

	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		<i>Pruritus (Gr. 2)</i>
	Rash maculo-papular		<i>Rash maculo-papular(Gr. 2)</i>
	Urticaria		<i>Urticaria (Gr. 2)</i>
VASCULAR DISORDERS			
Hypertension			<i>Hypertension (Gr. 3)</i>
	Thromboembolic event		<i>Thromboembolic event (Gr. 3)</i>
		Vascular disorders - Other (arterial thromboembolic event) ¹²	

¹This 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.

²Gastrointestinal 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.

³Gastrointestinal 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.

⁴Gastrointestinal 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.

⁵Gastrointestinal 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.

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

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

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

⁹Cases 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.

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

¹¹Ovarian 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.

¹²Arterial 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
HEPATOBIILIARY 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.

(For a more complete listing of reported AEs, please refer to the Investigator's Brochure)

- 4.37 General Information on Adverse Effects of Bevacizumab(06/22/09)
 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 controls in randomized studies.

The following is a description of major adverse events associated with bevacizumab therapy. A list of Comprehensive Adverse Events and Potential Risks (CAEPR) in NCI-CTCAE v3.0 terms is included above. Reference may also be made to the Investigators' Brochure and the FDA package insert (www.fda.gov/cder/foi/label/2004/1250851bl.pdf).

Infusion-Related Reactions: Infusion reactions with bevacizumab were uncommon (<3%) and rarely severe (0.2%). Infusion reactions may include rash, urticaria, fever, rigors, hypertension, hypotension, wheezing, or hypoxia. Currently, there is no adequate information on the safety of retreatment with bevacizumab in patients who have experienced severe infusion-related reactions.

Hypertension: Hypertension is common in patients treated with bevacizumab, with an incidence of 20-30% across trials. Initiation or increase of anti-hypertensive medications may be required, but in most cases, blood pressure (BP) can be controlled with routine oral drugs. However, incidents of hypertensive crisis with encephalopathy or cardiovascular sequelae have been rarely reported. BP should be closely monitored during bevacizumab therapy and the goal of BP control should be consistent with general medical practice. Bevacizumab therapy should be suspended in the event of uncontrolled hypertension.

Proteinuria: Proteinuria has been seen in all bevacizumab studies to date, ranging in severity from an asymptomatic increase in urine protein (incidence of about 20%) to rare instances of nephrotic syndrome (0.5% incidence). Pathologic findings on renal biopsies in two patients showed proliferative glomerulonephritis. NCI-CTCAE grade 3 proteinuria (> 3.5gm/24 hour urine) is uncommon, but the risk may be higher in patients with advanced RCC. In the phase 2 randomized study in RCC, 24-hour urine was collected in a subset of patients enrolled, and grade 3 proteinuria was found in 4 patients in the 10 mg/kg-arm (n=37), 2 patients in the 3mg/kg arm (n=35) and none in the placebo arm (n=38). The safety of continuing bevacizumab in patients with moderate or severe proteinuria has not been adequately tested.

Hemorrhage: The incidence of hemorrhage is increased with bevacizumab therapy. Epistaxis is common, occurring in 20-40% of patients, but it is generally mild and rarely requires medical intervention. Life-threatening and fatal hemorrhagic events have been observed in bevacizumab studies and included pulmonary hemorrhage, CNS bleeding and gastrointestinal (GI) bleeding. In a phase 2 study in non-small cell lung cancer, 6 cases of life-threatening hemoptysis or hematemesis were reported among 66 patients treated with bevacizumab and chemotherapy; 4 of these events were fatal.⁹⁷ In the pivotal phase 3 trial in advanced colorectal cancer, the rate of GI hemorrhage (all grades) was 24% in the IFL/bevacizumab arm compared to 6% in the IFL arm; grade 3-4 hemorrhage was 3.1% for IFL/bevacizumab and 2.5% for IFL. Serious GI hemorrhage has also been observed in clinical trials with bevacizumab in patients with pancreatic cancer or varices treated with bevacizumab.

