The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

A Randomized Phase III Trial of Gemcitabine + Docetaxel + Bevacizumab or Placebo as First-Line Treatment for Metastatic Uterine Leiomyosarcoma: An NRG Oncology/Gynecologic Oncology Group Study

Hensley, et al

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PROTOCOL GOG-0250

A RANDOMIZED PHASE III EVALUATION OF DOCETAXEL (NSC #628503) AND GEMCITABINE (NSC #613327) PLUS G-CSF WITH BEVACIZUMAB (NSC #704865, IND #113912) VERSUS DOCETAXEL (NSC #628503) AND GEMCITABINE (NSC #613327) PLUS G-CSF WITH PLACEBO IN THE TREATMENT OF RECURRENT OR ADVANCED LEIOMYOSARCOMA OF THE UTERUS. NCI-SUPPLIED AGENT: BEVACIZUMAB (NSC #704865, IND #113912)

NCI Version Date: December 5, 2011
Includes Revisions #1-5

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PARTICIPATION ON THIS TRIAL WILL BE LIMITED TO THE CONTINENTAL U.S. DUE TO LIMITED DRUG SUPPLY

OPEN TO PATIENT ENTRY NOVEMBER 9, 2009
REVISED DECEMBER 21, 2009
REVISED FEBRUARY 22, 2010
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REVISED DECEMBER 19, 2011
CLOSED TO PATIENT ENTRY APRIL 23, 2013

SCHEMA (02/22/10)

Enroll patients with uterine LMS, measurable disease, no prior cytotoxic therapy

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STRATIFY for prior whole pelvic radiation

then

RANDOMIZE to:

REGIMEN I:

DAY 1: Gemcitabine 900 mg/m^2 IV over 90 minutes,
followed by Placebo (for Bevacizumab)[see Section 5.2]
DAY 8: Gemcitabine 900 mg/m^2 IV over 90 minutes,
followed by plus Docetaxel 75 mg/ m^2 IV over 60 minutes
every 3 weeks (one cycle) until disease progression or adverse effects prohibit further therapy

or

REGIMEN II:

DAY 1: Gemcitabine 900 mg/m^2 IV over 90 minutes
followed by Bevacizumab 15 mg/kg IV [see Section 5.2]
DAY 8: Gemcitabine 900 mg/m^2 IV over 90 minutes,
followed by Docetaxel 75 mg/ m^2 IV over 60 minutes
every 3 weeks (one cycle) until disease progression or adverse effects prohibit further therapy

↓

CT scan every other cycle to assess disease response (RECIST) and time to progression

*Notes:

-All patients receive granulocyte growth factor on Day 9. Treatment may be with either filgrastim (Neupogen) Days 9-15 or pegfilgrastim (Neulasta) Day 9

-Patients with history of prior pelvic RT receive lower doses of the gemcitabine and docetaxel: gemcitabine 675 mg/m^2 IV over 70-90 minutes Days 1 and 8 plus docetaxel 60 mg/m^2 IV Day 8.
-See Section 5.2 for bevacizumab or placebo infusion time.
-All patients will receive dexamethasone pre-medication for docetaxel; administration will be documented with a pill calendar (See Appendix VI)

1.0 OBJECTIVES

1.1 Primary Objective

1.11 To determine whether the addition of bevacizumab to fixed-dose rate gemcitabine-docetaxel reduces the progression-free survival (PFS) event rate when compared to gemcitabine-docetaxel plus placebo in patients with advanced or recurrent uterine leiomyosarcoma (LMS).

1.2 Secondary Objectives

1.21 To determine the objective response rate, as measured by RECIST, of patients treated with fixed-dose rate gemcitabine-docetaxel with bevacizumab, compared with the objective response rate of patients treated with fixed-dose rate gemcitabine-docetaxel with placebo.

1.22 To determine if the addition of bevacizumab to the combination of gemcitabine and docetaxel increases overall survival in patients with advanced or recurrent uterine LMS.

1.23 To determine the toxicity profile of fixed-dose rate gemcitabine-docetaxel with and without bevacizumab in this patient population.

1.24 To bank formalin-fixed and paraffin-embedded (FFPE) tumor tissue for research.

2.0 BACKGROUND AND RATIONALE

Patients who present with advanced or recurrent uterine leiomyosarcoma (LMS) have a poor prognosis. Few chemotherapy agents have been identified with activity against LMS. Negligible activity was observed in Phase II trials testing the following single agents: cisplatin,[1,2] mitoxantrone,[3] amonifide,[4] oral etoposide,[5] diazoquone,[6] topotecan,[7] paclitaxel,[8,9] thalidomide,[10] and trimetrexate.[11] Single agents with moderate activity in LMS include ifosfamide (response rate 17%),[12] intravenous etoposide (one study response rate 11%, other studies negative),[13] doxorubicin (response rate 25%),[14] and gemcitabine (response 20% in patients with 0-1 prior).[15] Combination chemotherapy regimens with activity in previously untreated patients include hydroxyurea, dacarbazine and etoposide (overall response rate 18%)[16] and doxorubicin plus ifosfamide (response rate 30%).[17] No standard second-line chemotherapy agents have been identified.

In a Phase II study at Memorial Sloan-Kettering Cancer Center (MSKCC), patients with unresectable LMS who had failed 0-2 prior chemotherapy regimens received gemcitabine Days 1 and 8, plus docetaxel Day 8 with G-CSF support. Three patients achieved CR, 15 PR, for ORR 53% (95% confidence interval 35-70%). Fifty percent (50%) of patients previously treated with doxorubicin responded.[18]

In GOG-0131G, as second-line therapy gemcitabine plus docetaxel achieved CR 6.3%, PR 20.8%, stable disease 50%.[19]

In GOG-0087L, as first-line therapy, gemcitabine plus docetaxel achieved CR 4.8%, PR 31%, stable disease 26.2%.[20]

VEGF and/or VEGF receptors are expressed in a wide variety of tumor types, including gynecologic cancers, and higher levels of vascularity have been associated with poorer prognosis. Interruption of the VEGF pathway is a novel approach to cancer therapy that may work by reducing tumor vascularity, thus limiting tumor growth. VEGF-trap has been shown to inhibit tumor growth in mouse xenograft models, including rhabdomyosarcoma. In a Phase I study of single-agent, intravenous VEGF-Trap conducted at MSKCC, one objective response was observed in a heavily pre-treated patient with metastatic uterine LMS.[21] Sorafenib, which inhibits several receptor tyrosine kinases involved in angiogenesis and tumor proliferation, achieved an objective response rate of 5% (2 PR/37 patients) and 40% progression-free at 24 weeks among patients with leiomyosarcoma on a Phase II trial.[22] The single agent activity of the multi-kinase inhibitor Sunitinib is currently being tested in GOG-0231C for patients with metastatic uterine LMS who have received 1-2 prior lines of therapy.

Bevacizumab is a humanized IgG1 monoclonal antibody (MAb) that binds all biologically active isoforms of human vascular endothelial growth factor (VEGF, or VEGF-A) with high affinity (k_d = 1.1 nM).[28] The antibody consists of a human IgG1 framework and the antigen-binding complementarity-determining regions from the murine anti-VEGF MAb A.4.6.1.[27-29]

The murine parent MAb of bevacizumab, A4.6.1, has demonstrated potent growth inhibition *in vivo* in a variety of human cancer xenograft and metastasis models, including those for SK-LMS-1 leiomyosarcoma, G55 glioblastoma multiforme, A673 rhabdo myosarcoma, Calu-6, and MCF-7 cell lines.[28-31] The antitumor activity was enhanced with the combination of A4.6.1 and chemotherapeutic agents compared to either agent alone. Combined blockage of the VEGF and other growth factor pathways (e.g., EGFR or PDGFR) has also demonstrated additive effects *in vivo*.[32,33] Associated with the anti-tumor activity of anti-VEGF MAbs were findings of reduced intratumoral endothelial cells and microcapillary counts, as well as reduced vascular permeability and interstitial pressure

Nonclinical toxicology studies have examined the effects of bevacizumab on female reproductive function, fetal development, and wound healing. Fertility may be impaired in cynomolgus monkeys administered bevacizumab, which led to reduced endometrial proliferation and uterine weight, as well as a decrease in ovarian weight and number of corpora lutea. Bevacizumab is teratogenic in rabbits, with increased frequency of fetal resorption, specific gross and skeletal alterations. In juvenile cynomolgus monkeys with open growth plates, bevacizumab induced physeal dysplasia which was partially reversible upon cessation of therapy. Bevacizumab also delays the rate of wound healing in rabbits, and this effect appeared to be dose-dependent and characterized by a reduction of wound tensile strength.

To date, over 7000 patients have been treated in clinical trials with bevacizumab as monotherapy or in combination regimens.[27]

The pharmacokinetics (PK) of bevacizumab have been characterized in several Phase I and Phase II clinical trials, with doses ranging from 1 to 20 mg/kg administered weekly, every 2 weeks, or every 3 weeks. The estimated half-life of bevacizumab is approximately 21 days (range 11-50 days). The predicted time to reach steady state was 100 days. The volume of distribution is consistent with limited extravascular distribution.

The maximum tolerated dose (MTD) of bevacizumab has not been determined; however, the dose level of 20 mg/kg was associated severe headaches.[34] The dose schedule of either 10 mg/kg q2w, or 15 mg/kg q3w is used in most Phase II or III trials with only [illegible] (e.g., the pivotal Phase III trial in colorectal cancer, in which bevacizumab was given at 5 mg/kg q2w).

Clinical proof of principle for anti-VEGF therapy with bevacizumab has been observed in several solid tumors. In first- and second-line metastatic colorectal cancer, combination of bevacizumab with 5-FU-based chemotherapy improved the overall survival (OS), progression-free survival (PFS) and response rate (RR) as compared to chemotherapy alone.[26,34] There was also improved overall survival in first-line NSCLC patients (E4599) treated with carboplatin/paclitaxel + bevacizumab compared with chemotherapy alone. Bevacizumab in combination with chemotherapy has been approved by the FDA for treatment in advanced/metastatic colorectal cancer (first and second lines) and in NSCLC.

In untreated advanced and metastatic breast cancer, addition of bevacizumab to paclitaxel significantly improved the RR and PFS.[35] However, in the Phase III trial in doxorubicin and paclitaxel-refractory metastatic breast cancer, the addition of bevacizumab to capecitabine did not show an improvement in PFS despite an increase in the RR.[36] In locally advanced and metastatic pancreatic cancer, a Phase III also failed to demonstrate OS or PFS advantage by adding bevacizumab to gemcitabine (CALGB 80303).[37]

Bevacizumab has been studied as monotherapy in renal cell cancer (RCC). In a 3-arm, double-blind, placebo-controlled Phase II trial,[38] patients with previously treated Stage IV RCC were randomized to high-dose (HD) bevacizumab (10 mg/kg q2w), low-dose (LD) bevacizumab (3 mg/kg q2w) or placebo. The study demonstrated a highly significant prolongation of time to progression (TTP) in the HD arm (4.8 months) as compared with the placebo (2.6 months) (hazard ratio = 2.55, p = 0.0002); the LD arm was associated with a smaller difference in TTP (3.0 months) of borderline significance. The tumor response rate was 10% in the HD arm but 0% in the LD and placebo groups.

Additional clinical trials are ongoing in a variety of solid tumors and hematological malignancies using bevacizumab as monotherapy or in combination with chemotherapy, radiation, or other targeted/biological agents.

Based on clinical trials with bevacizumab as monotherapy or in combination with chemotherapy, the most common adverse events of any severity include asthenia, pain, headache, hypertension, diarrhea, stomatitis, constipation, epistaxis, dyspnea, dermatitis and proteinuria. The most common Grade 3-4 adverse events were asthenia, pain, hypertension, diarrhea and leukopenia.

