450mg/45mL, or 600g/60mL of carboplatin.

4.22 Storage: Unopened vials of carboplatin are stable to the date indicated on the package when stored at 25°C (77°F). Excursions from 15 to 30°C (59 to 86°F) are permitted. Protect from light. Carboplatin multi dose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries.

4.23 Preparation: Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5mg/mL with 5% Dextrose in Water or 0.9% Sodium Chloride for Injection, USP. When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C / 77°F). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded 8 hours after dilution.

Calvert Formula for Carboplatin (AUC) Dosing

total dose (mg) = target AUC (in mg/mL/minute) * [GFR (in mL/minute) + 25]

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must NOT be used for the preparation or administration of carboplatin.

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

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

4.3 Bevacizumab (NSC #704865, IND #7921) 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.

4.31 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.

4.32 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) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. For "Placebo", each 0mg (0mg/mL – 4mL fill) glass vial

contains phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. **DO NOT USE COMMERCIAL BEVACIZUMAB OR AVASTIN.**

Bevacizumab being provided in this study is for investigational use only and is not the commercially marketed product. The commercially available bevacizumab is marketed under the name Avastin. Investigational bevacizumab and commercially available Avastin may be produced at separate facilities. Although investigational bevacizumab and Avastin are expected to be very similar it is possible that some differences may exist. For further details and molecule characterization, see the updated bevacizumab Investigator Brochure. **(1-16-06) (06/26/06)**

4.33 Storage and Stability: Bevacizumab is shipped on blue ice for next day delivery. On receipt, 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 lots have expired. The sterile single use vials contain no antibacterial preservatives; therefore, vials should be discarded eight hours after initial entry.

4.34 Preparation: Bevacizumab should be prepared by a healthcare professional using aseptic technique. Vials contain no preservative and are intended for single use only. The calculated dose of bevacizumab should be diluted with sodium chloride (0.9%) solution for injection, up to a total volume ranging from 100 ml to 250 ml such that the final concentration of bevacizumab ranges between 1.4 and 16.5 mg/ml (the constituted solution is stable in this concentration range). Once diluted in 0.9% Sodium Chloride for Injection, the bevacizumab solution must be administered within 8 hours. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. **(08/06/07)**

4.35 Administration: Bevacizumab 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.

4.36 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). **DO NOT USE COMMERCIAL BEVACIZUMAB OR AVASTIN. (08/06/07)**

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. The blinded, patient-specific vials will be sealed in a cardboard box with a tamper-evident seal.

For **Phase A (cycles 2 through 6)**, each box will be labeled with …

- the protocol number (i.e., "GOG-0218")
- the box number (i.e., "Box 1 of 2" and "Box 2 of 2")
- the number of vials (e.g., "48 vials")
- the patient ID number (e.g., "999-0218-001"; where "999" indicates the GOG – assigned institution code for the registering site, "0218" 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., "**Phase A** - bevacizumab 100 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

At the completion of chemotherapy cycle 6, ALL remaining PHASE A clinical supplies of bevacizumab / placebo should be returned to PMB (see "Drug Returns" below). DO NOT UTILIZE PHASE A DRUG SUPPLY FOR TREATMENT DURING PHASE B. (10/14/08)

For **Phase B (cycles 7 through 22)**, each box will be labeled with …

- the protocol number (i.e., "GOG-0218")
- the box number (i.e., "Box 1 of 2" and "Box 2 of 2")
- the number of vials (e.g., "48 vials")
- the patient ID number (e.g., "999-0218-001"; where "999" indicates the GOG – assigned institution code for the registering site, "0218" 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., "**Phase B** - bevacizumab 100 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., 2005 = 05, 2006 = 06) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a box labeled and shipped on January 1, 2005 would have a Julian date of '05001' and a box labeled and shipped on December 31, 2006 would have a Julian date of '06365'. 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.

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.

