure is provided in the table below using simulation studies (n = 10,000) with exponential survival (median PFS = 5 months in the control group) and a study accrual rate of 4 patients per month with a maximum sample size of 110 (55 patients per arm)

Table 11.1: Operating Characteristics of Study

Hazard Ratio	**Probability Reject Rx**	**Theoretical[1] P(Rej. Rx)**	**Probability Accept[2] Rx**	**PET[3]**	**Time of Interim Analysis (mos.)**	**Time of Final Analysis (mos.)**
0.500	0.0361	0.0339	0.9639	0.0120	19.1	31.8
0.625	0.1992	0.1999	0.8008	0.0638	18.4	30.4
0.667	0.2976	0.2909	0.7024	0.0962	18.2	30.0
1.000	0.8999	0.8999	0.1001	0.5017	17.0	28.0

1.250	0.9882	0.9892	0.0118	0.7607	16.5	27.3
1.500	0.9989	0.9991	0.0011	0.8974	16.0	26.9

[1] Theoretical calculations provided with the methods of Jennison and Turnbull[60].
[2] Accept = Declaring the regimen interesting and worthy of further investigation.
[3] PET = Probability of early termination.

It is unlikely that the interim analysis will be conducted at precisely 50% of the information time. The realized information at the interim and final analyses will be used to determine the critical value of c_2 under the null hypothesis so that the probability of a type I error does not exceed 10%, i.e. c_2 will be found so that: $F\left(0, c_2 \mid \theta = 0, I_1, I_2\right) = 0.10$.

Figure 11.1

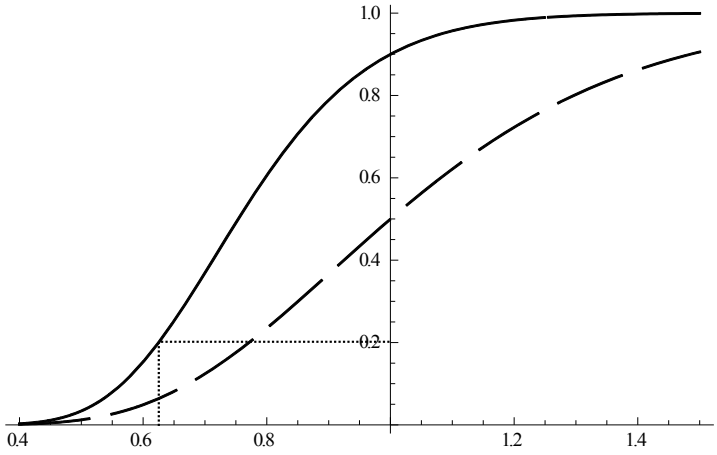


Figure 11.1: Probability of rejecting the treatment (solid line) and probability of early termination (dashed line) as a function of the hazard ratio.

11.4 Data sheets from studies on this protocol will be reviewed before each semi-annual meeting and will also be reviewed by the Study Chair in conjunction with the Statistical and Data Center. In some instances, because of unexpectedly severe toxicity, the Statistical and Data Center may elect, after consultation with the Study Chair and the Medical Oncology Committee, to recommend early closure of a study.

The frequency and severity of all toxicities are tabulated from submitted case report forms and summarized for review by the Study Chair, Developmental Therapeutics Committee, and GOG SRC in conjunction with each semi-annual GOG meeting. For studies sponsored by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI), standardized toxicity reports are

also submitted to the drug and disease monitors at the Investigational Drug Branch (IDB) and Clinical Investigation Branch (CIB).

All serious and/or unexpected events are communicated to the Study Chair, sponsor, and regulatory agencies as mandated in the protocol. These reports are reviewed by the Study Chair (or designated co-chair) for consideration of investigator notification, amendment, or immediate study suspension. All participating institutions will then receive notification of the toxicities and reason for study suspension. Under these circumstances, accrual cannot be re-activated until the study is reviewed by the GOG Data Safety Monitoring Board. However, patients currently receiving treatment may continue to receive treatment in accordance with protocol guidelines at the discretion of their physicians, unless directed otherwise.

11.5 Secondary and Exploratory Analyses:

Toxicities will be characterized by their frequency and severity. Differences in the level of toxicities by treatment regimen will be assessed by classifying them as severe or not severe and examining the relative proportion of severe toxicities. Differences between measurable versus non-measurable disease status on PFS and OS will be examined with plots of survival curves, estimates of quartiles and hazard ratios. Formal tests for differences will be carried out with a Cox model or log-rank test if appropriate. The effects of treatment on the proportion responding by RECIST and possibly by CA125 will be examined. An examination of response by CA125 (stratified by treatment) will also be conducted in those patients who have measurable disease to assess the level of agreement between the two methods of evaluation. The impact of additional, various prognostic factors or biological markers will be examined with exploratory analyses including log-rank tests with characterization with hazard ratio estimates.