The most serious AEs include life-threatening or fatal hemorrhage, arterial thromboembolic events, gastrointestinal perforation and wound dehiscence; these events were uncommon but occurred at an increased frequency compared to placebo or chemotherapy control in randomized studies. Increased rates of severe neutropenia have been observed in patients treated with some chemotherapy regimens plus bevacizumab. Other SAEs observed with bevacizumab therapy include hypertensive crisis, nephrotic syndrome and reversible posterior leukoencephalopathy syndrome.

In a Phase I study in which gemcitabine (1500 mg/m^2), docetaxel (50 mg/m^2), and bevacizumab (5 mg/kg) were all given concurrently every 2 weeks to patients with previously untreated soft tissue sarcoma (LMS-5 patients, angiosarcoma-3 patients, other histologies-19 patients). Eleven of 25 assessable patients had objective responses, including 3 with a complete remission.[23] The median survival has not been reached. Reported adverse events were: Grade 5 bowel perforation (4%) (patient died of pulmonary embolism 7 days after a successful surgery), Grade 4 pneumothorax (4%), Grade 3 fatigue (8%), wound dehiscence (4%), and hemorrhage (4%).[43] These early data suggest that the addition of a VEGF-pathway targeted agent to cytotoxic chemotherapy may result in higher response rates and possibly prolong duration of response.

To date, GOG Phase II trials have been designed with objective response as the primary endpoint for the assessment of agents in advanced and recurrent uterine leiomyosarcoma. Drugs that interfere with tumor vasculature, however, rarely have meaningfully high RECIST-objective response rates as single agents. Nevertheless, the addition of agents such as bevacizumab to active cytotoxic chemotherapy has yielded increases in progression-free and overall survival in non-small cell lung cancer,[24] breast cancer, [25] and colon cancer[26]. It is notable, however, that in each of these trials the addition of bevacizumab to the cytotoxic chemotherapy was also associated with a higher objective response rate.

We propose a randomized Phase III design with progression-free survival as the primary endpoint for the assessment of whether adding bevacizumab to fixed-dose rate gemcitabine-docetaxel holds promise for improving patient outcomes. Using PFS, rather than objective response, as the primary endpoint should prevent us from discarding a potentially useful agent.

While several single-arm trial designs with PFS as the target endpoint were considered, in this case the inherent shortcomings of these designs render the final results of such a trial difficult to interpret. First, the potential for patient selection bias undermines the validity of inferring that any difference in response rates seen in GOG-0087L and the current study is attributable to bevacizumab only. Second, the observed response (CR and PR) rate to first-line gemcitabine and docetaxel from GOG-0087L was 35.8% (95% CI: 23.5-49.6%) and the median time to progression was 4 months (95% CI: 1.6-7.0 months). These wide confidence bounds indicate that the currently available data are consistent with a broad range of true treatment effect sizes. The limited precision of these estimates undermine the reliability of estimating the relative benefit of bevacizumab from a single arm trial. Therefore, due to the risk of selection bias and the limited precision of the currently available treatment effect estimates, a randomized Phase III design is the most reliable and valid design for determining whether bevacizumab contributes to prolonging progression-free survival when combined with fixed-dose rate gemcitabine-docetaxel. A positive result from this study indicating that the addition of bevacizumab contributes to increasing the PFS compared to gemcitabine and docetaxel with placebo, would provide a strong justification for considering fixed-dose rate gemcitabine plus docetaxel plus bevacizumab as an active first-line treatment for women with advanced or recurrent leiomyosarcoma of the uterus.

Rationale for conducting this trial in the Gynecologic Oncology Group: This table serves to demonstrate the track record for GOG in conducting multi-institution studies of novel agents in advanced uterine leiomyosarcoma. Although uterine leiomyosarcoma is a relatively rare disease, the GOG has a superb track record in accruing to LMS trials.

GOG-0231C (CTEP LOI # 7736) is a Phase II study of sunitinib for metastatic uterine leiomyosarcoma. The trial met its first stage of accrual (20 patients) within seven months of activation. In addition, comparisons can be made to other recent studies of single agents. This table also serves to demonstrate the track record for GOG in conducting multi-institution studies of novel agents in advanced uterine leiomyosarcoma.

Trial	Drug	No. of prior treatments	Objective Response	% PFS at 6 months
GOG-0231B	Thalidomide	1	0/29 (0%)	7%
GOG-0131E	Gemcitabine	0-1	9/42 (20%)	Not reported
GOG-0087J	Doxil	0	5/32 (16%)	Not reported
GOG-0131C	Paclitaxel	0-1	4/48 (8%)	
GOG-0087G	Paclitaxel	0	3/33 (9%)	Not reported
GOG (Thigpen)[1]	cisplatin	1	1/19 (5%)	Not reported
GOG (Thigpen)[2]	cisplatin	0	1/33 (3%)	Not reported
GOG (Omura)[14]	doxorubicin	0	7/28 (25%)	Not reported
GOG-0087B	Ifosfamide	0	6/35(17%)	Not reported
GOG-0087D	Etoposide IV	0	0/28 (0%)	Not reported
GOG-0131B	Etoposide PO	1	2/29 (7%)	Not reported
GOG-0087H	Topotecan	0	4/36 (11%)	Not reported
GOG-0131D	Trimetrexate	0-1	1/23 (4%)	Med PFS 2.2 mo

Rationale for collecting archival tumor specimens for research. **08/02/2010)**

Archival tumor specimens will be collected from women with advanced or recurrent leiomyosarcoma who provide permission for their tumor tissue, if available from a previous surgery or biopsy, to be submitted and used for research. The GOG Committee for Experimental Medicine will make decisions regarding when specimens will be distributed to approved investigators for approved research connected specifically to women with advanced or recurrent leiomyosarcoma who participated in GOG-0250. This may include research to study which patients in the future might or won't be likely to develop cancer, respond to treatment, have side effects or have a good prognosis. Specimens that remain after completion of GOG-0250 will be made available for future research as described in the last section in Appendix III.

2.1 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 uterine leiomyosarcoma population treated by participating institutions.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

3.11 Patients must have advanced or recurrent uterine leiomyosarcoma with documented disease progression. Histologic confirmation of the original primary tumor is required.

3.12 All patients must have measurable disease as defined by RECIST 1.1. 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 ≥ 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI.

3.13 Patient 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 have a GOG Performance Status of 0, 1, or 2.

3.15 Patients must have recovered from effects of recent surgery, radiotherapy or other therapy.

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

3.17 Any hormonal therapy directed at the malignant tumor must be discontinued at least one week prior to first day of study treatment. Continuation of hormone replacement therapy is permitted. **(08/02/2010)**

3.18 Patients must have adequate:

3.181 Bone marrow function: Platelet count greater than or equal to 100,000/mm^3, and ANC count greater than or equal to 1,500/mm^3.

3.182 Renal function: creatinine less than or equal to 1.5 x institutional upper limit normal (ULN), per NCI CTCAE Version 4.0 Grade 1. **(08/02/2010)**

3.183 Hepatic function: Bilirubin within normal range (CTCAE Version 4.0 Grade 0). SGOT and alkaline phosphatase less than or equal to 2.5 x ULN, per the CTCAE Version 4.0 Grade 1). **(08/02/2010)**

3.184 Neurologic function: Neuropathy (sensory and motor) less than or equal to Grade 1 per the CTCAE Version 4.0. No history of transient ischemic attack (TIA) or stroke or CNS hemorrhage within the previous 6 months. **(08/02/2010)**

3.185 Urine Protein Creatinine: Urine protein creatinine (UPC) ratio must be < 1.0 gm. If UPC ratio ≥ 1, collection of 24-hour urine measurement of urine protein is recommended.

UPC ratio of spot urine is an estimation of the 24-hour urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm. UPC ratio is calculated using one of the following formulas:

1. [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
2. [(urine protein) x0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L

3.186 Blood coagulation parameters: PT such that international normalized ratio (INR) is ≤ 1.5 and a PTT ≤ 1.5 times the institutional upper limit of normal (or an in-therapeutic-range INR, usually between 2 and 3, if a patient is on a stable dose of therapeutic warfarin)

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

3.110 Patients must meet pre-entry requirements as specified in Section 7.0.

3.111 Patients of childbearing potential must have a negative serum pregnancy test prior to the study entry and be practicing an effective form of contraception.

3.2 Ineligible Patients

3.21 Patients who have received prior cytotoxic chemotherapy for management of uterine sarcoma. Patients who have received prior VEGF-pathway targeted agent such as bevacizumab, PTK787, VEGF-trap, or who have received prior treatment with a multi-kinase inhibitor such as sorafenib or sunitinib are not eligible.

3.22 Patients who have had prior therapy with docetaxel or gemcitabine or bevacizumab

3.23 Patients with a history of other invasive malignancies, with the exceptions of non-melanoma skin cancer, carcinoma in situ of the cervix, and ductal carcinoma in situ of the breast, are excluded if there is any evidence of other malignancy being present within the last five years. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.

3.24 Patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder, coagulopathy, or tumor involving major vessels. (Necessary use of warfarin or low molecular weight heparin is

permitted, provided the INR is maintained in the therapeutic range of approximately 2-3. See Section 5.29).

3.25 Patients with major surgery or significant traumatic injury within 28 days prior to study entry.

3.26 Patients with a history of abdominal fistula or perforation within the past 12 months

3.27 Patients with a current, serious, non-healing wound, ulcer, or bone fracture.

3.28 Patients with history or evidence upon physical examination of CNS disease, including history of primary brain tumor, or any history of brain metastases, or seizures not controlled with standard medical therapy.

3.29 Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies.

3.210 Cardiovascular function. Specifically, patient may not have:

3.2101 Uncontrolled hypertension, defined as systolic > 150 mm Hg or diastolic > 100 mm Hg in a patient with no history of hypertension. Patients with a history of hypertension before enrollment on study are permitted, but such patients must have BP less than or equal to 140/90 mmHg. Use of blood pressure medications to achieve and maintain blood pressure control is permitted. **(02/22/10)**

3.2102 Myocardial infarction or unstable angina within 6 months of the first date of bevacizumab/placebo therapy.

3.2103 New York Heart Association (NYHA) Grade II or greater congestive heart failure (please see Appendix IV) or serious cardiac arrhythmia requiring medication. Women who have received prior treatment with an anthracycline (including doxorubicin and/or liposomal doxorubicin) and have an ejection fraction < 50% will be excluded from the study.

3.2104 Grade 1, Category 2 or greater, peripheral vascular disease (please see Appendix IV). Patient cannot have anything worse than mild, symptomatic claudication with exercise.

3.2105 History of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) or subarachnoid hemorrhage within six months of the first date of bevacizumab/placebo therapy.

3.2106 History of pulmonary embolism or deep vein thrombosis in the past 6 months.

3.211 Patients with, or with anticipation of, invasive procedures as defined below:

3.2111 Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to the first date of bevacizumab/placebo therapy.

3.2112 Major surgical procedure anticipated during the course of the study.

3.2113 Minor surgical procedures (i.e., mediport insertion), fine needle aspirates, or core biopsies within 7 days prior to the first date of bevacizumab/placebo therapy.

3.212 Patients under the age of 18 years.

3.213 Patients who are pregnant or nursing.

4.0 STUDY MODALITIES

4.1 Gemcitabine, Gemzar ® (NSC #613327)

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

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

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

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

4.15 Administration: The mixed solution will be continuously infused over 90 minutes (See Section 5.2).

4.16 Adverse effects:

Hematologic: The following Grade 3 and 4 toxicities can be expected after single agent therapy with doses between 800 and 1250 mg/m^2: neutropenia 25%, leukopenia 9%, anemia 8%, and thrombocytopenia 5%. Infection occurred in 16% of patients; sepsis occurred in less than 1%. 17% of patients experienced hemorrhage of Grade 2 or less.
Gastrointestinal: Nausea and vomiting is frequent, up to 69%, but usually mild to moderate. Grade 3 and 4 nausea and vomiting were noted in 14%. Diarrhea was seen in 19%, stomatitis in 11%, and constipation in 23%.
Pulmonary: Dyspnea was seen in 23%, severe in 3%. Rarely parenchymal toxicity including pneumonitis has been reported. Treatment should be discontinued immediately, if suspicious symptoms occur.
Hepatic: Transient elevation of hepatic enzymes was seen in 70%, however, this was not dose dependent and no increase was noted during prolonged therapy. Serious hepatotoxicity, including liver failure and death, has been reported very rarely.