4.37 Drug Ordering: **(1-16-06)**

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 1572 form. **(08/06/07)**

4.371 Phase A

Phase A - Begins with cycle 2 and continues through cycle 6 [during chemotherapy]. By definition, Phase A of treatment ends at the beginning of cycle 7. **(08/06/07)**

No blinded starter supplies will be available for this phase. Blinded, patient-specific supplies **for Phase A** will be sent to the registering investigator at the time of randomization. This randomization will be performed by the GOG Statistical and Data Center (SDC) in Buffalo, NY. The assigned patient ID number must be recorded by the registering institution for proper vial dispersion. Once a patient has been registered with the GOG SDC, the GOG SDC will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the GOG SDC the day the patient is registered and will be processed by the PMB the next business day and shipped the following business day. 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. 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.

Request for Clinical Supplies for Phase A – *Submitted by the GOG SDC*

The web registration process for Phase A described in Section 5.11 will allow the GOG SDC to automatically submit an electronic request for the blinded, patient-specific clinical supplies of bevacizumab / placebo for Phase A of GOG-0218 to the PMB at the time of the initial registration / randomization. The Phase A clinical supplies should arrive at the clinical

site within approximately seven to ten days of randomization. This shipment will provide the entire patient-specific amount needed for each patient to complete cycles 2 through 6 of Phase A based on the order submitted to the PMB by the GOG SDC for Phase A. All drug orders will be shipped directly to the physician registering the patient.

4.372 Phase B

Phase B - Begins with cycle 7 [first cycle post chemotherapy] and continues through cycle 22 [approximately **(06/26/06)** 15 months total treatment duration]

In order to obtain Phase B clinical supplies, **patients must be re-registered** with the GOG SDC (see section 5.12) after completing the administration of all drugs on day 1 of cycle 6 of treatment which signals the completion of chemotherapy (cycle 6) for logistical purposes. **No blinded starter supplies will be available for this phase.** Blinded, patient-specific supplies **for Phase B** will be sent to the registering investigator at the time of re-registration. This re-registration will be performed by the GOG SDC.. **The patient ID number will NOT change.** Once a patient has been re-registered with the GOG SDC, the GOG SDC will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the GOG SDC the day the patient is re-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 re-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. 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.

Initial Request for Clinical Supplies for Phase B - *Submitted by the GOG SDC*

The web re-registration process for Phase B described in Section 5.12 will allow the GOG SDC to automatically submit an electronic request for blinded patient-specific clinical supplies of bevacizumab / placebo for Phase B to the PMB at the time of the completion of chemotherapy / re-registration. The Phase B clinical supplies should arrive at the clinical site within approximately seven to ten days of re-registration. The initial request for Phase B will provide a patient-specific amount needed for each patient to complete cycles 7 through 10 of Phase B based on the initial request submitted to the PMB by the GOG SDC for Phase B. All drug orders will be shipped directly to the physician re-registering the patient.

Institutions enrolling patients through CTSU, refer to Appendix VIII for special instructions for Phase B completion of chemotherapy / re-registration.

Re-Order Request for Clinical Supplies for Phase B - *Submitted by the Institution*

The institution will need to re-order clinical supplies three times to complete Phase B. Complete an NCI Clinical Drug Request form and fax 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 assigned patient ID number (e.g., "999-0218-001"), the patient initials (e.g., "FML"), the number of vials remaining from the prior shipment, and the patient's weight (in KG) should be entered on each order. Each re-order request submitted to the PMB by the institution for clinical supplies for Phase B will provide a patient-specific amount needed for each patient to complete four cycles of Phase B.

- The first re-order request submitted by the institution to PMB immediately after completion of cycle 10 will provide a patient-specific amount needed for each patient to complete cycles 11 through 14 of Phase B.
- The second re-order request submitted by the institution to PMB immediately after the completion of cycle 14 will provide a patient-specific amount needed for each patient to complete cycles 15 through 18 of Phase B.
- The third re-order request submitted by the institution to PMB immediately after the completion of cycle 18 will provide a patient-specific amount needed for each patient to complete cycles 19 through 22 of Phase B.

GOG-0218 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 / shipments sent by Federal Express**

4.38 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 principal investigator at a given clinical site changes) must be approved

in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 301-402-0429) 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., "999-0218-001") 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-0218**").