11.6 Translational Research

Translational research (TR) data can be fairly difficult to analyze statistically for various reasons including data that are highly skewed (non-normal) or of ordinal quality where differences between observations are not meaningful. It has become customary to dichotomize biomarker data[61] to help overcome these difficulties and ease the interpretation of the results.

For this study, biomarker data will be dichotomized (if feasible) at the median or, less commonly, whether or not expression is observed in the patients. Dichotomizing at the median tends to have an advantage by increasing the sensitivity of the analysis (relative to other cut points) when there is a significant association between the biomarker and clinical outcome.

Depending on the number of events and biomarkers under examination, one of two strategies will be taken with regard to prognostic variable assessment. If the number of biomarkers is relatively large (but no more than 25) and the nature of

the analysis fairly exploratory, then the data will be randomly split into two groups. One of the groups will be designated for exploratory analysis. This dataset will be used to generate hypotheses of interest. After consultation with the TR co-chair, a finalization of the primary questions (relatively few) will be done and recorded. The other half of the data will then be addressed with these specific questions for validation. On the other hand, if the number of questions is relatively small to begin with (no more than 3 questions) or the total number of events relatively small, then the entire dataset can be used to ask these questions. The benefit to having a smaller number of questions is greater statistical power, but important questions may be overlooked. The benefit to data splitting is having validated conclusions after screening many prospects.

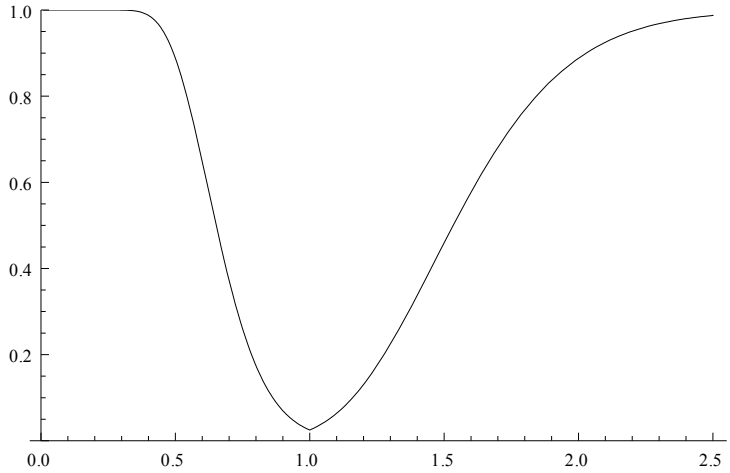
The marginal probability of detecting a biomarker's prognostic effects on the hazard of death or progression depends on its true hazard ratio, θ, the level of significance, α, and the number of events in the study, D, through the normal cdf, provided by $\Phi(\cdot)$ as follows:

$$\text{Power} = \Phi\left(\frac{\sqrt{D}}{2}|\theta| - z_{\alpha/2}\right)$$

The equation above holds since we expect ½ of the patients to score high. This study is planning a total of 84 PFS endpoints, so the probabilities of detection under this assumption are provided in Figure 11.2 (assuming a high proportion of patients participating in the TR aspect of this study).

Figure 11.2

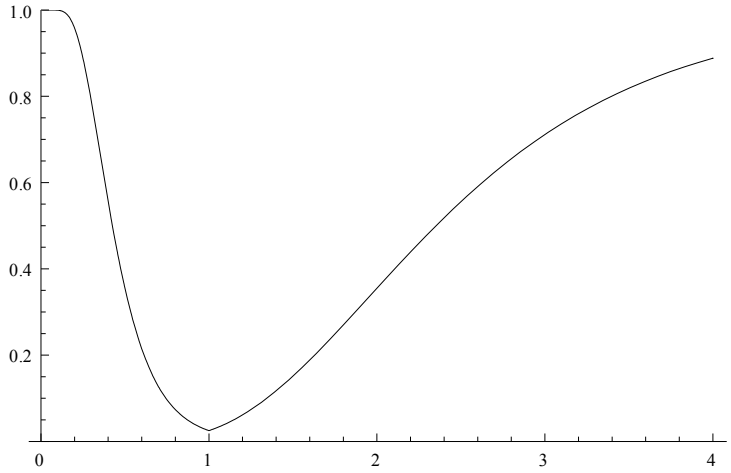
Power as a function of the hazard ratio for patients with high levels of expression versus those with low levels of expression when assessed with the entire dataset (D=84)



Often the predictive value of a biomarker is of considerable interest. Such a biomarker could help direct the physician towards one treatment over another because the effectiveness of the treatment depends on the level of expression of the biomarker. In statistical terms, the hazard ratio for progression on the experimental treatment to the control treatment depends on the level of biomarker expression (high versus low). Using Peterson and George's notation, let Delta1 be the hazard ratio for low levels of biomarker expression and Delta2 be the hazard ratio for the high levels of biomarker expression. When $\Delta_1 / \Delta_2 = 1$, the biomarker contains no predictive value for treatment effectiveness. The hazard ratios are the same regardless of the level of biomarker expression (however, the biomarker could still be prognostic).