Fever: This is seen in up to 41%, but usually of a mild degree. Fever may be accompanied by flu-like symptoms in 19%.
Renal: Reversible proteinuria, hematuria are frequent; increased BUN and creatinine in 16% and 8% of patients, respectively. However, renal insufficiency or hemolytic uremic syndrome is very rare. If suspicious symptoms are noted therapy should be discontinued immediately.
Dermatologic/Skin: Alopecia is seen in 15%; a reversible macular or macular-papular rash is seen in 30%; pruritus occurs in 13%. Peripheral edema is seen in up to 20% of the patients treated. Infusion site reactions occurred in 4% of patients.
Neurologic: There was a 10% incidence of mild paresthesias; somnolence occurred in 11% of patients.
Pain at the site of injection: Seen in 48% of patients; Grade 3 in 9%.
Other: Cardiovascular or allergic reactions are seen very rarely.

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

4.2 Docetaxel, Taxotere® (NSC# 628503)

4.21 Formulation: Docetaxel is a semisynthetic agent belonging to the taxoid family.

4.22 Supplier/How Supplied: Docetaxel is commercially available from Aventis Pharmaceuticals. Docetaxel Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic diluent (13% Ethanol in Water for Injection) vial. The following strengths are available: 80 mg/2 ml and 20 mg/0.5 ml.

4.23 Stability/Storage: Store between 2 and 25° C (36-77° F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product. Premixed docetaxel solutions should be used within 4 hours.

4.24 Preparation of the Premix Solution: Docetaxel vials should be stored between 2-25° C. If refrigerated, remove the appropriate number of vials of docetaxel for injection concentrate and diluent from the refrigerator. Allow the vials to stand at room temperature for approximately 5 minutes.

Aseptically withdraw the entire contents of the diluent vial into a syringe and transfer it to the vial of docetaxel for injection concentrate. This will assure a final premix concentration of 10 mg docetaxel/ml.

Gently rotate each premix solution vial for approximately 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.

The docetaxel premix solution (10 mg docetaxel/ml) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the premix solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

4.25 Preparation of the Infusion Solution: Aseptically withdraw the required volume of docetaxel premix solution (10 mg docetaxel/ml) with a calibrated syringe and inject the required volume of premix solution into a 250 ml infusion bag or bottle of 0.9% Sodium Chloride or 5% Dextrose solution to produce a final concentration of 0.3 to 0.74 mg/ml. If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/ml docetaxel is not exceeded.

Thoroughly mix the infusion by manual rotation.

As with all parenteral products, Docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the Docetaxel for Injection premix solution or infusion solution is not clear or appears to have precipitation, the solution should be discarded.

In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

4.26 Administration: Docetaxel is given intravenously as a one-hour infusion. All patients should be pre-medicated with oral corticosteroids such as dexamethasone 16 mg per day (8 mg BID) for three days starting one day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

4.27 Adverse Effects:

Hematologic: Reversible bone marrow suppression is the major dose limiting toxicity. If given every three weeks, the median time to nadir was 7 days. If bolus therapy is given, severe neutropenia occurred in 75% of the patients. Infection occurred in 22% of patients, and severe infectious episodes occurred in 6% of the patients.
Fever: Fever in absence of infection occurred in 31% of patients.
Hypersensitivity Reactions: Hypersensitivity reactions, regardless of pre-medication, occurs in 21% of patients. Severe hypersensitivity characterized by hypotension and/or bronchospasm or generalized rash erythema occurs in 4% of the patients in spite of pre-medication with Dexamethasone.
Fluid retention: Despite pre-medication, fluid retention occurred in 64% of patients; 6.5% of these patients had severe fluid retention which may present as peripheral edema, generalized edema, pleural effusion, dyspnea at rest, cardiac tamponade or abdominal distension due to ascites.
Dermatologic/Skin: Cutaneous localized erythema of the extremities with edema followed by desquamation; alopecia, nail changes. Severe skin toxicity

necessitating discontinuation of the medication was seen in 1.6% of the patients. Infusion site reactions occurred in 4% of patients.
Neurologic: Nerve damage resulting in severe neurosensory symptoms (paresthesia, dysesthesia, pain) were observed in 5.5% of the patients and resulted in treatment discontinuation in 6.1%; some neurosensory symptoms occurred in 49% of patients.
Asthenia: Asthenia occurred in 62% of patients; severe asthenia has been reported in 14.9% of the patients leading to discontinuation in 1.8%.
Gastrointestinal: Nausea, vomiting, and diarrhea; reactions leading to severe nausea and vomiting occur at a severe grade in 3-5%. Stomatitis occurred in 42% of patients, severe stomatitis in 5.5%.
Cardiovascular: Reactions include hypotension in 2.8% necessitating treatment in 1.2%.
Hepatic: In patients with normal LFT's, increase in bilirubin occurred in 8.9% and SGOT or SGPT in 18.9% and 7.3%.
Pain: myalgia, arthralgia

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

4.3 Filgrastim (G-CSF), Neupogen® (NSC #614629)

4.31 Formulation: Filgrastim (G-CSF), Neupogen® (recombinant granulocyte-colony stimulating factor) is a protein produced by E. Coli into which has been inserted the human G-CSF gene. Filgrastim differs from the natural protein in that the N-terminal amino acid is a methionine and it is not 0-glycosylated. G-CSF functions as a hematopoietic growth factor; it increases the proliferation, differentiation, maturation and release of precursor cells into mature blood cells of the neutrophil lineage. G-CSF has demonstrated *in vitro* effects on mature neutrophils, including an increase expression of chemotactic receptors, enhanced phagocytosis and intracellular killing of certain organisms, as well as enhanced killing of target cells that are bound by antibodies.

Approximately 6,400 patients in US and international based trials have participated in clinical trials of filgrastim to date, and the worldwide commercial populations receiving filgrastim totaled approximately 190,000. The drug has been found to be well tolerated at dosages up to 69 mcg/kg/d given IV or subcutaneously, with no toxic effects attributable to filgrastim. A maximum tolerated dose has not yet been determined.

4.32 Supplier/How Supplied: Filgrastim is commercially available. Filgrastim is supplied as a clear, colorless preservative-free liquid for parenteral administration. The product is available in single use vials and pre-filled syringes.

Single use vials: Single use vials contain filgrastim 300 mcg/ml in a preservative-free solution with 0.59 mg/ml acetate, 50 mg/ml sorbitol, 0.004% Tween 80, 0.035 mg/ml sodium, and water for injection, USP, pH 4.0 to make 1

ml filgrastim. Neupogen is commercially available in two vial sizes: 300 mcg/1 ml and 480 mcg/1.6 ml.

Single use pre-filled syringes: Single use pre-filled syringes contain either 300 mcg or 480 mcg of filgrastim at a fill volume of 0.5 ml or 0.8 ml, respectively.

4.33 Storage and Stability: Filgrastim should be stored in the refrigerator at 2 - 8°C (36 to 46° F). Avoid shaking. Prior to injection, filgrastim may be allowed to reach room temperature for a maximum of 24 hours. Any vial or pre-filled syringe left at room temperature for greater than 24 hours should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit; if particulates or discoloration are observed, the container should not be used.

4.34 Administration: Filgrastim is administered as a single daily injection by subcutaneous bolus injection, by short IV infusion (15-30 minutes), or by continuous subcutaneous or continuous IV infusion. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, do not use filgrastim in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy.

4.35 Dilution: If required, filgrastim may be diluted in 5% dextrose. Filgrastim diluted to concentrations between 5 and 15 mcg/ml should be protected from adsorption to plastic materials by addition of albumin (human) to a final concentration of 2 mg/ml. When diluted in 5% dextrose or 5% dextrose plus albumin, filgrastim is compatible with glass bottles, PVC and polyfilm IV bags, and polypropylene syringes. Dilution of filgrastim to a final concentration of less than 5 mcg/ml is not recommended at any time. Do not dilute with saline at any time; product may precipitate.

4.36 Precautions: Filgrastim should be used with caution in patients with pre-existing cardiac conditions such as hypertension, angina pectoris and cardiac dysrhythmias. Until further data become available, precaution should be exercised if filgrastim is administered to those patients with myeloid malignancies.

4.37 Pregnancy and lactation: No clinical trials have been performed in pregnant or lactating women. Therefore, administration of filgrastim during pregnancy or lactation is not recommended until further data are available.

4.38 Contraindications: Filgrastim is contraindicated in these patients with known hypersensitivity to *E. coli* -derived proteins.

4.39 Adverse Effects:

Medullary bone pain: Occurring in 20-25% of patients in phase II and III trials. When bone pain was reported it often preceded a rise in the circulating neutrophil count; it occurred more frequently in patients treated with 20-100 mcg/kg/d of intravenously administered filgrastim, and less often in lower

subcutaneous doses. The pain was generally mild to moderate in severity and usually controlled with non-narcotic analgesics such as acetaminophen.

Other side effects include transient but reversible increases of alkaline phosphatase, lactate dehydrogenase, and uric acid levels. These occurred in 17-58% of patients, without clinical sequelae observed. Transient decreases in blood pressure that did not require clinical treatment were reported in 7/176 patients in Phase III clinical studies following administration of filgrastim. Cardiac events (myocardial infarctions, arrhythmias) have been reported in 11/375 cancer patients receiving filgrastim in clinical studies but the relationship to filgrastim therapy is unknown.

Less frequently reported adverse events related to filgrastim administration include subclinical splenomegaly, exacerbation of pre-existing skin rashes, alopecia, and thrombocytopenia, and cutaneous vasculitis. Ischemic events of the colon, sometimes with involvement of other parts of the gastrointestinal tract, has been seen in patients receiving paclitaxel and G-CSF therapy. Patients reporting abdominal discomfort should be monitored closely. The specific etiologic role of paclitaxel, other chemotherapeutic agents, or G-CSF is not entirely defined. It is conceivable that the high doses of chemotherapy used in these studies induced sufficiently severe neutropenia that these patients were at risk for complications based on the myelotoxicity alone. If this is the case, then the use of G-CSF may actually assist in preventing this occurrence in other patients receiving high-dose paclitaxel chemotherapy. A review of the Amgen database of over 10,000 patients treated on company-sponsored trials revealed the occurrence of only one case of typhlitis, two instances of intestinal ischemia, and six occurrences of intestinal perforation. However, it is remotely possible that the G-CSF may have contributed in some unforeseen way to these events.

Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving filgrastim, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving filgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, filgrastim should be discontinued until resolution of ARDS and patients should receive appropriate medical management for this condition.

Rare cases of splenic rupture have been reported following the administration of filgrastim in both healthy donors and patients with cancer. Some of these cases were fatal. Patients who report left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Rarely, allergic-type reactions have occurred. Since the commercial introduction of filgrastim there have been reports (< 1 in 4,000 patients) of symptoms suggestive of an allergic-type reaction, but in which an immune component has not been demonstrated. These have generally been characterized by systemic symptoms involving at least two body systems, most often skin (rash, urticaria, edema), respiratory (wheezing, dyspnea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure.

Reactions tended to occur within the first thirty minutes after administration and appeared to occur more frequently in those patients who received filgrastim intravenously. Rapid resolution of symptoms occurred in most cases after administration of standard supportive care, and symptoms recurred in more than half the patients when re-challenged.