4.39 Drug Returns: Only unreconstituted drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed **Phase A** vials remaining when a patient completes cycle 6, sealed **Phase A or Phase B** 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., "999-0218-001") and the patient initials (e.g., "FML") should be entered in the "Lot Number" field. A separate line item is required for EACH patient ID number returned.

4.310 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., "999-0218-001") on this protocol.

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

The GOG Statistical and Data Center will require the protocol number (i.e., "GOG-0218"), the patient ID number (e.g., "999-0218-001"), and the patient initials (e.g., "FML") to unblind the patient.

4.312 Comprehensive Adverse Events and Potential Risks List (CAEPR) For Bevacizumab (NSC #704865) **(1-16-06) (06/26/06) (10/14/08)**

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This

subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/reporting/adeers.html for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for bevacizumab.

Category (Body System)	Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)	'Agent Specific Adverse Event List' (ASAEL)
ALLERGY/IMMUNOLOGY		
	Allergic reaction/hypersensitivity (including drug fever)	***Allergic reaction/hypersensitivity (including drug fever)***
	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	***Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)***
BLOOD/BONE MARROW		
	Hemoglobin	***Hemoglobin***
	Leukocytes (total WBC)	***Leukocytes (total WBC)***
	Neutrophils/granulocytes (ANC/AGC)	***Neutrophils/granulocytes (ANC/AGC)***
CARDIAC ARRHYTHMIA		
	Supraventricular arrhythmia NOS	***Supraventricular arrhythmia NOS***
	Ventricular fibrillation	
CARDIAC GENERAL		
	Cardiac ischemia/infarction	***Cardiac ischemia/infarction***
	Cardiac troponin I (cTnI)	
	Hypertension	***Hypertension***
	Hypotension	
	Left ventricular diastolic dysfunction	
	Left ventricular systolic dysfunction	
CONSTITUTIONAL SYMPTOMS		
	Fatigue (asthenia, lethargy, malaise)	***Fatigue (asthenia, lethargy, malaise)***
	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	***Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)***
	Rigors/chills	***Rigors/chills***
	Weight loss	
DERMATOLOGY/SKIN		
	Pruritus/itching	***Pruritus/itching***
	Rash/desquamation	***Rash/desquamation***
	Ulceration	
	Urticaria (hives, welts, wheals)	***Urticaria (hives, welts, wheals)***
	Wound complication, non-infectious	
GASTROINTESTINAL		
	Anorexia	***Anorexia***
	Colitis	
	Constipation	***Constipation***
	Diarrhea	***Diarrhea***
	Fistula, GI - Select	
	Heartburn/dyspepsia	***Heartburn/dyspepsia***
	Ileus (functional obstruction of bowel, i.e., neuroconstipation)	
	Leak (including anastomotic), GI: large bowel	
	Mucositis/stomatitis (functional/symptomatic) - Select	***Mucositis/stomatitis (functional/symptomatic) - Select***
	Nausea	***Nausea***
	Perforation, GI - Select	
	Ulcer, GI - Select	
	Vomiting	***Vomiting***
HEMORRHAGE/BLEEDING		
	Hemorrhage, GI - Select	***Hemorrhage GI - Select***
	Hemorrhage, CNS	***Hemorrhage, CNS***
	Hemorrhage, GU: vagina	***Hemorrhage, GU: vagina***
	Hemorrhage, pulmonary/upper respiratory: lung	***Hemorrhage, pulmonary/upper respiratory: lung***
	Hemorrhage, pulmonary/upper respiratory: nose	***Hemorrhage, pulmonary/upper respiratory: nose***
INFECTION		
	Infection with normal ANC or Grade 1 or 2 neutrophils - Select	