Arterial Thromboembolic Events: The risk of arterial thromboembolic events is increased with bevacizumab therapy, and such events included cerebral infarction, transient ischemic attack (TIA), myocardial infarction and other peripheral or visceral arterial thrombosis. In the pivotal trial in CRC

(AVF2107), the incidence of arterial thromboembolic events was 1% in the IFL/placebo arm compared to 3% in the IFL/ bevacizumab arm. A pooled analysis of five randomized studies showed a two-fold increase in these events (4.4% vs 1.9%). Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk.⁹⁸ In patients ≥ 65 years treated with bevacizumab and chemotherapy, the rate of arterial thromboembolic events was approximately 8.5%.

Gastrointestinal Perforation/Fistula: GI perforations/fistulas were rare but occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal phase 3 trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving 5-FU/bevacizumab compared to 0.3% in patients receiving IFL alone. GI perforation has also been reported in patients with gastric/esophageal cancer, pancreatic cancer, ovarian cancer or co-morbid GI conditions such as diverticulitis and gastric ulcer. **GI perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain, fever of unclear source, or rectal/abdominal abscess.**

Wound Healing Complications: Bevacizumab delays wound healing in rabbits, and it may also compromise or delay wound healing in patients. Bowel anastomotic dehiscence and skin wound dehiscence have been reported in clinical trials with bevacizumab. The appropriate interval between surgery and initiation of bevacizumab required to avoid the risk of impaired wound healing has not been determined. However, all clinical trials with bevacizumab have required a minimum of 28 days from prior major surgery; experience in the pivotal trial in advanced CRC suggests that initiation of bevacizumab 29-50 days following surgery should be associated with a very low incidence of wound dehiscence. The optimal interval between termination of bevacizumab and subsequent elective surgery has not been determined either. In the pivotal study in CRC, 40 patients on the IFL/bevacizumab arm and 25 patients on the IFL/placebo arm underwent major surgery while on study; among them, significant post-operative bleeding or wound healing complications occurred in 4 of the 40 patients from the IFL/bevacizumab arm and none of the 25 patients

from the IFL alone arm. Decisions on the timing of elective surgery should take into consideration the half-life of bevacizumab (average 21 days, with a range of 11-50 days).

Congestive Heart Failure: The risk of left ventricular dysfunction may be increased in patients with prior or concurrent anthracycline treatment. In phase 3 controlled clinical trials in metastatic breast cancer (AVF 2119g) in which all patients had received prior anthracyclines, congestive heart failure (CHF) or cardiomyopathy were reported in 7 patients (3%) in the bevacizumab/capecitabine arm compared to 2 (1%) in the capecitabine-only arm. No increase in CHF was observed in CRC trials with bevacizumab in combination with IFL or 5-FU.

Venous Thrombosis: Venous thromboembolic events reported in bevacizumab trials included lower extremity deep vein thrombosis (DVT), pulmonary embolism and rarely, mesenteric or portal vein thrombosis. In the pivotal phase 3 trial of IFL ± bevacizumab (given at 5 mg/kg q2w), the overall incidences of G3-4 venous thromboembolic events were comparable in the two arms (15.1 vs 13.6%).

Fertility and Pregnancy: Clinical data are lacking regarding the immediate or long-term effect of bevacizumab on fertility and pregnancy. However, bevacizumab is known to be teratogenic and detrimental to fetal development in animal models. In addition, bevacizumab may alter corpus luteum development and endometrial proliferation, thereby having a negative effect on fertility. As an IgG1, it may also be secreted in human milk. Therefore, fertile men and women on bevacizumab studies must use adequate contraceptive measures and women should avoid breast feeding. The duration of such precautions after discontinuation of bevacizumab should take into consideration the half-life of the agent (average 21 days, with a range of 11 to 50 days).

Immunogenicity: As a therapeutic protein, there is a potential for immunogenicity with bevacizumab. With the currently available assay with limited sensitivity, high titer human anti-bevacizumab antibodies have not been detected in approximately 500 patients treated with bevacizumab.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), or similar leukoencephalopathy syndrome: RPLS/PRES are clinical syndromes related to vasogenic edema of the white matter and have rarely been reported in association with bevacizumab therapy (<1%). Clinical presentations may include altered mental status, seizure, and cortical blindness. MRI scans are required for diagnosis: typical findings are vasogenic edema in the white matter of the posterior parietal and occipital lobes, and less frequently in the anterior distributions and the gray matter.