*Please see the FDA-approved filgrastim package insert for a comprehensive list of adverse events associated with filgrastim.

4.4 Neulasta®, Pegfilgrastim (G-CSF) (NSC #725961)

4.41 Formulation: Pegfilgrastim is a covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol. To produce pegfilgrastim, a 20 kD monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of filgrastim. The average molecular weight of pegfilgrastim is approximately 39 kD.

4.42 Supplier/How Supplied: Pegfilgrastim is commercially available. Pegfilgrastim is supplied in 0.6 ml pre-filled syringes for subcutaneous injection. Each syringe contains 6 mg pegfilgrastim (based on protein weight), in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), sorbitol (30.0 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in water for injection, USP.

4.43 Storage and Stability: Pegfilgrastim should be stored refrigerated at 2 to 8° C (36 to 46° F); syringes should be kept in their carton to protect from light until time of use. Shaking should be avoided. Before injection, pegfilgrastim may be allowed to reach room temperature for a maximum of 48 hours but should be protected from light. Pegfilgrastim left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen, pegfilgrastim should be allowed to thaw in the refrigerator before administration. If frozen a second time, it should be discarded.

4.44 Administration: Pegfilgrastim is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle.

4.45 Precautions: Pegfilgrastim should be visually inspected for discoloration and particulate matter before administration and should not be administered if discoloration or particulates are observed.

4.46 Pregnancy and lactation: No clinical trials have been performed in pregnant or lactating women. Therefore, administration of pegfilgrastim during pregnancy or lactation is not recommended until further data are available.

4.47 Contraindications: Pegfilgrastim is contraindicated in patients with known hypersensitivity to *E. coli* -derived proteins, pegfilgrastim, filgrastim, or any other component of the product.

4.48 Adverse Effects:

Medullary bone pain: The most common adverse event attributed to pegfilgrastim in clinical trials was medullary bone pain, reported in 26% of subjects. This bone pain was generally reported to be of mild-to-moderate severity. Approximately 12% of all subjects utilized non-narcotic analgesics and less than 6% utilized narcotic analgesics in association with bone pain.

Other side effects include reversible elevations in LDH, alkaline phosphatase, and uric acid, which did not require treatment intervention.

One case of splenic rupture has been reported following the administration of pegfilgrastim. Patients who report left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving filgrastim, the parent compound of pegfilgrastim, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving pegfilgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, pegfilgrastim should be discontinued until resolution of ARDS and patients should receive appropriate medical management for this condition.

Allergic-type reactions, including anaphylaxis, skin rash, and urticaria, occurring on initial or subsequent treatment have been reported with filgrastim. In some cases, symptoms have recurred with re-challenge, suggesting a causal relationship. Allergic-type reactions to pegfilgrastim have rarely been reported in post-marketing experience. If a serious allergic reaction or an anaphylactic reaction occurs, appropriate therapy should be administered and further use of pegfilgrastim should be discontinued.

In subjects receiving pegfilgrastim in clinical trials, the only serious event that was not deemed attributable to underlying or concurrent disease or to concurrent therapy was a case of hypoxia.

*Please see the FDA-approved pegfilgrastim package insert for a comprehensive list of adverse events associated with pegfilgrastim.

4.5 Bevacizumab (NSC #704865, IND #113912) 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.

4.51 Clinical Supplies: Bevacizumab (NSC 704865) and matching placebo will be provided free of charge by Genentech and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP),

Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Bevacizumab and matching placebo will be supplied in 4 mL fill glass vials each containing 100 mg (Bevacizumab) or 0 mg (Placebo for Bevacizumab) of bevacizumab. In the future, only 400 mg vials of bevacizumab or placebo for 400 mg bevacizumab will be available. At that time, bevacizumab and matching placebo will be supplied in 16 mL fill glass vials each containing 400 mg (Bevacizumab) or 0 mg (Placebo for Bevacizumab) of bevacizumab. The blinded, patient-specific vials will be sealed in a cardboard box with a tamper-evident seal.

For **BLINDED (bevacizumab or placebo) THERAPY**, each box of bevacizumab / placebo will be labeled with …

- the protocol number (i.e., ""GOG-0250")
- the box number (e.g., "Box 1 of 2" and "Box 2 of 2")
- the number of vials (e.g., "45 vials")
- the patient ID number (e.g., "999-0250-001"; where "999" indicates the GOG – assigned institution code for the registering site, "0250" indicates the protocol number, and "001" indicates the patient sequence number for the registering site)
- the patient initials (i.e., First initial, Middle initial, Last initial [e.g., "FML"])
- the agent identification (i.e., "Bevacizumab 100 mg or Placebo" or "Bevacizumab 400 mg or Placebo")
- a blank line for the pharmacist to enter the patient's name
- storage instructions (i.e., "Store in refrigerator [2 – 8°C]. Do not freeze. Do not shake.")
- emergency contact instructions
- a Julian date

The Julian date indicates the day the box 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 box labeled and shipped on January 1, 2009 would have a Julian date of '09001' and a box 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 vials (i.e., both Bevacizumab and Placebo) shipped on or before that date thus eliminating any chance of breaking the blind. The Julian date will be documented in the "Lot Number" field on the Investigational Agent Accountability Record.

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.

4.52 Drug Ordering:

Note: Supplies of bevacizumab/placebo will be shipped by PMB to the investigator linked to the assigned patient ID number. The address used by PMB for shipments is the one specified in that investigator's currently filed NCI Registration Documents (NCI 1572).

4.521 **BLINDED (bevacizumab or placebo) THERAPY (Active and Placebo Arms)**

No blinded starter supplies will be available for this phase. Blinded, patient-specific clinical supplies will be sent to the registering investigator at the time of randomization and should arrive within 7 to 10 days. This randomization will be performed by the GOG Statistical and Data Center. The patient ID number assigned by the GOG Statistical and Data Center must be recorded by the registering institution for proper study medication dispersion. Once a patient has been registered with the GOG Statistical and Data Center, the GOG Statistical and Data Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the GOG Statistical and Data Center the day the patient is registered and will be processed by the PMB the next business day and shipped the following business day. All shipments will be sent on blue ice by FedEx (generally one to two day delivery). Thus, if a patient is registered on Monday, GOG would enter a clinical drug request for that patient on Monday and PMB would process the request on Tuesday and ship the drug on Wednesday. Both United States and Canadian sites could expect to receive their order either Thursday or Friday. All other international sites should allow for a minimum of four additional days for the shipment to arrive from the day that PMB receives the order. Note that PMB will only send blue ice shipments on Monday through Thursday for delivery on Tuesday through Friday. Thus, if a patient is registered on Wednesday, the order will be processed on Thursday and shipped the following Monday for delivery on Tuesday or Wednesday. The initial request will be for a sufficient number of vials to **complete the 3 cycles of bevacizumab or placebo (i.e., a 9 week supply at 15mg/kg IV every three weeks)** based on the patient's weight in "kg" provided by GOG at the time of patient registration. When the third dose (week nine) is administered (i.e., three weeks before the next bevacizumab or placebo vials are needed), sites may reorder an additional **3 cycles (i.e., a 9 week supply at 15mg/kg IV every three weeks)** by completing an NCI Clinical Drug Request form and faxing it to the PMB at 301-480-4612. The NCI Clinical Drug Request form is available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The protocol number (i.e., GOG-0250), the assigned patient ID number (e.g., "999-0250-001"), the patient initials (e.g., "FML"), the number of vials remaining from the previous shipment, and the patient's weight (in

"kg") should be entered on each order. All drug orders will be shipped directly to the physician registering the patient.

GOG-0250 Shipment Schedule

Patient Randomized with GOG	Initial e-Order Transmitted by GOG	Initial e-Order Received and Approved by PMB	Initial Order Shipped By PMB	Initial Order Received at Site *
Monday	Monday	Tuesday	Wednesday	Thursday
Tuesday	Tuesday	Wednesday	Thursday	Friday
Wednesday	Wednesday	Thursday	Monday	Tuesday
Thursday	Thursday	Friday	Monday	Tuesday
Friday	Friday	Monday	Tuesday	Wednesday

*** arrival time approximate and will be longer for international sites / shipments sent by Federal Express**

NOTE: At the time of disease progression, ALL remaining clinical supplies of blinded bevacizumab / placebo should be returned to PMB (see "Drug Returns" below).

4.53 Drug Transfers:
Vials **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 responsible 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 301-402-0429) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The patient ID number (e.g., "999-0250-001") 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-0250").

4.54 Drug Returns: **Only unopened clinical supplies should be returned to the PMB.**
When it is necessary to return study drug (e.g., sealed vials remaining when a patient completes blinded therapy, sealed vials remaining when a patient completes open-label therapy, sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials 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) or by calling the PMB at 301-496-5725. The patient ID number (e.g., "999-0250-001"), the patient initials (e.g., "FML"), and the Julian date should be entered in the "Lot Number" field. A separate line item is required for each patient ID (e.g., "999-0250-001") supply that is being returned.

4.55 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) or by calling the PMB at 301-496-5725. A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "999-0250-001") on this protocol.

4.56 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 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 bevacizumab or a placebo to manage 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-250"), the patient ID number (e.g., "999-0250-001"), and the patient initials (e.g., "FML") to unblind the patient.

4.57 Description: Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody, consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions. Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.

4.58 How Supplied: "Bevacizumab" and "Placebo" are supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. For "Bevacizumab", each 100mg (25mg/mL – 4mL fill) and 400 mg (25 mg/mL – 16 mL) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. For "Placebo", each 0mg (0mg/mL – 4mL fill or 16 mL fill) glass vial contains phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

4.59 Storage and Stability: Bevacizumab and placebo for bevacizumab are shipped on blue ice for next day delivery. On receipt, bevacizumab and placebo for bevacizumab should be stored in the refrigerator (2° to 8°C) and should remain refrigerated until just prior to use. Do not freeze. Do not shake. Shelf-life studies of bevacizumab are continuing. Investigators will be notified when vials have expired. The sterile single use vials contain no antibacterial preservatives; therefore, vials should be discarded eight hours after initial entry.

4.510 Preparation: Vials contain no preservative and are intended for single use only. The calculated dose should be placed in a total volume 100 mL of 0.9% Sodium Chloride for Injection. Once diluted in 0.9% Sodium Chloride for Injection, the

bevacizumab solution must be administered within 8 hours. **NOTE: Each vial of bevacizumab/placebo will be labeled with the intended patient ID number. Please verify that all of the patient ID labels match the patient ID for which the dose is being prepared.**

4.511 Administration: Bevacizumab/placebo is administered intravenously as a continuous infusion. The initial dose should be administered over a minimum of 90 minutes. If no adverse reactions occur after the initial dose, the second dose should be administered over a minimum of 60 minutes. If no adverse reactions occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

To ensure complete delivery of bevacizumab/placebo, the IV infusion line must be flushed with 0.9% Sodium Chloride for Injection. Please note that this flush is not included in the infusion times. The following are two recommended methods for flushing the bevacizumab/placebo IV infusion line:

- When the bevacizumab/placebo infusion is complete, add an additional 50mL of 0.9% Sodium Chloride for Injection to the bevacizumab/placebo infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.

- Replace the empty bevacizumab/placebo infusion bag with a 50mL bag of 0.9% Sodium Chloride for Injection and infuse a volume equal to the volume contained in the tubing.

4.512 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Bevacizumab (NSC #704865) **(08/02/2010) (12/19/11)**
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.