Because these tests amount to tests of interaction between treatment and biomarker level, the amount of power is drastically reduced. Therefore, there is no luxury of data splitting. All analyses will involve the full dataset and be exploratory (hypothesis generating) in nature. The equation for calculating power is similar to the one above except the relevant number of events is now only 21 (84 events for 2 treatments cut into four cells is 21; see Peterson and George for full details). Note that roughly equal numbers of patients with high levels of biomarker expression are expected to be randomized to the treatments; also, the power calculations are robust as shown in Table 3 of publication.

Figure 11.3
Marginal power of tests for detecting predictive biomarkers.



TR analyses that examine the impact of changes in biomarker values over time on the hazard of progression will be adjusted with the Landmark Method (see Buyse and Piedbois[62]). Patients that progress before the last time of tissue collection (in the entire sample) will not be included in the analysis. The starting point will be adjusted from the date of entry to approximately the start of cycle 2 (when the post-treatment samples are collected) for these particular analyses. Because a number of patients (and some events) will be eliminated, the overall power of these analyses will not be as high as described previously. However, the powers listed previously should be fair approximations since the number of patients that progress should be few.

11.7 Women and Minority Inclusion

Based on previous studies in the GOG-0186 series, the following table gives the projected number of patients by ethnicity and race*:

Accrual Targets					
	Sex/Gender				
	Females		**Males**		**Total**
Ethnic Category					
Hispanic or Latino	8	+	0	=	8
Not Hispanic or Latino	102	+	0	=	102
Ethnic Category: Total of all subjects	110	+	0	=	110
Racial Category					
American Indian or Alaskan Native	3	+	0	=	3
Asian	1	+	0	=	1
Black or African American	4	+	0	=	4
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	102	+	0	=	102

Racial Category: Total of all subjects	110	+	0 (B2)	=	110

*The projected racial and ethnic distributions are obtained from previously enrolled patients in the GOG-0186 series.

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APPENDIX I

Congestive Heart Failure – New York Heart Association Classification

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

Patient Medication Calendar

This is a calendar on which you are to record the number of Pazopanib or Placebo tablet(s) you take each day. The instructions on how to take the Pazopanib or Placebo are below.

Use the calendar to record date, time and number of tablet(s) taken each day. You will start taking a total of 800 mg of Pazopanib or placebo each day for 28 days. (It is possible your doctor may reduce the amount of Pazopanib or placebo you take while participating in this study. Your doctor will discuss the new treatment plan with you at that time.) A 28-day period of time is called a cycle. These cycles will be repeated as long as your tumor is not growing and you are not experiencing any unacceptable side effects. Each medication calendar sheet should last you 4 weeks (one cycle). Medication should be taken as instructed without skipping any days. If you have missed a dose please mark down as "0" on the # slot for that day. If your doctor changes the amount of Pazopanib or placebo you take, please be sure to write down the correct number of pills and correct amount taken in the columns below.

Tablet(s) should be taken either 1 hour before or 2 hours after meals. Tablets should be swallowed whole and can not be crushed or broken. If you develop any side effects, please write side effects the day they occurred and anything else you would like to tell the doctor in the space provided below the calendar.

Please note: You must not take Grapefruit juice or St. John's Wort while on this study.

Bring any unused tablets, empty medication containers, and your completed calendar to your next appointment. Please use the upper left hand box in each square to record the date drug was taken.

Note to staff: Please give patient a drug log at initial enrollment and at every week 4 visit. Instruct patient how to complete the diary log. If they are taking the first pill at a visit complete the log with them. Remind them they must bring the log back at each visit along with pill bottles, empties included.

PATIENT MEDICATION CALENDAR

Patient Name_____ Patient Study ID_____
Patient Signature _____

Cycle # _____

Date	Day	# of tablet/s taken	Comments	Date	Day	# of tablet/s taken	Comments
	1				16		
	2				17		
	3				18		
	4				19		
	5				20		
	6				21		
	7				22		
	8				23		
	9				24		
	10				25		
	11				26		
	12				27		
	13				28		
	14						
	15						

The above information has been reviewed with the patient. Staff Signature: _____
Date:_____

Please note: Medication Calendar should be brought to each appointment along with medication bottles (empty included).