In RPLS associated with bevacizumab mild or significant BP elevations were seen in some but not all cases. RPLS/ PRES should be in the differential diagnosis in patients presented with unexplained mental status change, visual disturbance, seizure or other CNS finding. MRI is the key to diagnosis. This syndrome is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent irreversible tissue damage.(06/22/09)

Neutropenia: when combined with chemotherapy, bevacizumab increased the risk of neutropenia compared to chemotherapy alone. In a phase 3 trial with IFL +/- bevacizumab in colorectal cancer, grade 3-4 neutropenia was 21% in the bevacizumab arm + IFL vs 14% in the IFL arm (grade 4 neutropenia was 3% vs 2%). In a phase 3 trial with carboplatin and paclitaxel +/- bevacizumab in NSCLC, the bevacizumab-containing arm was associated with an increased rate of grade 4 neutropenia (27% vs 17%), febrile neutropenia (5.4% vs 1.8%), and an increased risk of infection with neutropenia (4.4% vs 2.0%) with three fatal cases in the bevacizumab + chemotherapy arm vs none in the chemotherapy control arm.(06/22/09)

4.38 Agent Ordering and Agent Accountability(08/04/08)

NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

- 4.39 Agent may be requested by completing a Clinical Drug Request (NIH-986) and mailing it to the Drug Management and Authorization Section, PMB, DCTD, NCI, 9000 Rockville Pike, EPN Room 7149, Bethesda, MD 20892-7422 or faxing it to (301) 480-4612. For questions call (301) 496-5725.
- 4.40 Agent Inventory Records - The investigator, or a responsible party designated by the investigator, must maintain a careful record of the

inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record (DAR) Form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)(6/22/09)

4.4 Docetaxel (Taxotere® RP-56976, NSC #628503)

- 4.41 Formulation: Docetaxel is supplied as a sterile, non-pyrogenic, non-aqueous viscous solution in single dose vials containing 20mg/0.5mL or 80mg/2mL of docetaxel. Each mL contains 40mg docetaxel (anhydrous) and 1040mg polysorbate 80.
- 4.42 Docetaxel requires dilution prior to use. A sterile, non-pyrogenic, single dose diluent is supplied for this purpose. The diluent for docetaxel contains 13% (w/w) ethanol in water for injection and is supplied in vials.
- 4.43 Storage: Unopened vials of docetaxel are stable to the date indicated on the package when stored between 2 and 25°C (36 and 77°F). Protect from light.
- 4.44 Preparation: Docetaxel must be combined with its supplied diluent (final concentration = 10mg/mL) and then further diluted prior to infusion. Docetaxel should be diluted in 0.9% Sodium Chloride for Injection, USP or 5% Dextrose Injection, USP to produce a final concentration of 0.3 to 0.74mg/mL. The fully prepared docetaxel infusion solution should be used within 4 hours (including the infusion duration).

NOTE: In order to minimize patient exposure to the plasticizer DEHP, 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 (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.

All patients should be premedicated with oral corticosteroids for 3 days starting 1 day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

- 4.45 Adverse Effects: Consult the package insert for the most current and complete information.
- 4.46 Supplier: Commercially available from Aventis. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