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 2.2, October 21, 2011[1]

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term)			Specific Protocol Exceptions to Expedited Reporting (SPEER) (formerly known as ASAEL)
Likely (>20%)	Less Likely (<=20%)	Rare but Serious (<3%)	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		*Anemia (Gr. 3)*
		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		*Febrile neutropenia (Gr. 3)*
CARDIAC DISORDERS			
		Acute coronary syndrome	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Supraventricular tachycardia		*Supraventricular tachycardia (Gr. 3)*
		Ventricular arrhythmia	
		Ventricular fibrillation	
EAR AND LABYRINTH DISORDERS			
	Vertigo		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		*Abdominal pain (Gr. 3)*
	Colitis		*Colitis (Gr. 3)*
	Constipation		*Constipation (Gr. 3)*
	Diarrhea		*Diarrhea (Gr. 3)*
	Dyspepsia		*Dyspepsia (Gr. 2)*
		Gastrointestinal fistula[2]	
	Gastrointestinal hemorrhage[3]		*Gastrointestinal hemorrhage[3] (Gr. 2)*
	Gastrointestinal obstruction[4]		
		Gastrointestinal perforation[5]	
		Gastrointestinal ulcer[6]	
	Ileus		
	Mucositis oral		*Mucositis oral (Gr. 3)*
	Nausea		*Nausea (Gr. 3)*
	Vomiting		*Vomiting (Gr. 3)*
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		*Fatigue (Gr. 3)*
	Infusion related reaction		*Infusion related reaction (Gr. 2)*
	Non-cardiac chest pain		*Non-cardiac chest pain (Gr. 3)*
	Pain		*Pain (Gr. 3)*
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		*Allergic reaction (Gr. 2)*
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[7]		*Infection[7] (Gr. 3)*
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Gastrointestinal anastomotic leak	
	Wound dehiscence		*Wound dehiscence (Gr. 2)*

INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr. 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase***
	Aspartate aminotransferase increased		***Aspartate aminotransferase (Gr. 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr. 2)***
	Cardiac troponin I increased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr. 3)***
	Weight loss		***Weight loss (Gr. 3)***
	White blood cell decreased		***White blood cell decreased (Gr. 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr. 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr. 3)***
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[8]		
	Myalgia		***Myalgia (Gr. 3)***
	Osteonecrosis of jaw[9]		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr. 2)***
	Headache		***Headache (Gr. 3)***
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
	Peripheral sensory neuropathy[10]		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Hematuria		***Hematuria (Gr. 3)***
	Proteinuria		***Proteinuria (Gr. 2)***
		Renal and urinary disorders - Other (Nephrotic Syndrome)	
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Reproductive system and breast disorders - Other (ovarian failure)[11]			
		Vaginal fistula	
	Vaginal hemorrhage		***Vaginal hemorrhage (Gr. 3)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr. 3)***
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		***Cough (Gr. 3)***
	Dyspnea		***Dyspnea (Gr. 2)***
	Epistaxis		***Epistaxis (Gr. 3)***
	Hoarseness		***Hoarseness (Gr. 3)***
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal	

		perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		*Pruritus (Gr. 2)*
	Rash maculo-papular		*Rash maculo-papular (Gr. 2)*
	Urticaria		*Urticaria (Gr. 2)*
VASCULAR DISORDERS			
Hypertension			*Hypertension (Gr. 3)*
	Thromboembolic event		*Thromboembolic event (Gr. 3)*
		Vascular disorders - Other (arterial thromboembolic event)[12]	

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

[2]Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, Small intestinal perforation, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[6]Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[7]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[8]Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

[9]Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

[10]Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

[11]Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

[12]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

Also reported on Bevacizumab (rhuMAb VEGF) trials but with the relationship to Bevacizumab (rhuMAb VEGF) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura); Disseminated intravascular coagulation
CARDIAC DISORDERS - Pericardial effusion
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Gait disturbance; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS - Infections and infestations - Other (aseptic meningitis)
INVESTIGATIONS - Platelet count decreased
METABOLISM AND NUTRITION DISORDERS - Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone); Musculoskeletal and connective tissue disorder - Other (myasthenia gravis)
NERVOUS SYSTEM DISORDERS - Dysgeusia; Peripheral motor neuropathy; Seizure
PSYCHIATRIC DISORDERS - Confusion
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Pneumonitis; Pneumothorax; Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Palmar-plantar erythrodysesthesia syndrome; Skin ulceration

Note: Bevacizumab (rhuMAb VEGF) 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.

4.6 Pathology Requirements

4.61 Eligibility Criteria: Patients must have advanced or recurrent uterine leiomyosarcoma with documented disease progression.

4.62 Ineligibility Criteria: Patients with early stage (FIGO Stage I or II) uterine leiomyosarcoma are not eligible. Tumors other than leiomyosarcoma are not eligible.

4.63 Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility. At least one representative H&E stained slide (or slides) demonstrating primary site, histologic cell type and grade will be required. At least one representative H&E stained slide documenting the most advanced stage of disease will be required if the most advanced stage is documented by histology or cytology. If the patient is enrolled with recurrent disease, at least one representative H&E stained slide demonstrating recurrent disease will be required if documented by histology. See Sections 7.2 and 10.2 for additional instructions for submitting the stained pathology slides this material to the GOG Statistical and Data Center in Buffalo, NY.

4.64 See Section 7.3 and Appendix III for information and instructions regarding the specimen requirements for Translational Research.

5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

All initial and continuing reviews must be submitted to the CTSU Regulatory Office. 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).(08/02/2010)** IRB submissions can be faxed or mailed to:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
1-888-823-5923
FAX 215-569-0206

5.1 Telephone Entry

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

5.11 The patient must have signed an approved informed consent and authorization permitting release of personal health information. Current FDA, NCI and institutional regulations concerning informed consent will be followed.

5.12 All eligibility requirements indicated in Section 3.0 must be satisfied.

5.13 The Fast Fact Sheet data must be gathered.

5.14 The institution must register the patient using the web-based registration application or by phone if necessary (800-523-2917). Instructions for web-based registration and randomization can be found by going to the GOG Web Menu page, selecting "Start/finish a patient registration," and then selecting "Directions" found on the left side of the page.

5.15 The institution will enter the patient's name and GOG number in the appropriate place in their Log Book to verify the patient's entry.

5.16 **This is a randomized, double-blind trial.** The registration process will allow the GOG Statistical and Data Center to automatically load the Drug Order for the patient and submit an electronic request for the blinded, patient-specific clinical supplies of bevacizumab / placebo to the Pharmaceutical Management Branch (PMB), CTEP at the NCI at the time of the initial registration / randomization. Clinical supplies of bevacizumab/placebo should arrive at the clinical site within approximately seven to ten days of randomization.

5.2 Treatment Plan

5.21 Patients assigned to REGIMEN I:

Day 1: Gemcitabine 900 mg/m^2 intravenously over 90 minutes, followed by placebo (for bevacizumab) intravenously over 90 minutes (subsequent cycles of placebo can be given over 60 minutes, and if tolerated, then subsequently over 30 minutes) given AFTER the gemcitabine infusion is completed. The placebo (for bevacizumab) dose will be based on the subject's weight at baseline and will remain the same throughout the study. **However the dose will be recalculated if the patient has a weight change of >10% from baseline. (02/22/10)**

Day 8: Gemcitabine 900 mg/m^2 intravenously over 90 minutes, followed by Docetaxel 75 mg/ m^2 intravenously over 60 minutes. **(02/22/10)**

Filgrastim (Neupogen) 5 micrograms/kg will be given subcutaneously (sc) on days 9-15 OR **Pegfilgrastim (Neulasta)** 6 mg subcutaneously on Day 9 or Day 10 (ideally 24 hours after the Day 8 chemotherapy, but up to 48 hours after). The Neupogen dose may be rounded to the nearest vial size. Patients may receive Neupogen or Neulasta by self-injection if they so desire. If these medications are delivered outside the treating institution, the patient should record the use of the medication on the Patient Pill and G-CSF Calendar, Appendix VI. **(02/22/10) (08/02/2010)**

Note: **PATIENTS with a history of PRIOR WHOLE PELVIC RADIATION** receive lower doses of both gemcitabine and docetaxel:
Day 1: Gemcitabine 675 mg/m^2 IV over 70-90 minutes followed by **placebo** (for bevacizumab) intravenously over 90 minutes (subsequent cycles of placebo can be given over 60 minutes, and if tolerated, then subsequently over 30 minutes). **(02/22/10)**

Day 8: Gemcitabine 675 mg/m^2 IV over 70-90 minutes followed by **docetaxel** 60 mg/m^2 IV over 60 minutes. These patients also receive Neupogen or Neulasta as described above. **(02/22/10)**

Patients assigned to REGIMEN II:

Day 1: Gemcitabine 900 mg/m^2 on intravenously over 90 minutes, followed by **bevacizumab** 15 mg/kg IV over 90 minutes (subsequent cycles can be over 60 minutes, and if tolerated, then subsequently over 30 minutes), given AFTER the gemcitabine infusion is completed. The bevacizumab dose will be based on the subject's weight at baseline and will remain the same throughout the study. **However the dose will be recalculated if the patient has a weight change of >10% from baseline. (02/22/10)**

Day 8: Gemcitabine 900 mg/m^2 intravenously over 90 minutes, followed by Docetaxel 75 mg/ m^2 intravenously over 60 minutes. **(02/22/10)**

Filgrastim (Neupogen) 5 micrograms/kg will be given subcutaneously (sc) on days 9-15 OR **pegfilgrastim (Neulasta)** 6 mg subcutaneously on Day 9 or Day 10 (ideally 24 hours after the day 8 chemotherapy, but up to 48 hours after). The neupogen dose may be rounded to the nearest vial size. Patients may receive Neupogen or Neulasta by self-injection if they so desire. If these medications are delivered outside the treating institution, the patient should record the use of the medication on the Patient Pill and GCSF Calendar, Appendix VI. **(02/22/10)(08/02/2010)**

Note: **PATIENTS with a history of PRIOR WHOLE PELVIC RADIATION** receive lower doses of both gemcitabine and docetaxel:
Day 1: Gemcitabine 675 mg/m^2 IV over 70-90 minutes followed by **bevacizumab** intravenously over 90 minutes (subsequent cycles of bevacizumab can be given over 60 minutes, and if tolerated, then subsequently over 30 minutes). **(02/22/10)**

Day 8: Gemcitabine 675 mg/m^2 IV over 70-90 minutes followed by **docetaxel** 60 mg/m^2 IV over 60 minutes. These patients also receive Neupogen or Neulasta as described above. **(02/22/10)**

There is no dose reduction of the bevacizumab for patients with a history of prior pelvic RT.

5.22 Maximum body surface area used for dose calculations will be 2.0 m^2 as per GOG Chemotherapy Procedures Manual.

5.23 The initial **recommended pre-medication for the docetaxel** is: dexamethasone 8 mg orally X 2 doses the day prior to chemotherapy (Day 7), and 8 mg orally twice daily for the next 2 days (Days 8-9). The dexamethasone dosing schedule may be adjusted at the discretion of the treating physician. Patient should document use on pill use calendar (Appendix VI)

5.24 Patients who develop **peripheral edema as a side effect of docetaxel and/or gemcitabine** may be treated with diuretics at the discretion of the treating physician. Recommended treatment for edema includes starting with Dyazide (25/37.5) or (25/50) up to 3 times a day, or hydrochlorothiazide (HCTZ) 25-50 mg once or twice daily. Furosemide may be used if Dyazide or HCTZ does not adequately control the edema.

5.25 Treatment is designed to be administered in the outpatient setting, with patients receiving treatments on Days 1 and 8 in the outpatient setting, and the duration of each cycle of therapy being approximately 3 weeks. Cycles will be repeated approximately every 3 weeks.

5.26 **Supportive Care Guidelines for Bevacizumab or Placebo (REGIMEN I and REGIMEN II patients):**

Prior to each treatment, the patient should be carefully assessed with special attention to blood pressure, proteinuria, bleeding and cardiovascular events. Decisions for retreatment/interruption should follow the dose modification guidelines in Section 6.0.