APPENDIX III

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

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

APPENDIX IV

Recommended Hypertension Monitoring and Management

(BP in mmHg)

Grade (CTCAE v4)	Antihypertensive Therapy	Blood Pressure Monitoring	Pazopanib/Placebo Dose Modification
Persistent Grade 1 Pre-hypertension Systolic 120-139 Diastolic 80-90		Standard	No Change
Persistent Grade 2- Moderate Systolic 140-159 Diastolic 90-99 Protocol-specific guidance supersedes any other management guidelines, including CTCAE v4	Step 1) Initiate BB treatment and if needed, after 24-48 hr Rx, increase dose in stepwise fashion every 24-48 hours until BP is controlled or at max dose of Rx Step 2) If BP still not controlled, add another anti-hypertensive Rx, a LA DHP CCB, ACE1, ARB, or ABB; increase dose of this drug as described in step 1 Step 3) If BP still not controlled, add 3rd drug from the list of antihypertensives in step 2; increase dose of this drug as described in step 1 Step 4) If BP still not controlled, consider either 1 dose reduction of pazopanib/placebo or stopping pazopanib/placebo *NOTE: Stopping or reducing the dose of pazopanib/placebo is expected to cause a decrease in BP. The treating physician should monitor the subject for hypotension and adjust the number and dose of*	BP should be monitored as recommended by the treating physician	No change except as described in step 4

	antihypertensive medication(s) accordingly		
Persistent Grade 3 Severe Systolic ≥160 Diastolic ≥100 Protocol-specific guidance supersedes any other management guidelines, including CTCAE v4	HOLD pazopanib/placebo until systolic BP ≤159 and diastolic BP ≤99. BP management is identical to that for Grade 2 (see steps 1-4 above) **with 2 major exceptions: 1) If systolic BP >180 or diastolic BP >110 and the subject is symptomatic: optimal management with intensive IV support in ICU; STOP pazopanib/placebo and notify hospital staff that stopping pazopanib/placebo may result in a decrease in BP and 2) If systolic BP >180 or diastolic BP >110 and the subject is asymptomatic, 2 new antihypertensives must be given together in step 1 (and dose escalated appropriately as in step 1).** *NOTE: Stopping or reducing the dose of pazopanib/placebo is expected to cause a decrease in BP. The treating physician should monitor the subject for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly*	BP should be monitored as recommended by the treating physician **unless the subject is symptomatic with systolic BP >180 or diastolic BP >110 in which case, monitoring should be intensive.**	HOLD pazopanib/placebo until systolic BP ≤159 and diastolic BP ≤99. After this, pazopanib/placebo may be re-administered. If BP is still grade 2, manage as described above for grade 2 hypertension. In most circumstances, if BP cannot be controlled after an optimal trial of antihypertensive medications, consider either 1 dose reduction of pazopanib/placebo when systolic BP ≤159 and diastolic BP ≤99 or stopping pazopanib/placebo. **HOWEVER, If the subject requires hospitalization for management of symptomatic systolic BP >180 or diastolic BP >110,** permanently discontinue pazopanib/placebo or if BP is controlled to systolic BP ≤159 and diastolic BP ≤99, consider re-starting pazopanib/placebo at 1 lower dose level after consultation with

			the study Principal Investigator
Grade 4 Life-threatening consequences of hypertension	**Optimal management with intensive IV support in ICU; STOP pazopanib/placebo and notify hospital staff that stopping pazopanib may result in a decrease in BP**	Intensive	Permanently discontinue pazopanib/placebo or if systolic BP ≤159 and diastolic BP ≤99, consider re-starting pazopanib/placebo at 1 lower dose level after consultation with the study Principal Investigator

Abbreviations: Dihydropyridine calcium-channel blockers (DHP-CCB), selective beta blockers (BB), Angiotensin Converting Enzyme Inhibitors (ACEI), Angiotensin II Receptor Blockers (ARB), alpha beta blocker (ABB)

- *See table below for suggested antihypertensive medications by class
- If subjects require a delay of >2 weeks for management of hypertension, discontinue protocol therapy
- If subjects require >2 dose reductions, discontinue protocol therapy
- Subjects may have up to 2 drugs for management of hypertension prior to any dose reduction in pazopanib/placebo
- 24-48 hours should elapse between modifications of antihypertensive therapy

- Hypertension should be graded using CTCAE v4

In some instances of treatment for hypertension, a lower dose of the medication may be sufficient to provide the required antihypertensive control. In other instances, the standard dose of such a medication may be associated with AEs because of increased exposure. Alternatively, the investigator may choose to replace the medication with another in the same pharmacologic class that is less likely to interact with pazopanib/placebo. If such a medication is discontinued and replaced, the transition period should occur no less than 7 days prior to the first dose of pazopanib. Based on prior clinical experience with pazopanib, the use of calcium channel blockers (dihydropyridine category) and ACE inhibitors as first-line and second-line therapy is recommended.

Oral Antihypertensive Medications

Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug-interactions with pazopanib/placebo through CYP450.