4.5 Gemcitabine(10/01/12)

- 4.51 Formulation: Gemcitabine is supplied as a lyophilized powder in sterile vials containing 200 mg or 1 gram of gemcitabine as the hydrochloride salt (expressed as the free base), mannitol and sodium acetate.
- 4.52 Gemcitabine requires dilution prior to use. The lyophilized product will be reconstituted with normal saline added to the vial in order to make a solution ideally containing 10 mg/ml or \leq 40 mg/ml for 200 mg and 1 gram vials.
- 4.53 Storage: Unopened vials of gemcitabine are stable to the date indicated on the package when stored between 2 and 25°C (36 and 77°F). Once the drug has been reconstituted, it should be stored at controlled room temperature (range, 20 to 25°C) and used within 24 hours.
- 4.54 Preparation: An appropriate amount of drug will be administered as prepared or diluted with an additional 100 ml of normal saline. Once the drug has been reconstituted, it should be stored at controlled room temperature (range, 20 to 25°C) and used within 24 hours.
- 4.55 Administration: Gemcitabine will be infused over 1 hour
- 4.56 Adverse Effects: Consult the package insert for the most current and complete information.
- 4.57 Supplier: Commercially available from Eli Lilly Pharmaceuticals. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.
- 4.6 **Pathology Requirements (6/22/09)**
- 4.61 **Eligible Patients:** Patients must have histologic diagnosis of epithelial ovarian carcinoma, peritoneal primary or Fallopian tube carcinoma, which is now recurrent. Patients with the following histologic epithelial cell types are eligible: Serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's Tumor, or adenocarcinoma not otherwise specified (N.O.S.).
- 4.62 **Ineligible Patients:** Patients with a gynecologic malignancy other than epithelial ovarian carcinoma, peritoneal primary or Fallopian tube carcinoma.
- 4.63 **Requirements and Instructions:** Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility for

the protocol. See section 7.2 and 10.2 for specific requirements and instructions for the stained pathology slides, pathology reports and forms.

5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

Before patient entries will be accepted, an official signed CTSU IRB Certification Form and a CTSU IRB/Regulatory Approval Transmittal Sheet (forms can be downloaded at www.ctsu.org) must be received by the CTSU Regulatory Office. These forms 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 Patient Entry and Registration

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

- 5.11 An approved informed consent form and authorization permitting the release of personal health information must be signed by the patient or guardian. 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 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. Assistance is available from the Statistical and Data center by phone if necessary (800-523-2917).
 - 5.141 In order to obtain investigational drug from the Pharmaceutical Management Branch (PMB), the treating physician must have an active NCI Investigator Number. If the treating physician's investigator number is not active, the drug order will **not** be processed. To obtain or renew an NCI Investigator Number, please visit the CTEP's Investigator Registration page at <http://ctep.info.nih.gov/resources/investigator2.html>.
- 5.15 The institution will enter the patient's name, GOG number, and assigned regimen in the appropriate place in their Log Book to verify the patient's entry.

5.2 Treatment Plan (06/22/09)

- 5.21 Patients meeting eligibility requirements will be considered first for the surgical randomization aspect of the trial. Suitability for secondary cytoreduction will be made by the individual patient's Attending Physician. Guidelines for consideration in assessing candidacy for secondary cytoreduction are listed in Section 5.211. If the patient is considered to be a suitable surgical candidate she will undergo randomization as outlined in Section 5.22.

(The following two sentences do not apply to patients enrolled onto the study after August 28, 2011): If the patient is considered not to be a suitable surgical candidate she will be allowed to participate in the chemotherapy randomization aspect of the trial as outlined in Section 5.23. Patients undergoing surgical randomization will also be randomized to a chemotherapy regimen at the same time. (08/29/11)(12/19/11)

- 5.211 Guidelines for Secondary Cytoreduction: The goal of secondary cytoreduction is **COMPLETE REMOVAL OF ALL VISIBLE DISEASE**. While no specific eligibility can be globally provided, patients with recurrent disease which will not be addressed at surgery should not undergo surgical randomization. In general, women with carcinomatosis and/or ascites make poor surgical candidates as the diffusion of disease usually precludes complete cytoreduction. Similarly, women with parenchymal organ disease (e.g. lung, liver, pancreas, kidney, bone, etc) are poor candidates, if the disease is felt unresectable by preoperative evaluation. Assessment of candidacy will be made by physical exam, laboratory and imaging (MRI, PET/CT and/or CT). Although it is recognized that patients with longer treatment-free intervals may be considered better surgical candidates (providing some expansion of the preoperative tumor volume characteristics) than those with shorter treatment-free intervals, the primary tenet of surgery for this study in all women enrolled in this arm is complete surgical resection (no visible residual).
- 5.22 Randomization I: ***Surgery***: Patients entered onto the surgical arm of the trial will undergo abdominal exploration with cytoreduction as outlined in (Appendix II) within 4 weeks of registration. Chemotherapy will be administered following recovery up to 6 weeks after surgery. A discussion with the study chair is required if study treatment is not initiated within 6 weeks of surgery.(6/22/09) (03/15/10)
- 5.23 Randomization II: ***Chemotherapy***. (Between Dec 6, 2007 and August 28, 2011 the following 4 treatment arms were randomly assigned to