The initial dose will be delivered over a minimum of 90 minutes. If the first infusion is tolerated without infusion-associated adverse events, the second infusion may be delivered over a minimum of 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over a minimum of 30 minutes. If an infusion reaction occurs, subsequent doses of bevacizumab/placebo should be administered over the shortest period that was well tolerated.

5.27 If a subject experiences a bevacizumab or placebo infusion-associated adverse event, such as Grade 1 anaphylactoid reaction, she may be pre-medicated for the next bevacizumab/placebo infusion (see details below in bullet points). Patients who experience a Grade 2 or greater bevacizumab/placebo infusion-associated adverse event will not receive any additional bevacizumab/placebo.

Anaphylaxis precautions should be observed during bevacizumab or placebo administration (see Appendix V).

In the event of a prior bevacizumab/placebo hypersensitivity reaction, the following prophylactic regimen is recommended upon re-exposure to bevacizumab/placebo:

- H1 blocker (diphenhydramine 25-50 mg IV or orally one hour prior to infusion; or an equivalent dose of an alternate H1 blocker)
- H2 blocker (ranitidine 50 mg IV or 150 mg orally one hour prior to infusion; or an equivalent dose of an alternate H2 blocker)
- Dexamethasone (Suggested dosing for dexamethasone, if needed prior to bevacizumab/placebo administration, is10 mg administered PO 12 and 6 hours prior to bevacizumab injection OR 20 mg IV prior to bevacizumab/placebo infusion).

5.28 Hypertension: Hypertension is a known and potentially serious adverse event associated with bevacizumab treatment. Patients receiving bevacizumab/placebo (Regimen I or Regimen II) should have their blood pressure monitored weekly during the first cycle of therapy, and subsequently, prior to each infusion of bevacizumab/placebo. Home monitoring is permitted. Patients who elect to monitor blood pressure at home will be provided with a **Blood Pressure Check Calendar** (Appendix VII). Patients who monitor their blood pressure at home should be instructed to call their doctor if the systolic blood pressure is >140 mmHg or the diastolic blood pressure is > 90 mmHg. Hypertensive medication should be initiated or increased per routine practice.

Bevacizumab/placebo treatment modifications due to hypertension should follow the instructions in Section 6.0.

5.29 Therapeutic anticoagulation: Patients on therapeutic anticoagulation should have PT/INR or PTT (whichever is appropriate) monitored closely during bevacizumab/placebo therapy. Bevacizumab/placebo should be held if the coagulation parameters are higher than the intended therapeutic range.

5.210 Wound complications and surgery: The appropriate interval from discontinuation of bevacizumab/placebo to subsequent elective surgery required to reduce the risk of impaired wound healing has not been determined. Decision on such an interval should take into consideration the half-life of bevacizumab. It is generally recommended that bevacizumab/placebo should be discontinued at least 4 weeks prior to major elective surgery. In addition, bevacizumab/placebo should not be restarted until at least 4 weeks after major surgery provided that the wound has adequately healed.

5.211 Re-imaging of measurable disease sites **by CT scan of the chest/abdomen/pelvis** will be performed prior to every other cycle. Patients who have complete response (CR), partial response (PR), or stable disease will continue for additional cycles. Patients who have progression of disease will be removed from study treatment. See Section 8.2 for instructions on unblinding for disease progression. If the patient's response is CR, PR, or stable disease, and if side effects are not severe, a patient may remain on a study agent indefinitely at the investigator's discretion. **(08/02/2010)**

5.212 Chemotherapy Guidelines

If a patient receiving chemotherapy (with bevacizumab/placebo) experiences a > 10% weight change, the chemotherapy dose to be administered with a subsequent cycle must be recalculated.

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

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

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

For recommendations regarding scheduling deviations in protocols with regimens other than the above (#3 and #4 above), contact study chair or nurse contact.

Chemotherapy doses can be "rounded" to +/- 5% of the calculated dose without being considered a protocol violation.

Please note: If bevacizumab/placebo is interrupted for ANY reason for > 8 weeks, the patient should discontinue bevacizumab/placebo therapy on protocol. Patients will continue to receive gemcitabine and docetaxel on study.

5.213 If side effects are not severe, a patient may remain on a study agent indefinitely at the investigator's discretion.

5.214 Patients who have an ongoing study agent-related serious adverse event upon study completion or at discontinuation from the study treatment will be contacted by the investigator or his/her designee periodically until the event is resolved or determined to be irreversible.

5.3 Dexamethasone and G-CSF (Neupogen) Compliance

To help promote and monitor compliance with dexamethasone, the use of a Patient Pill Calendar (see Appendix VI) will be utilized by the patient and the treating clinic during study therapy. Patients who are treated with G-CSF (Neupogen) or Neulasta at home will also record G-CSF use on this calendar.

5.4 Blood Pressure Check Compliance

To help promote and monitor compliance with this study parameters, the use of a Blood Pressure Check Calendar (see Appendix VII) during study therapy will be utilized by the patient whenever blood pressure is taken at home. Patients may elect to check their blood pressure at home if they have access to a blood pressure monitor (home blood pressure monitors will not be provided by the study). Alternatively, blood pressure checks may be done in other outside settings, such as a pharmacy or outside physician's office, with results recorded on the Blood Pressure Check Calendar.

5.5 Criteria for removal from study treatment

5.51 Inability to tolerate the lowest doses because of toxicity (for dose modifications and specific criteria for removal from treatment due to toxicity, see Section 6.0).

5.52 Clinically evident progression of disease (see Section 8.0).

6.0 TREATMENT MODIFICATIONS

Note: Version 4.0 of the NCI Common Terminology for Adverse Events (CTCAE) is the reference for all grade specifications included in this study's dose modifications. **(12/21/09) (08/02/2010)**

6.1 Dose level definitions

For patients with **NO history of prior whole pelvic radiation**
(08/02/2010)

Study Drug	**2 Level reduction**	**1 Level reduction**	**Initial dose level**
Gemcitabine	500 mg/m^2 over 50-60 minutes	675 mg/m^{2}over 70-90 minutes	900 mg/m^2 over 90 minutes
Docetaxel	45 mg/m^2	60 mg/m^2	75 mg/m^2
Bevacizumab or Placebo	15 mg/kg	15 mg/kg	15 mg/kg

For patients **WITH history of prior whole pelvic radiation**

(08/02/2010)

Study Drug	**2 Level reduction**	**1 Level reduction**	**Initial dose level**
Gemcitabine	375 mg/m^{2}over 30-40 minutes	500 mg/m^{2}over 50-60 minutes	675 mg/m^2 over 70-90 minutes
Docetaxel	35 mg/m^2	45 mg/m^2	60 mg/m^2
Bevacizumab or Placebo	15 mg/kg	15 mg/kg	15 mg/kg

6.2 Hematologic toxicity

6.21 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:

6.211 Patients will receive prophylactic growth factors [filgrastim (G-CSF), or pegfilgrastim (Neulasta)] on Day 9 of each cycle of therapy as detailed in Section 5.2.

6.212 Patients will NOT receive prophylactic thrombopoietic agents unless they experience recurrent Grade 4 thrombocytopenia after treatment modifications as specified below.

6.213 Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia. Treating physicians should be aware of the recent changes in prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit); this information notes a potential risk of shortening the time to tumor progression or disease-free survival and recommends that these agents be 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

6.214 Patients may NOT receive amifostine or other protective reagents, as this would be considered a protocol violation.

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

6.23 Subsequent cycles of therapy will not begin until the ANC is $\geq$ 1500 cells/mm^3 (Grade 1 per CTCAE Version 4.0) and the platelet count is $\geq$ 100,000/mm^3. Gemcitabine and docetaxel and bevacizumab/placebo 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 the study treatment. Imaging studies (CT scans) should still be performed on time (approximately every 6 weeks) in order to document time to progression, even in patients removed from study treatment for toxicity. Note: Patients who must be removed from study for failure to recover adequate counts within 2 weeks are removed from ALL study treatment. Such patients will not continue to receive bevacizumab/placebo. **(08/02/2010)**

6.24 For first occurrence of febrile neutropenia (ANC < 1,000 and fever $\geq$ 38.5 C), and/or documented Grade 4 neutropenia persisting $\geq$ 7 days, OR Grade 3 thrombocytopenia (platelet count 25,000 to < 50,000/mcl) that is associated with bleeding or platelet transfusion, OR Grade 4 thrombocytopenia (platelet count < 25,000/mcl), reduce the doses of both gemcitabine and docetaxel by one dose level on all subsequent cycles.

6.25 For recurrent febrile neutropenia, reduce chemotherapy dose again by one dose level. If there is a third occurrence of febrile neutropenia despite 2 dose reductions, the patient should be removed from study treatment. Imaging studies (CT scans) should still be performed on time (approximately every 6 weeks) in order to document time to progression, even in patients removed from study treatment for toxicity.

6.26 There will be no dose modifications on the basis of uncomplicated granulocyte nadirs lasting less than 7 days.

6.27 In addition to the dose modifications listed above **Day 8** Gemcitabine and Docetaxel dose adjustments should be made according to the table below:

(10/18/2010)

Study Drug	**ANC ≥ 1000 AND Plt ≥ 100K**	**ANC 500-999 OR Plt 50-99K**	**ANC < 500 OR Plt < 50K**
Gemcitabine	100% of dose	Use the next lower dose level from the appropriate Table (prior RT or no prior RT, whichever pertains) in section 6.1	Omit on day 8
Docetaxel	100% of dose	Use the next lower dose level from the appropriate Table (prior RT or no prior RT, whichever pertains) in section 6.1	Omit on day 8

Dose reduction on Day 8 does not count as one of the two permitted protocol dose reductions for toxicity. Patients may start the next cycle at their previous doses, provided that blood counts have recovered as detailed in 6.23. If a dose reduction is required on Day 8 of a cycle, subsequent Day 8 doses should only be reduced in subsequent cycles if the criteria for reduction or omission of the day 8 doses are met on that cycle's Day 8 of treatment.

6.3 Hepatic Dysfunction

6.31 If bilirubin increases to greater than institutional upper limits of normal when checked on Day 1, repeat the bilirubin prior to Day 8 prior to giving the docetaxel. If the bilirubin has returned to normal, proceed with docetaxel on Day 8. If the bilirubin remains greater than institutional normal limits on Day 8, give only gemcitabine on Day 8. The patient will thus receive no docetaxel that cycle. If the bilirubin does not recover by Day 8 of the next cycle, the patient may continue on study treatment but will continue to receive no docetaxel until the bilirubin returns to within institutional normal limits. If the bilirubin returns to within institutional normal limits, the docetaxel may be added back to the regimen. Patients should continue to receive the bevacizumab/placebo on Day 1 of each cycle even when the Day 8 docetaxel treatment has to be held.

6.32 Grade 3 (or greater) elevations in SGOT (AST), SGPT (ALT), or alkaline phosphatase requires reduction of one dose level and delay in subsequent study treatment for a maximum of 2 weeks until recovered to Grade 1. Patients who

fail to recover SGOT, SGPT, or alkaline phosphatase elevations to Grade 1 or less will discontinue both gemcitabine and docetaxel. Patients will continue to receive bevacizumab/placebo, and imaging studies (CT scans) should continue to be done on time (approximately every 6 weeks) in order to document time to progression.

6.4 Hypersensitivity reactions to Docetaxel

There are no dose reductions for hypersensitivity reactions.

MANAGEMENT OF ACUTE HYPERSENSITIVITY TO DOCETAXEL

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

6.5 Other Non-hematologic toxicity likely attributable to gemcitabine and/or docetaxel

6.51 In the event of **Grade 3 or 4 neurotoxicity,** treatment will be delayed 1 week. If neurotoxicity has resolved to less than or equal to Grade 1, then the patient may continue on study with docetaxel dose reduction of one dose level in the current and all subsequent cycles (no dose adjustment is required for gemcitabine or bevacizumab).