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Dihydro-pyridine Calcium-Channel Blockers (DHP CCB)	**nifedipine XL**	**30 mg daily**	**60 mg daily**	**90 mg daily**	**CYP 3A4 substrate**
	amlodipine	**2.5 mg daily**	**5 mg daily**	**10 mg daily**	**CYP 3A4 substrate**
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate and inhibitor
Selective β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	atenolol	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	Yes (CYP450 unknown)
Angiotensin Converting Enzyme Inhibitors (ACEIs)	captopril	12.5 mg 3x daily	25 mg 3x daily	50 mg 3x daily	CYP 2D6 substrate
	enalapril	5 mg daily	10-20 mg daily	40 mg daily	CYP 3A4 substrate
	ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	lisinopril	**5 mg daily**	**10-20 mg daily**	**40 mg daily**	**No**

	fosinopril	10 mg daily	20 mg daily	40 mg daily	Yes (CYP450 unknown)
	Rarely used: **perindopril**	**4 mg daily**	**none**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
Angiotensin II Receptor Blockers (ARBs)	losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 substrate
	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	telmisartan	**40 mg daily**	**none**	**80 mg daily**	**Yes, but not CYP450**
	valsartan	**80 mg daily**	**none**	**160 mg daily**	**Yes, but not CYP450**
α and β Blocker	labetalol	100 mg twice daily	200 mg twice daily	400 mg twice daily	CYP 2D6 substrate and inhibitor

APPENDIX V

GOG General Chemotherapy Guidelines

- For 21 or 28 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 or 28 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 are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for <10% weight changes. **(10/09/2012)**
- 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).

APPENDIX VI

NCI/ DCTD Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA) a Cooperative Research and Development Agreement (CRADA) or a Clinical Supply Agreement, hereinafter referred to as Collaborative Agreement:

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)" and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator." (http://ctep.cancer.gov/industry/ipo.html) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data":

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order, as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). (Agent may be requested by completing a Clinical Drug Request (NIH-986) and faxing it to the

Pharmaceutical Management Branch at (301) 480-4612. For questions about drug orders, transfers, returns, or accountability call (301) 496-5725 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime). –Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   Executive Plaza North, Suite 7111
   Bethesda, Maryland 20892
   FAX 301-402-1584
   Email: anshers@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborators confidential proprietary information.

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APPENDIX VII

Specimen Procedures (10/09/2012)

I. Summary of Specimen Requirements

If the patient gives permission for her specimens to be collected for this optional translational research study component, then the participating Institution is required to submit the patient's specimens as outlined below (unless otherwise specified).

Required Specimens (Specimen Codes)	Form SP	Collection Time Points	Deadlines and Recommendations
Whole Blood (WB01) 7-10mL drawn into a purple-top (EDTA) tube	SP-WB01-186J	Collect prior to or after starting therapy	Ship to the GOG Tissue Bank the day the blood is collected[1] Submit Form SP online within 26 weeks of registration
Pre-Cycle 1 Plasma (PB01) prepared from 7-10mL of blood drawn into a purple top (EDTA) tube	SP-PB01-186J	Collect within 14 days of starting cycle 1 of therapy	Ship to the GOG Tissue Bank within 26 weeks of registration[1] Submit Form SP online within 26 weeks of registration
Pre-Cycle 2 Plasma (PB02) prepared from 7-10mL of blood drawn into a purple top (EDTA) tube	SP-PB02-186J	Collect prior to starting cycle 2 of therapy or at the time the patient goes off-study due to disease progression or toxicity	
Pre-Cycle 6 Plasma (PB03) prepared from 7-10mL of blood drawn into a purple top (EDTA) tube	SP-PB03-186J	Collect prior to starting cycle 6 of therapy or at the time the patient goes off-study due to disease progression or toxicity	

[1] Ship specimens to: GOG Tissue Bank / Protocol GOG-186J, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, E-mail: gogbank@nationwidechildrens.org.

II. Obtaining a GOG Bank ID (10/09/2012)

Only one GOG Bank ID (# # # # - # # - G # # #) is assigned per patient. All specimens and accompanying paperwork must be labeled with this coded and confidential tracking number. A GOG Bank ID can be obtained online via the Tissue Bank Portal on the GOG website (under Tools on the Web Menu page).

Obtain the patient study ID for all protocols with specimen requirements before requesting a GOG Bank ID from the Tissue Bank Portal. **Be sure to indicate if the patient has a previous GOG # when registering.** This will ensure that the patient is only assigned one Bank ID.

The GOG ID – Bank ID Lookup on the Tissue Bank Portal can be used to search for an existing Bank ID. To lookup an existing Bank ID, enter the patient's GOG # and click Lookup Bank ID. To lookup GOG #(s) associated with a given Bank ID, enter the Bank ID (without dashes) and click Lookup GOG #.

Please contact User Support at the GOG Statistical and Data Center if you need assistance or have assigned more than one Bank ID to a patient (Email: support@gogstats.org; Phone: 716-845-7767).