patients enrolled into this study. Beginning August 29, 2011 all patients are required to be surgical candidates, and only the surgical component of treatment is randomized. For these later patients the systemic treatment, which consists of either paclitaxel+carboplatin (as described for arms I and III) or gemcitabine+carboplatin (as described for arms V and VII) or paclitaxel+carboplatin+bevacizumab (as described for arms II and IV) or gemcitabine+carboplatin+bevacizumab (as described for arms VI and VIII) is selected and declared prior to enrolling onto the study. (08/29/11)(12/19/11) (10/01/12)

Patient chooses systemic treatment with either:

- a) carboplatin + paclitaxel or gemcitabine or
- b) carboplatin + paclitaxel or gemcitabine + bevacizumab

5.231 Regimens: (06/22/09) (03/15/10) (10/01/12)

Arm	Surgery	Chemotherapy*	Schedule	Maintenance Regimen
I	No	Paclitaxel 175 mg/m ² ** Carboplatin AUC 5	Every 21 days (Section 5.24)	None
II	No	Paclitaxel 175 mg/m ² ** Bevacizumab 15 mg/kg Carboplatin AUC 5	Every 21 days (Section 5.25)	Bevacizumab 15 mg/kg every 21 days until progression or toxicity precludes further treatment.
V	No	Gemcitabine 1000 mg/m ² d1 & d8 Carboplatin AUC 4 day 1	Every 21 days (Section 5.24)	None
VI	No	Gemcitabine 1000 mg/m ² d1 & d8 Bevacizumab 15 mg/kg Carboplatin AUC 4 day 1	Every 21 days (Section 5.25)	Bevacizumab 15 mg/kg every 21 days until progression or toxicity precludes further treatment.
III	Yes	Paclitaxel 175 mg/m ² ** Carboplatin AUC 5	Every 21 days (Section 5.24)	None
IV	Yes	Paclitaxel 175 mg/m ² ** Bevacizumab 15 mg/kg Carboplatin AUC 5	Every 21 days (Section 5.25)	Bevacizumab 15 mg/kg every 21 days until progression or toxicity precludes further treatment.

VII	Yes	Gemcitabine 1000 mg/m ² d1 & d8 Carboplatin AUC 4 day 1	Every 21 days (Section 5.24)	None
VIII	Yes	Gemcitabine 1000 mg/m ² d1 & d8 Bevacizumab 15 mg/kg Carboplatin AUC 4 day 1	Every 21 days (Section 5.25)	Bevacizumab 15 mg/kg every 21 days until progression or toxicity precludes further treatment.

*All chemotherapy doses on day one unless otherwise indicated. For those patients randomized to cytoreductive surgery, bevacizumab is to be started at the 2nd cycle of therapy.

** Note: docetaxel 75mg/m² IV over 1 hour may be substituted for paclitaxel (see Sections 5.233 and 6.161).

5.232 Patients continue to receive maintenance treatment until disease progression or until adverse events prohibit further therapy.

5.233 Sequence and timing of drug administration: **(08/04/08)**
(03/15/10)(08/29/11)(12/19/11)(10/01/12)

- **Paclitaxel** will be infused over 3 hours. (Note, for circumstances in which docetaxel should be substituted for paclitaxel: Docetaxel will be administered as a 1 hour IV infusion at a starting dose of 75 mg/m² see Sections 6.161 and 6.167).
- **Bevacizumab** administration will be as a short intravenous infusion following paclitaxel infusion. Anaphylaxis precautions should be observed during bevacizumab administration. The initial dose would be administered over 90 ± 15 minutes. If no adverse reactions (including fever and or chill) occur, the second dose should be administered over a minimum of 60 ± 10 minutes. If no adverse reactions occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes.
- **Bevacizumab has been associated with an increase in wound complications and bowel perforations in post-operative patients. Thus, patients in Randomization I who undergo surgery and are to receive bevacizumab after Randomization II will have the first cycle of therapy without bevacizumab. They will receive it in cycle #2.**
- **Gemcitabine will be administered over 60 minutes on days 1 and 8 of each 21-day cycle. Patients will be monitored prior to each dose with a complete blood count, including differential counts.**