If the Grade 3 or 4 neurotoxicity has not resolved to less than or equal to Grade 1 after a two-week delay, the docetaxel will be discontinued. Patients will continue to receive gemcitabine and bevacizumab/placebo.

A patient who presents with **Grade 2 peripheral neuropathy** requires a docetaxel dose reduction of one dose level and delay in subsequent therapy for a maximum of 2 weeks until recovery to Grade 1. If the patient is re-treated with a docetaxel dose reduction after recovery from a Grade 2 peripheral neuropathy, the dose reduction should remain in the current and all subsequent cycles.

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

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

6.54 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 and delay in subsequent study treatment for a maximum of 2 weeks until recovered to Grade 1.

6.55 Other non-hematologic toxicities with an impact on organ function of Grade 2 (or greater) require reduction of one dose level and delay in subsequent study treatment for a maximum of 2 weeks until recovered to Grade 1, or pre-therapy baseline.

6.56 In patients who develop Grade 4 edema gemcitabine and docetaxel will be discontinued. Patients may continue with bevacizumab/placebo as a single agent. For both groups, imaging studies (CT scans) should continue to be done on time (approximately every 6 week) in order to document time to progression.

6.57 The total number of dose reductions will be limited to two; if toxicity persists after two dose reductions, the patient will be removed from study treatment.

6.6 Dose adjustments for toxicities at least possibly attributable to bevacizumab or placebo

Bevacizumab Dose Modifications/Delays guidelines (based on CTCAE v4.0) (12/21/09)

Note: There will be no dose reduction for bevacizumab. Treatment should be interrupted or discontinued for certain adverse events, as described below

Note 2: If bevacizumab is interrupted for ANY reasons for > 8 weeks (unless otherwise specified), the patient should discontinue bevacizumab therapy on protocol. **(02/22/10)**

Treatment Modification for Bevacizumab-Related Adverse Events **(12/21/09)**

Event	CTCAE, v4.0 Grade	Action to be Taken
Allergic reactions or Infusion-related reactions Or Anaphylaxis	Grade 1-2	Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. For infusion-associated symptoms not specified above, infusion should be slowed to 50% or less or interrupted. Upon complete resolution of the symptoms, infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle. Subjects who experience bronchospasm (regardless of grade) should discontinue bevacizumab.
	G3-4	Discontinue bevacizumab
Thromboembolic Event (Arterial); arterial ischemia - Cardiac ischemia - Myocardia infraction - CNS ischemia (TIA, CVA) - any peripheral or visceral arterial ischemia/thrombosis	Grade 2 (new or worsening since bevacizumab	Discontinue bevacizumab.
	Grade 3-4	Discontinue bevacizumab
Thromboembolic Event (Venous)	Grade 3 OR asymptomatic Grade 4	▪ Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is <2weeks, bevacizumab should be held until the full-dose anticoagulation period is over. ▪ If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during full-dose anticoagulation IF all of the criteria below are met: – The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions) – The subject must not have had hemorrhagic events while on study – The subject must on stable dose of heparin or have an in-range INR (usually 2-3) on a stable dose of warfarin prior to restarting bevacizumab. ▪ If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab
	Grade 4 (symptomatic)	Discontinue bevacizumab

Event	CTCAE v4.0 Grade	Action to be Taken
Hypertension*	[Treat with anti-hypertensive medication as needed. The goal of BP control should be consistent with general medical practice]	
	Grade 1 (SBP 120-139 mmHg or DBP80-89 mm Hg)	Consider increased BP monitoring, start anti-hypertensive medication if appropriate.
	Grade 2 asymptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg)	Begin anti-hypertensive therapy and continue bevacizumab
	• Grade 2 symptomatic (SBP 140-160 mmHg or DBP 90-100 mm Hg) - Grade 3 (≥ SBP 160 mmHg or ≥ DBP 100 mmHg	• Start or adjust anti-hypertensive medication • Hold bevacizumab until symptoms resolve AND BP ≤ 160/90mmHg*
	Grade 4 Hypertensive crisis or malignant hypertension	Discontinue bevacizumab.
Heart Failure or LV dysfunction	Grade 3	Discontinue bevacizumab
	Grade 4	Discontinue bevacizumab
Proteinuria	[Proteinuria should be monitored by urine analysis for urine protein creatinine (UPC) ratio or dipstick prior to every other dose of bevacizumab. If dipstick shows 2+ proteinuria, 24-hour urine protein should be obtained]	
	UPC ratio < 3.5 or 24-h urine protein < 3.5 gm	Continue bevacizumab.
	UPC ratio ≥ 3.5 or 24-h urine protein ≥ 3.5 gm	Hold bevacizumab until UPC recovers to < 3.5, or 24-h urine protein < 3.5 gm. Discontinue bevacizumab if urine protein does not recover to < 3.5 after 8 weeks or bevacizumab interruption
	Nephrotic syndrome	Discontinue bevacizumab.
Hemorrhage (intracranial or pulmonary)	Grade 2-4	• Discontinue bevacizumab
	Grade 1	• Patients receiving full-dose anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and Hb is stable - there is no bleeding diathesis that would increase the risk of therapy • there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence
Hemorrhage (any other organ systems)	Grade 3	• Patients receiving full-dose anticoagulation should discontinue bevacizumab. • For patients not on full-dose anticoagulation, hold bevacizumab until ALL of the following criteria are met: - the bleeding has resolved and Hb is stable - there is no bleeding diathesis that would increase the risk of therapy - there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence. • Patients who experience recurrence of grade 3 hemorrhage should discontinue study therapy.
	Grade 4	Discontinue bevacizumab
RPLS (Reversible Posterior Leukoencephalopathy syndrome or PRES (Posterior Reversible Encephalopathy Syndrome)		• **Discontinue bevacizumab upon diagnosis of RPLS.**
Wound dehiscence requiring medical or surgical intervention		•**Discontinue bevacizumab**

Event	CTCAE. v4.0 Grade	Action to be Taken
Perforation (GI, or any other organ)		Discontinue bevacizumab
Fistula (GI, pulmonary or any other organ)		Discontinue bevacizumab
Obstruction of GI tract	G2 requiring medical intervention	• Hold bevacizumab until complete resolution
	G3-4	• Hold bevacizumab until complete resolution • If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion
Other Unspecified bevacizumab-related AEs (except controlled nausea/vomiting).	Grade 3	• Hold bevacizumab until symptoms resolve to ≤ grade 1
	Grade 4	• Discontinue bevacizumab • **Upon consultation with the study chair,** resumption of bevacizumab may be considered if a patient is benefiting from therapy, and the G4 toxicity is transient, has recovered to ≤ grade 1 and unlikely to recur with retreatment.

***Current CTCAE definitions used by CTEP:**

- Grade 1: asymptomatic, transient (< 24 hours) increase by > 20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated
- Grade 2: recurrent or persistent (> 24 hours) or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100 if previously WNL; monotherapy may be indicated
- Grade 3: requiring more than one drug or more intensive therapy than previously
- Grade 4: life threatening (e.g. hypertensive crisis)

Patients who interrupt or discontinue bevacizumab or placebo for bevacizumab or placebo-related toxicity should continue on-time treatment with gemcitabine and docetaxel. Imaging (CT scans) should continue to be performed on time in order to determine if there is evidence of progression of disease.

6.7 Dose escalations

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

8.0 EVALUATION CRITERIA

8.1 Parameters of Response – RECIST (Version 1.1) Criteria

Please refer to the following reference for complete details:

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (Version 1.1). *European Journal of Cancer.* 2009; 45:228-247.

8.11 Measurable disease ("Target") is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT (CT scan slice thickness no greater than 5 mm*); ≥ 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable); and ≥ 20 mm by chest x-ray.

*If CT scan with slice thickness > 5 mm is used, the minimum lesion size must have a longest dimension twice the actual slice thickness.

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.**

Clinical lesions will only be considered measureable when they are superficial and ≥ 10 mm diameter as assessed using **calipers** (e.g., skin nodules). When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and my also be reviewed at the end of the study.

CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI may be substituted for contrast enhanced CT for some sites (e.g., for abdomen and/or pelvis), but NOT lung. The minimum size for measurability is the same as for CT (10 mm), as long as the scans are performed with slice thickness of 5 mm and no gap. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness.

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.

Bone lesions:

- Bone scan, PET scan or plain films are NOT considered adequate imaging techniques to measure bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques

such as CT or MRI can be considered as measurable if the **soft tissue component** meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:
- Lesions that meet the criteria for radiographically-defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable).
- Cystic lesions thought to represent cystic metastases can be considered 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.

8.12 Non-measurable disease ("Non-Target") is defined as all other lesions, including small lesions (<10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions.

Lesions considered truly non-measurable include:
- Leptomeningeal disease
- Ascites
- Pleural or pericardial effusion
- Inflammatory breast disease
- Lymphangitic involvement of skin or lung
- Abdominal masses/abdominal organomegaly indentified by physical exam that is not measureable by reproducible imaging techniques

8.13 Baseline documentation of "Target" and "Non-Target" lesions

*All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) 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. 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**. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.*

All other lesions (or sites of disease) should be identified as *non-target* lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent." It is possible to record multiple non-target lesions involving the same organ as a single item on the D2M form (e.g. "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

All baseline evaluations of disease status should be performed as close as possible to the start 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 should ALWAYS be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

8.14 Response Criteria

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

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

8.143 Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). **In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.** (Note: The appearance of one or more NEW lesions is also considered progression. Guidance on when a lesion is to be considered new is provided in the reference cited above). **Unequivocal progression of existing non-target lesions** is also considered progression (a detailed description and examples of unequivocal progression of existing non-target lesions is provided in the reference cited above).

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If progression is confirmed at the next scheduled assessment, the date of progression should be the earlier date when progression was suspected.

8.144 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.

8.145 Not evaluable (NE) is when no imaging/measurement is done at all at a particular time point. The patient is not evaluable (NE) at that time point.

8.146 Early death is defined as the death of a patient for whom no repeat tumor assessments were completed after the initiation of study therapy; death resulted from disease and/or treatment.

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

Confirmation of response (for both CR and PR): Complete or partial response may only be claimed if the criteria for each are met at a subsequent time point (≥ 4 weeks later) in studies with a primary endpoint that includes response rate. When response rate is a secondary endpoint (e.g., randomized Phase II or III studies with progression-free survival or overall survival as primary endpoint), confirmation is NOT required.

Special note on lymph nodes: Lymph nodes identified as target lesions should always have the actual short-axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD and PD, the actual short-axis measurement of the nodes is to be included in the sum of target lesions.

Special note on target lesions that become "too small to measure": While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure." When this occurs it is important that a value be recorded on the D2M form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a **default value of 5 mm** should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well).

8.15 Evaluation of best overall response is according to Tables 1-3:

Table 1 is used for patients with measurable disease at baseline.
Table 1: Time point response: patients with target (+/– non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 2 is used for patients with non-measurable disease.
Table 2: Time point response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

8.16 Duration of response is defined as the time measurement criteria are first met for CR/PR until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurement recorded on study).

8.17 Duration of stable disease is measured from the start of the treatment (in randomized trials, from the date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

8.18 Progression-Free Survival is the period from study entry until recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurement recorded on study), death or date of last contact.

8.19 Survival is the observed length of life from entry into the study to death or the date of last contact.

8.2 Unblinding for Disease Progression **(08/02/2010)**
Assigned treatment arm can be revealed to patients with progressive disease, at the time such disease progression is confirmed by the Study Chair or the GOG Statistical & Data Center (SDC). The information will be transmitted confidentially by way of the study site investigator of record for that patient.

8.21 Unblinding for progression will only occur during NORMAL GOG SDC business hours: Monday-Friday, 9:00 AM – 5:00 PM Eastern Time. The emergency unblinding contact number indicated in the protocol is NOT to be used for unblinding for progression alone. It will still be available for after-hours emergency situations.