III. Requesting Specimen Kits

A. Ordering Specimen Kits (10/09/2012)

One specimen kit can be ordered for each patient enrolled on GOG-0186J. Specimen kits may be ordered online via the Kit Management link on the GOG website (under Data Entry on the Web Menu page). Each site may order two kits per protocol per day (daily max = 6 kits).

Please contact the GOG Tissue Bank if you need assistance (Email: GOGBank@nationwidechildrens.org; Phone: 866-GOG-BANC/866-464-2262).

Please plan ahead to allow time for kits to be shipped by ground transportation.

B. Materials Provided in the Specimen Kits (10/09/2012)

The GOG-0186J specimen kit (for frozen plasma) will contain:

* single-chamber shipping container
* three 15mL conical tubes
* three transfer pipettes
* 15 cryovials in zip-lock bags
* one biohazard envelope with absorbent material
* one Tyvek envelope
* dry ice label (UN1845)
* Exempt Human Specimen Sticker

C. Unused Materials or Unused Specimen Kits

Specimen kits should only be used for the submission of GOG-0186J frozen plasma specimens.

Unused materials or unused Specimen Kits need to be returned to the GOG Tissue Bank. Contact the Bank if you have any questions about the return of unused material.

IV. Submitting Whole Blood Specimens

A. Requirement

If the patient gives permission for her blood to be collected for this optional translational research study component, then the participating Institution is required to submit the patient's specimens as outlined in Section I.

A purple top (EDTA) tube should be used for blood collection.

The type of blood collection tube (EDTA) should be specified on Form SP.

B. Purpose

The GOG Tissue Bank will isolate DNA from whole blood specimens. DNA will be used for analysis of single nucleotide polymorphisms (SNPs).

C. Time Points

Whole blood should be collected prior to or after starting therapy.

Please note that whole blood should be shipped to the GOG Tissue Bank *the day the blood is collected*. Blood may be shipped Monday through Friday for Tuesday through Saturday delivery. Please do not ship blood the day before a holiday.

D. Format for Labeling the Specimen

Label the specimen with the GOG protocol number (GOG-186J), GOG Bank ID (# # # # - # # - G # # #), specimen code (WB01), and collection date (mm/dd/yyyy).

E. Instructions for Preparing the Whole Blood Specimen

1. Label the Whole Blood Collection Tube.

Label a purple top whole blood collection tube (containing EDTA) as described above.

2. Draw Blood.

Draw 7-10mL of blood into the labeled purple top tube**.**

3. Mix Blood with EDTA.

Mix the blood with the EDTA by gently inverting the tube 5-10 times.

4. Complete Form SP.

Complete Form SP online using SEDES as specified in Section VI. Submit a copy of Form SP with the specimen when it is shipped to the GOG Tissue Bank and retain a copy in your files.

5. Ship the Blood.

Ship the whole blood specimen to GOG Tissue Bank *the day the specimens are collected** as specified in Section VII.

*** If the whole blood absolutely cannot be shipped the day it is collected, the tube may be placed in the refrigerator overnight. Please note that the blood was refrigerated overnight in the comment box on Form SP (item 15).*

V. Submitting Plasma Specimens

A. Requirement

If the patient gives permission for her blood to be collected for this optional translational research study component, then the participating Institution is required to submit the patient's specimens as outlined in Section I.

A purple top (EDTA) tube should be used for blood collection to prepare plasma.

The type of blood collection tube (EDTA) should be specified on Form SP.

B. Purpose

Plasma will be used for multiplex ELISA analysis of plasma cytokines and angiogenic markers (e.g., IL-6, IL-8, IL 11, IL-1a, Il-3, IL-4, VEGF, TPO, G-CSF, GM-CSF, osteopontin, and sVEGFRs).

C. Time Point

Plasma specimens should be prepared from blood drawn:

1. prior to cycle 1 (PB01),
2. prior to cycle 2 (PB02)*, and
3. prior to cycle 6 (PB03)* of therapy.

**If the patient goes off-study due to disease progression or toxicity prior to cycle 2 or 6, the final plasma specimen should be collected at that time.*

D. Format for Labeling the Specimen

Label the specimen with the GOG protocol number (GOG-186J), GOG Bank ID (# # # # - # # - G # # #), specimen code (PB##, see above), and collection date (mm/dd/yyyy).

E. Instructions for Preparing Plasma

1. Label Cryotubes.

Label five screw-cap cryotubes as described above.

2. Draw Blood.

Draw 7-10mL of blood into a purple top tube (containing the anticoagulant EDTA).

3. Mix the Blood with EDTA.

Mix the blood with the EDTA by gently inverting the tube 5-10 times.

4. **Centrifuge Blood**.

   Centrifuge the blood at 1000g for 15 minutes at 4ºC or room temperature to separate the plasma (top, straw-colored layer) from the red blood cells (bottom, red layer).

5. **Aliquot Plasma**.

   Evenly dispense (aliquot) the plasma into the pre-labeled cryotubes and cap the tubes securely.