- **Carboplatin** will be administered as a 60-minute infusion. When administered in conjunction with other medications, carboplatin will be infused after the other agents. Carboplatin, either alone or in combination should be premedicated with dexamethasone (either IV or PO), anti-histamine H1 (such as diphenhydramine) and anti-histamine H2 (such as cimetidine, ranitidine, or famotidine).

5.234 Pre-Medication:(10/01/12)

For all courses where paclitaxel is to be administered, it is recommended that a preparative regimen be employed one hour prior to the treatment regimen on that day to reduce the risk associated with hypersensitivity reactions. This regimen should include dexamethasone (either IV or PO), anti-histamine H1 (such as diphenhydramine) and anti-histamine H2 (such as cimetidine, ranitidine, or famotidine).

When carboplatin and paclitaxel are administered with bevacizumab, it is recommended that the preparatory regimen as outlined above should be given 30 minutes if IV or 60 minutes if PO before infusion to reduce the risk of hypersensitivity associated with these agents.

In the event of a prior bevacizumab hypersensitivity reaction the prophylactic regimen should be repeated prior to subsequent doses of bevacizumab (Section 5.2551). Thus, the patient will be premedicated prior to paclitaxel AND prior to bevacizumab.

For all courses where docetaxel is to be administered, (see Sections 6.161 and 6.167) it is recommended that patients be premedicated with dexamethasone 8 mg orally taken the night before, morning of, and evening after each treatment (total dose, 24 mg/wk), and an anti-histamine H1 (diphenhydramine 25-50 mg IVP or orally, or an equivalent dose of an alternate H₁ blocker such as loratadine or fexofenadine) one hour prior to docetaxel.

5.235 Antiemetic Regimens(10/01/12)

It is anticipated that nausea and vomiting may be a significant side effect of each regimen. The following representative antiemetic regimens are suggested:

- Ondansetron 8-32 mg IV 30 minutes prior to administration of chemotherapy and dexamethasone 10-20 mg IV 30 minutes prior to drug administration or,

- Granisetron 1 mg IV (or 2 mg PO) 30 minutes prior to chemotherapy plus dexamethasone 10 mg IV, with or without lorazepam 0.5 – 2.0 mg IV 30 minutes prior to chemotherapy.
- Be sure to give prescription(s) for prevention of delayed nausea/vomiting as per institutional guidelines/standards.

5.236 Dosing of Paclitaxel(06/22/09)

The initial dose of paclitaxel will be 175 mg/m². Alterations in this dose are presented in Section 6.1612. As such, patients whose body weight changes by 10% or more should undergo recalculation based on the adjusted body surface area.

5.237 Dosing of bevacizumab(06/22/09)(08/29/11)

Bevacizumab will be administered at 15 mg/kg IV. **For patients randomized to the chemotherapy arm, the weight at screening will be used to determine the bevacizumab dose to be used for the duration of the study.** For patients undergoing the second surgical procedure **the** baseline weight for calculating the bevacizumab dose should be post-op. If a patient's weight changes by $\geq 10\%$ during the course of the study, the bevacizumab dose will be recalculated.

5.2371 Supportive Care Guidelines for Bevacizumab

If an infusion-related adverse reaction occurs, the patient should be pre-medicated prior to subsequent doses of bevacizumab (Section 5.234); however, the infusion time for bevacizumab may not be decreased for the next infusion. If a patient experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90 minutes \pm 15 minutes.