8.22 Once a patient has been determined by the institution to have progressed, submit all required case report forms (CRF), including those that document progression (Forms D2M, D2R, Q0, and Q) via SEDES.

8.23 At least one day following submission of the CRFs, call the Randomization line at 1-800-523-2917. The Randomization Specialist will first ask if the data has been submitted as outlined above. If the appropriate information has not been submitted, then you will need to submit the information and re-request an unblinding.

8.24 On this initial call, the Randomization Specialist will ask for the patient's GOG study number and initials. These identifiers will be matched to the registration information to make sure that there is no mistaken identification. They will also obtain your contact information and call-back number.

8.25 Within two working days following the request, a senior Clinical Data Coordinator (CDC) in the SDC will review the CRFs, which must provide unequivocal evidence of progression. If progression is based on symptomatic deterioration, then the CDC will request one of the clinical study chairpersons to review the evidence of progression.

8.26 After confirming the documentation of progression, the patient's treatment assignment will be unblinded by the Randomization Specialist. Following verification of the treatment assignment by a second Randomization Specialist, the institutional contact person will be called at the call-back number provided above. Please note: If you are unavailable to take the call, the assignment will not be left on voice mail. Thus, you will be required to call back to receive the treatment assignment.

8.27 A record will be maintained of each patient unblinding. Upon specific request a copy of the unblinding log will be faxed to the institution.

11.0 STATISTICAL CONSIDERATIONS

11.1 **Randomization:** The study is a two-arm, double-blind, placebo-controlled, randomized clinical trial. All patients enrolled onto the trial are to receive gemcitabine on day 1 and gemcitabine and docetaxel on Day 8 of every 21-day treatment cycle until toxicity or progression precludes further treatment. Whether a patient will also receive bevacizumab or placebo (for bevacizumab) on Day 1 of each cycle of treatment will be determined through randomization. The randomization procedure will tend to allocate the study regimens equally within patient groups defined by the following pretreatment characteristic:

11.11 Pelvic radiation prior to enrollment onto the study (yes vs. no).
Interim and final reports will include an accounting of all patients registered onto the study, regardless of their eligibility or compliance to the assign study treatment.

11.2 **Measures of efficacy and safety:** The principle observations for evaluating the therapeutic effects of treatment are:

11.21 Primary efficacy endpoint: Duration of progression-free survival.

11.22 Secondary efficacy endpoint: Duration of overall survival and response as measured by RECIST 1.1 criteria.

11.23 Safety endpoints: frequency and severity of adverse effects as assessed by the Common Terminology for Adverse Events- version 3.0.

11.3 Rationale of the study design

The primary goal of this study is to determine whether the addition of bevacizumab to a fixed-dose rate gemcitabine-docetaxel regimen increases the time to first progression or death when compared to gemcitabine-docetaxel with placebo.

Rationale for the proposed study design: Leiomyosarcoma of the uterus is a very rare disease. Therefore, several single-arm phase II trial designs with a PFS endpoint were considered. However, the inherent shortcomings of these designs render the final results difficult to interpret primarily for three reasons. Firstly, the potential for patient selection bias undermines the validity of inferring that the differences between expected and observed PFS distribution is attributable solely to bevacizumab. Secondly, the observed response (CR and PR) rate to first-line gemcitabine and docetaxel from GOG-087L was 35.8% (95% CI:23.5-49.6%) and the median time to progression was 4 months (95% CI: 1.6-7.0 months). These wide confidence bounds indicate that the currently available data are consistent with a broad range of true treatment effect sizes. The limited precision of these estimates undermine the reliability of estimating the relative benefit of bevacizumab from these historical data. Thirdly, a parallel study design permits standardizing the assessment schedule in order to minimize assessment bias. Therefore, due to the risk of selection bias, the limited precision of the currently available treatment effect estimates from historical data, and to control of assessment bias, a randomized Phase III design is the most reliable and valid design for determining

whether bevacizumab contributes to prolonging progression-free survival when combined with fixed dose rate gemcitabine-docetaxel. A positive result from this study, indicating that the addition of bevacizumab contributes to reducing the PFS event rate compared to gemcitabine, docetaxel and placebo, would provide a strong justification for adding bevacizumab to gemcitabine and docetaxel for the treatment of women with advanced or recurrent leiomyosarcoma of the uterus.

11.4 Accrual goal and study duration

Accrual goal, accrual rate and study duration: The targeted accrual is 130 patients. It is anticipated that 25-30 patients per year can be enrolled from GOG treatment centers. Therefore, the anticipated time required to accrue the targeted sample size is 4-5 years. This study will be considered sufficiently mature for a final analysis when at least 110 patients have experienced either progression or death. To accommodate a loss of power due to treatment noncompliance, 2 additional PFS events will be required for each patient who does not initiate bevacizumab among those randomized to Docetaxel+ Gemcitabine+ bevacizumab or placebo.[40] The total accrual may also need to be adjusted slightly in order to accommodate noncompliance. Accounting for a short time lag in reporting PFS events, it is anticipated that the timing of the final analysis will occur shortly after the termination of accrual.

Accrual Targets								
Ethnic Category	**Sex/Gender**							
	Females			**Males**			**Total**	
Hispanic or Latino	3		+	0		=	3	
Not Hispanic or Latino	127		+	0		=	127	
Ethnic Category: Total of all subjects	130	(A1)	+	0	(B1)	=	130	(C1)
Racial Category								
American Indian or Alaskan Native	3		+	0		=	3	
Asian	1		+	0		=	1	
Black or African American	26		+	0		=	26	
Native Hawaiian or other Pacific Islander	1		+	0		=	1	
White	99		+	0		=	99	
Racial Category: Total of all subjects		(A2)	+	0	(B2)	=	(C2)	

11.5 Assessing efficacy

Treatment efficacy: Type I error and power: Assuming a constant hazards, this trial size provides an 83% chance to detect a 40% reduction in the PFS event rate (hazard ratio = 1.67) due to bevacizumab, if it truly exists, while the type error is limited to 0.05 for a one-tail test (based on 500 simulated trials and assuming no loss to follow-up). This effect size is comparable to increasing the expected median PFS from 4 months to 5.7 months.

Primary hypothesis and hypothesis test: Let λ_{GD+P} and λ_{GD+B} represent the PFS event rate for patients randomized to the gemcitabine+docetaxel+placebo and the gemcitabine+docetaxel with bevacizumab regimens, respectively. The null hypothesis

to be evaluated in this study is H_0: $\lambda_{GD+P} / \lambda_{GD+B} \leq 1.0$. To ameliorate the affects of potential assessment time bias, the failure times will be grouped into intervals. In terms of weeks from each patient's date of randomization, the intervals will be [0, 8), [8, 16), [16, 24), [24, 36), [36, 52), [52-78), [78-104), [104+) [40, 41]. An individual will contribute to the interval if either her first progression (or death) occurred within the interval or she is known to have survived progression-free at least half-way through the interval. Those patients who are alive and progression-free until the final interval will be censored at the beginning of the final interval.

Interim Analyses: An interim analysis will be performed when there are at least 70 patients reported to have experienced either progression or death. The interim analysis will include an assessment of efficacy. The O'Brien and Fleming-like type I error spending function (described by Lan and Demets)[42] will be used to determine the upper boundary for rejecting the null hypothesis and accepting the hypothesis that bevacizumab is an effective addition to gemcitabine and docetaxel for the treatment of women with advanced or recurrent leiomyosarcoma of the uterus. The information time for the alpha-spending function will be calculated as the number of progression or death events reported in both treatment groups at the time of the interim analysis divided by the number of events required for the final analysis. If the null hypothesis can be rejected at the interim analysis, than termination of the accrual onto the study will be considered.

The interim analysis will also include a futility assessment of PFS. If the grouped logrank test, which stratifies patients by prior radiotherapy, indicates that the observed number of first progression or death events among those randomized to the bevacizumab regimen is greater than expected (under the null hypothesis), then consideration will be given to terminating accrual onto the study and concluding that adding bevacizumab does not significantly prolong PFS in women diagnosed with advanced or recurrent leiomyosarcoma of the uterus.

Finally, the interim analyses will include tabulations and descriptive statistics concerning the incidence and severity of adverse events. Some adverse events, including bowel perforation, gastrointestinal fistula formation, bleeding disorders and hypertension will be tabulated separately, since there is evidence that bevacizumab specifically increases the incidence or the severity of these AE's. Particular attention will be given to the estimated incidence of Grade 3 or worse gastro-intestinal events that are described as either fistula, necrosis, perforation, or bleeding among patients who were enrolled more than 2 months prior to the data freeze for the interim analysis, randomized to and received bevacizumab. Suppose that N_i is the number of patients in this subgroup analysis and n_i is the number of patients in this subgroup who have experienced one of these GI events. If the probability of observing n_i or more such events among N_i individuals is less than 0.08, while assuming that the true incidence is 5%, then consideration will be given to terminating accrual onto the bevacizumab arm. For example, if the effective sample size is 30 individuals for this subset analysis of whom 4 have experienced one of these GI events, then the probability of observing 4 or more such events is 6.1% (i.e., <0.08) and therefore consideration would be given to terminating accrual onto the bevacizumab arm. If the true rate of these events is 15%, then conditioned on the available data this decision rule would provide a 68% chance of terminating this trial early.

The results of interim analyses are scheduled to be reviewed by the GOG Data Monitoring Committee (DMC) at its semi-annual meetings. This committee meets in January and July each year. Once the prerequisite number of events has been observed, an interim analysis is prepared and presented to the DMC at their next scheduled meeting. The decision to terminate accrual to the trial includes consideration of toxicities, treatment compliance, progression-free survival and results from external studies. Additionally, the GOG Data Safety and Monitoring Board (DSMB) reviews accumulating summaries of toxicities and all serious adverse event (SAE) reports on an ongoing basis (not efficacy results). This committee also reviews those deaths in which study treatment may have been a contributing cause. The DSMB reports to the DMC and it may recommend study amendments to the DMC pertaining to patient safety.

Final Analyses - efficacy: At the final analysis, the null hypothesis will be assessed with a logrank test stratified by whether the patient had whole pelvic radiotherapy prior to starting the study treatment. The primary efficacy analysis will include all eligible patients enrolled regardless of their compliance with the assigned treatment plan, grouped by their assigned study treatment. The timing of the final analysis will be determined by the number of PFS events reported as described above. The critical value for assessing the null hypothesis will be determined so as to control the overall type I error to 5%, accounting for the error spent due to interim analyses.

The product-limit method will be used to estimate the cumulative distribution of PFS and overall survival times for the patients assigned to each treatment group. For the primary analyses these estimates will include all eligible patients regardless of their compliance to the planned study regimen. Any analyses based on subgroups, for example - only those patients, who received a certain amount of treatment, will be considered exploratory.

The primary analysis of response will include all eligible patients regardless of their compliance to study treatment. Patients will be grouped by their assigned treatments for estimating the probability of responding (complete or partial response). The proposed sample size will provide 90% confidence intervals no larger than $\pm$ 11% for the probability of response for each treatment group (unadjusted for multiplicity). The 90% confidence interval for difference in the response rates is limited to $\pm$ 15% (assuming the null hypothesis is true).

11.6 Analyses of safety data

Final Analyses – safety: Adverse events (AEs) that are considered to be at least possibly attributable to the study treatment will be tabulated by Version 4.0 of CTCAE major category. Also particular attention will be given to the incidence of bowel fistula, perforation, or necrosis. For the purpose of the final analyses, non-hematologic AEs will be dichotomized by CTCAE Grade 3 or worse and hematologic toxicities will be dichotomized by CTCAE Grade 4 or worse. These analyses of AEs will include only those patients who initiated any part of their study treatment. Due to the need to evaluate several categories of AEs, procedures which control the false discovery rate will be used rather than attempting to control the experiment-wide Type I error. **(08/02/2010)**