6. **Freeze Plasma**.

   Freeze the plasma in an upright position using an appropriate freezing/storage space (i.e., ultra cold ≤-70ºC freezer, liquid nitrogen, or direct exposure with dry ice).

7. **Complete Form SP.**

   Complete Form SP online using SEDES as specified in Section VI.

   Submit a copy of Form SP with the specimen when it is shipped to the GOG Tissue Bank and retain a copy in your files.

8. **Ship the Plasma to the GOG Tissue Bank**.

   Ship the frozen plasma to the GOG Tissue Bank using a specimen kit as described in Section VII.

VI. Submitting Form SP

A. Form SP Requirements

Form SP must be completed and submitted online to the GOG Statistical and Data Center (SDC) using the SDC Electronic Data Entry System (SEDES). Form SP must be submitted for each specimen required for the protocol regardless of the specimen submission status. Specific instructions for completing Form SP are available via SEDES by scrolling down to the SP Forms for the specific protocol.

B. Instructions for Submitting Form SP Online (10/09/2012)

Form SP must be submitted online using SEDES which is available on the GOG Web Menu under *Registration/Data Entry*. A copy of the completed form must also accompany each specimen shipped to the GOG Tissue Bank. Retain a printout of the completed form for your records. Form SP does not need to be sent to the GOG Tissue Bank when specimens are not collected.

To access Form SP for online submission, log onto the GOG Web Menu and use SEDES to electronically enter Form SP data. Any questions about access or problems

should be directed to User Support at the GOG SDC (Email: support@gogstats.org; Phone: 716-845-7767).

VII. Shipping Specimens

A. Whole Blood

Whole blood should be shipped to the GOG Tissue Bank *the day the specimens are collected**:

GOG Tissue Bank / Protocol GOG-0186J
Nationwide Children's Hospital
700 Children's Dr, WA1340
Columbus, OH 43205
Phone: 614-722-2865
Fax: 614-722-2897
E-mail: gogbank@nationwidechildrens.org

Please do not ship blood the day before a holiday. **Use your own shipping container to ship specimens using a pre-paid GOG Tissue Bank FedEx air bill obtained through the Kit Management application.**

*** If the whole blood absolutely cannot be shipped the day it is collected, the tube may be placed in the refrigerator overnight. Please note that the blood was refrigerated overnight in the comment box on Form SP (item 15).*

When shipping whole blood specimens, **please be aware that your Institution must comply with IATA standards** (www.iata.org). If you have questions regarding your shipment, please contact the GOG Tissue Bank at 614-722-2865.

To ship whole blood specimens you will need (1) a sturdy shipping container (e.g., a cardboard or styrofoam box), (2) a leak proof biohazard envelope with absorbent material*, (3) a puncture and pressure resistant envelope (e.g. Tyvek envelope), (4) an Exempt Human Specimen Sticker, and (5) a pre-paid FedEx air bill.

**If you will be shipping whole blood specimens from more than one patient, please put each specimen in a separate plastic zip-lock bag before placing the specimens in the shipping bag.*

If you do not have these materials available at your Institution, you may order them from any supplier (e.g., Saf-T-Pak; Phone: 800-814-7484; Website: www.saftpak.com).

Instructions for Shipping Whole Blood Using Your Own Shipping Container*

**Please note that you can include up to four different blood specimens in one biohazard envelope.*

1. Place the whole blood specimen in a biohazard envelope containing absorbent material. Expel as much air as possible before sealing the bag.

2. Wrap the biohazard envelope in bubble wrap or another padded material.

3. Place the padded tube(s) into a Tyvek envelope. Expel as much air as possible before sealing the envelope.

4. Place the Tyvek envelope in a sturdy shipping contained (e.g., cardboard FedEx box).

5. Insert a copy of the SP Form(s) into the box.

6. Attach an Exempt Human Specimen Sticker to the outside of the shipping container.

7. Print a pre-paid FedEx air bill using the Kit Management application (found under Data Entry on the Web Menu page) and attach to shipping container.

8. Make arrangements for FedEx pick-up through your usual institutional procedure or by calling 800-238-5355. Ship the specimens and SP Forms to the GOG Tissue Bank via FedEx Priority Overnight delivery. **Please ship whole blood specimens Monday through Friday for Tuesday through Saturday delivery.** If the whole blood is collected on a Friday, select "yes" for Saturday delivery when completing the label online. **Saturday delivery is only available for the shipment of whole blood.**

C. Frozen Plasma

All frozen plasma specimens should be shipped using the specimen kits provided to the GOG Tissue Bank (address above).

Frozen specimens should be shipped Monday through Thursday for Tuesday through Friday delivery. Do not ship frozen specimens the day before a holiday.

Frozen specimens should be stored in an ultra-cold freezing/storage space (i.e., ultra cold $\leq$-70^{o}C freezer, liquid nitrogen, or direct exposure with dry ice) until the specimens can be shipped.