5.238 Dosing of Carboplatin (03/15/10) (08/23/10) (1/3/11)

See Appendix V for current Carboplatin dose calculation instructions

5.239 Dosing of Gemcitabine (10/01/12)

See Section 5.233

5.24 Duration of treatment – Paclitaxel or Gemcitabine and Carboplatin (Arm I, Arm III, Arm V, and Arm VII): (06/22/09)

- 5.241 Patients with measurable disease achieving clinical complete response (negative physical exam, negative CT scan or MRI and normal CA-125) (CR; Section 8.131) during the chemotherapy phase will be treated with a minimum of 6 cycles of therapy or for 2 additional cycles following the CR designation (maximum of 8 cycles), whichever is greater.
- 5.242 If stable or partial regression is the maximum documented response, patients will continue their chemotherapy to a maximum of 8 cycles (see Section 8.15) or adverse effects (see Section 6.0). Patients will then be followed off therapy until documented progression occurs. (See Section 8.14) **(08/04/08)(6/22/09)**
- 5.243 If progressive disease is observed while on therapy, patients will have study therapy discontinued and will be treated with appropriate alternative chemotherapy.
- 5.244 Patients without measurable lesions as determined by a CT scan prior to initiating study treatment will continue therapy for 6 cycles or if CA-125 normalizes for 2 cycles beyond CA-125 normalization, whichever is greater as long as: the criteria for progression (See Section 8.14); and the criteria for study termination by drug toxicity (See Section 6.0) have not been met. Patients with normal CA-125 at the start of therapy (without measurable lesions) will have chemotherapy stopped after six cycles. .
- 5.25 Duration of treatment – Carboplatin, Bevacizumab and Paclitaxel or Gemcitabine (Arm II Arm IV, Arm VI, and Arm VIII) **(06/22/09) (03/15/10)(10/01/12)**
- 5.251 Patients with measurable disease achieving clinical complete response (CR; Section 8.131) during the chemotherapy phase will be treated for a minimum of 6 cycles of therapy or for 2 additional cycles following the CR designation (maximum of 8 cycles) and then begin the maintenance regimen. The maintenance phase will be continued until progression or adverse effects preclude additional treatment.
- 5.252 If stable or partial regression is the maximum documented response, patients will receive up to 8 cycles (minimum of 6 cycles) of therapy and then begin the maintenance regimen. The maintenance phase will be continued until progression or adverse effects preclude additional treatment.**(08/04/08)**

5.253 If progressive disease is observed while on therapy, patients in all arms will have study therapy discontinued and will be treated with appropriate alternative chemotherapy.

5.254 Patients without measurable lesions as determined by a CT scan prior to initiating study treatment will continue chemotherapy and the biologic agent for 6 cycles or if CA-125 normalizes for 2 cycles beyond CA-125 normalization, whichever is greater as long as: the criteria for progression (See Section 8.15); and the criteria for study termination by drug toxicity (See Section 6.0) have not been met. Patients with normal CA-125 at the start of therapy (without measurable disease) will have chemotherapy stopped after six cycles. The maintenance regimen will begin after completing chemotherapy and continue until progression or adverse effects preclude additional treatment.

5.26 Biometric considerations in dose calculation

Maximum body surface area used for dose calculations will be 2.0 m² as per GOG Chemotherapy Procedures Manual

5.3 Secondary Cytoreduction: (06/22/09)

The value of secondary surgical cytoreduction is being evaluated in this trial through a randomization of surgical candidates deemed appropriate by their treating physicians. Participation in the surgical randomization arm of this trial is **NOT** required for entry on this study. Patients with recurrent disease, meeting entry criteria but deemed not appropriate for surgical exploration are eligible to participate in the chemotherapy randomization. Those patients for whom their treating physicians consider appropriate for surgery will be randomized to either secondary cytoreduction or no surgery prior to a second randomization of chemotherapy. Surgical exploration should be undertaken within 28 days of registration onto this study.

5.31 Procedures and goals of secondary cytoreduction are outlined in Appendix II.

5.32 Please see Section 7.3 for a summary of the specimen requirements and laboratory testing for this protocol. In addition, please carefully review Appendix III for a detailed description of the Specimen Procedures for GOG-0213.