Instructions for Shipping Frozen Specimens in a Specimen Kit

1. Pre-fill the chamber of the specimen kit about 1/3 full with dry ice.

2. Place each set of frozen plasma specimens in a separate zip-lock bag.

3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Do not put more than 25 vials in the biohazard envelope. Put the secondary

envelope into a Tyvek envelope. Expel as much air as possible before sealing all envelopes.

4. Place the Tyvek envelope containing the frozen specimens into the chamber of the kit and fill the chamber to the top with dry ice.

5. Insert the SP Forms into the kit.

6. Place the foam cover on top of the kit. Tape the outer box of the kit closed with filament or other durable sealing tape. **(10/09/2012)**

7. Print a pre-paid FedEx air bill using the Kit Management application (found under Data Entry on the Web Menu page) and attach to kit.

8. Complete and attach the dry ice label; attach the Exempt Human Specimen Sticker.

9. Arrange for FedEx pick-up through your usual Institutional procedure or by calling 1-800-238-5355. Ship the specimens and SP Forms to the GOG Tissue Bank via Priority Overnight delivery. **Please ship frozen specimens Monday through Thursday for Tuesday through Friday delivery**.

VIII. Banking Specimens

The GOG Tissue Bank staff will be responsible for all of the general activities associated with receiving, banking, and distributing clinical specimens.

Upon receipt of specimen shipments, the GOG Tissue Bank will immediately (1) assess the type, quantity, and condition of the specimens received, (2) complete the appropriate fields in the GOG SP Form, (3) enter the specimens into their database system, and (4) store the specimens under the appropriate conditions.

The GOG Tissue Bank should complete the bottom part of Form SP for each specimen and submit the data electronically to the GOG Statistical and Data Center within three business days of receipt. A copy of the completed Form SP will be retained in the GOG Tissue Bank files.

As needed, the GOG Tissue Bank will work with the GOG Statistical and Data Center to reconcile specimen identifiers, information, condition, and quality.

A. Whole Blood

Whole blood will be processed by the Bank to isolate DNA. DNA will be stored at the Bank. Bank staff will make sure each whole blood and subsequent DNA specimen is labeled appropriately.

B. **Frozen Plasma**

Frozen plasma will be stored at the Bank in an ultra-cold ≤ -70ºC freezer or in a liquid nitrogen storage tank. Bank staff will make sure each frozen specimen is labeled appropriately.

IX. Distributing Specimens for Laboratory Testing

The GOG Statistical and Data Center and the GOG Tissue Bank will work together to coordinate the distribution of batches of specimens to approved Investigators for laboratory testing. Specimen selection will be based on information regarding specimen procurement and condition as well as patient eligibility, evaluation criteria, statistical considerations, and relevant clinical information.

For each shipment, the GOG Tissue Bank staff will provide the Investigator and the GOG Statistical and Data Center an electronic file that includes an inventory of all specimens included in the shipment (including the specimen specific identifiers and quantity and condition of the specimens being shipped).

The GOG Statistical and Data Center will provide the Investigator an electronic file containing the specimen identifiers with relevant information regarding specimen condition, suitability for testing, eligibility/evaluability for a given component of the research study, and fields for the laboratory data. Investigators will not be given access to any personal identifiers.

Investigators will be responsible for the direct supervision and oversight of the laboratory testing performed and for keeping accurate records of all specimen testing.

Investigators will ensure that the laboratory testing results are linked to the appropriate specimen-specific identifiers and are responsible for transferring relevant laboratory data to the GOG Statistical and Data Center.

A. Frozen DNA and Plasma

Frozen DNA and plasma will be distributed to DR. Anil Sood for analysis of plasma cytokines and angiogenic markers and SNPs.

Laboratory of Dr. Anil Sood
ATTN: Anil Sood and De-Yu Shen
Departments of Gynecologic Oncology and Cancer Biology
UT-MD Anderson Cancer Center
7777 Knight Rd SRB1.440 (Unit 173)
Houston, TX 77054
Phone: 713-563-9030
Fax: 713-792-3643
Email: asood@mdanderson.org

X. Banking Specimens for Future Research

Specimens will remain banked in the GOG Tissue Bank and made available for approved cancer and/or non-cancer research projects based on GOG Tissue Bank Specimen Distribution Policies if the following condition is satisfied: Each patient in question must have provided permission for the use of her specimens for cancer and/or non-cancer research. The patient's choices will be documented on the informed consent document that the patient signs for the protocol and on the online Specimen Consent Application (available on the GOG web-site).

GOG Institutions can amend a patient's choices regarding the future use of her specimens <u>at any time</u> if the patient changes her mind.

If the patient does not give permission for the use of her specimens, the GOG Tissue Bank will be instructed to destroy (incinerate) any remaining specimens to insure that the patient's wishes are honored.