6.0 TREATMENT MODIFICATIONS

6.1 Dose Modifications:

Since chemotherapy in the recurrent setting is largely palliative, infusion without routine use of growth factor support will be attempted. Certain chemotherapy combinations have additive hematologic toxicity and other combinations are characterized by differing hematologic toxicity. Therefore, dose modification will be based on dose-limiting toxicity (DLT) for either or both neutropenia (ANC) or thrombocytopenia (PLT) and conducted as outlined in the following table below.

If a dose reduction is indicated, recalculate chemotherapy dosages using the baseline weight and serum creatinine. **(03/15/10)**

6.11 Dose-limiting neutropenia (DLT-ANC) is defined as:

- Febrile neutropenia: febrile is defined as fever $\geq 38.5^{\circ}\text{C}$, with or without documented infection in the presence of an ANC of 1000 cells/mm³ or less
- Prolonged Grade IV ANC persisting ≥ 7 days.
- Uncomplicated Grade IV ANC, < 7 days, is NOT a DLT.

6.12 Dose-limiting thrombocytopenia (DLT-PLT) is defined as:

- Grade IV thrombocytopenia ($< 25,000/\text{mm}^3$)
- Grade III thrombocytopenia ($25,000$ to $50,000/\text{mm}^3$) complicated by bleeding, easy bruising, petechiae or requiring platelet transfusion (see Section 6.141)
- Uncomplicated Grade III thrombocytopenia is NOT a DLT

6.13 Guidelines for dose modification based on dose-limiting neutropenia and thrombocytopenia: (nadirs)

Table A

DLT ANC [‡]	DLT PLT [§]	First Occurrence	Second Occurrence	Third Occurrence
Yes	No	Reduce the REGIMEN drug doses by one level as in Table B-1 *	Add myeloid growth factor AND maintain all drug doses	Off Study Treatment, Follow-up Continued
Yes	Yes	Reduce the REGIMEN drug doses by one level as in Table B-1 *	Off Study Treatment, Follow-up Continued	
No	Yes	Decrease one AUC unit AND maintain other drug doses *	Off Study Treatment, Follow-up Continued	

[‡] DLT-ANC: Neutropenic Dose-Limiting Toxicity (Section 6.11)

§ DLT-PLT: Thrombocytopenic Dose-Limiting Toxicity (Section 6.12)

* For patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Sections 6.161 and 6.167, dose modifications can be found in Table B-2.

6.14 Adjustments for Hematologic Toxicity (03/15/10)

6.141 **Hemorrhage:** Patients receiving bevacizumab who develop a CTCAE V3.0 Grade 3 hemorrhage and receiving full-dose anticoagulation will be taken off study treatment. For all other patients with CTCAE V3.0

Grade 3 hemorrhage, bevacizumab should be held until ALL of the following criteria are met (continue carboplatin and paclitaxel):

- bleeding has resolved
- blood hemoglobin level is stable (serial measures with less than 10% change)
- there is no bleeding diathesis that would increase the risk of therapy
- there is no anatomical or pathologic condition that can increase the risk of hemorrhage recurrence.

Patients who experience delay of resolution according to the above criteria for greater than 3 weeks, recurrence of Grade 3 hemorrhage, or any CTCAE V3.0 Grade 4 hemorrhage will be taken off study treatment.

6.142 **Thrombosis:**(03/15/10)

Arterial Thrombosis

Patients will be taken off study treatment for \geq CTCAE Grade 3 arterial thrombotic events (including cerebrovascular ischemia, transient ischemic attack, cardiac ischemia/infarction, peripheral or visceral arterial ischemia) or CTCAE Grade 2 arterial thrombotic events new or worsened since beginning bevacizumab therapy.

Venous Thrombosis

All therapy (carboplatin, paclitaxel, and bevacizumab) will be held for CTCAE Grade 3 or asymptomatic CTCAE Grade 4 venous thrombosis. For patients on therapeutic anticoagulation, PT INR or PTT (whichever appropriate) should be monitored closely during bevacizumab therapy. If the planned duration of full-dose anticoagulation is \leq 3 weeks, treatment should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is $>$ 3 weeks, treatment may be resumed