Category (Body System)	Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)	'Agent Specific Adverse Event List' (ASAEL)
	Infection with normal ANC or Grade 1 or 2 neutrophils - Select (pelvis, peritoneal cavity, rectum, scrotum, skin, wound)	
METABOLIC/LABORATORY		
	Alkaline phosphatase	***Alkaline phosphatase***
	ALT, SGPT (serum glutamic pyruvic transaminase)	***ALT, SGPT (serum glutamic pyruvic transaminase)***
	AST, SGOT (serum glutamic oxaloacetic transaminase)	***AST, SGOT (serum glutamic oxaloacetic transaminase)***
	Bilirubin (hyperbilirubinemia)	***Bilirubin (hyperbilirubinemia)***
	Creatinine	
	Proteinuria	***Proteinuria***
NEUROLOGY		
	CNS cerebrovascular ischemia	***CNS cerebrovascular ischemia***
	Dizziness	***Dizziness***
	Neurology - Other: (Leukoencephalopathy syndrome including reversible posterior leukoencephalopathy syndrome [RPLS])	
PAIN		
	Pain - abdomen NOS	***Pain - abdomen NOS***
	Pain - chest/thorax NOS	***Pain - chest/thorax NOS***
	Pain - head/headache	***Pain - head/headache***
	Pain - joint	***Pain - joint***
	Pain - muscle	
	Pain - NOS	
PULMONARY/UPPER RESPIRATORY		
	Bronchospasm, wheezing	
	Cough	***Cough***
	Dyspnea (shortness of breath)	***Dyspnea (shortness of breath)***
	Fistula, pulmonary/upper respiratory - Select	
	Nasal cavity/paranasal sinus reactions	***Nasal cavity/paranasal sinus reactions***
	Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	***Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)***
	Pulmonary/Upper Respiratory - Other (nasal-septal perforation)	
RENAL/GENITOURINARY		
	Fistula, GU - Select	
	Renal failure	
SYNDROMES		
	Cytokine release syndrome/acute infusion reaction	***Cytokine release syndrome/acute infusion reaction***
VASCULAR		
	Thrombosis/thrombus/embolism	***Thrombosis/thrombus/embolism***
	Visceral arterial ischemia (non-myocardial)	

[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 ADEERSMD@tech-res.com. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Additional selected AEs reported on bevacizumab trials but with the relationship to bevacizumab still undetermined:

Blood/Bone Marrow – hemoglobin; idiopathic thrombocytopenia purpura; platelets
Cardiac general – cardiac arrest; pericardial effusion
Coagulation – DIC
Death – sudden death (cause unknown)
Dermatology/Skin – hypopigmentation
Gastrointestinal – small bowel obstruction; rectal abscess/necrosis; taste alteration
Metabolic/Laboratory –hyperglycemia; hypoglycemia; hypomagnesemia; hyponatremia
Musculoskeletal/Soft Tissue – aseptic necrotic bone; gait/walking; myasthenia gravis
Neurological – aseptic meningitis; confusion; encephalopathy; peripheral neuropathy; seizure; syncope
Ocular/Visual – cataract; watery eye
Pulmonary/Upper Respiratory – ARDS; pneumonitis/pulmonary infiltrates; pneumothorax
Renal/Genitourinary – urinary frequency
(for a more complete listing of reported AEs, please refer to the Investigator's Brochure)

Notes: Bevacizumab 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.

4.3121 General Information on Adverse Effects of Bevacizumab

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/2004/125085lbl.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.[108] **(03/16/09)** 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.[109] **(03/16/09)** In patients $\geq$ 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 comorbid GI conditions such as diverticulitis and gastric ulcer. Fistulae (e.g. tracheo-esophageal, recto-vaginal) have also been observed. A review of published data from phase II trials of bevacizumab and historical cohort studies of open-label use of bevacizumab as a single agent and in combination with cytotoxic drugs specifically for treatment of epithelial ovarian and primary peritoneal cancer revealed an overall incidence rate of 5.2% in 308 patients, about double the rate seen in other solid tumor populations.[110] **(03/16/09)** While not all of these GI perforations and fistulae required open surgical management and most patients recovered, prospective pre-clinical and clinical work

is needed to identify mechanisms and risk factors (10/14/08) **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 ILF/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 $\pm$ 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 .

Neutropenia and Infection: An increased incidence of neutropenia has been reported in patients receiving bevacizumab and chemotherapy compared to chemotherapy alone. In AVF2107g, the incidence of NCI-CTC Grade 3 or 4 neutropenia was increased in patients with mCRC receiving IFL+ bevacizumab (21%) compared to patients receiving IFL alone (14%). In E4599, the incidence of NCI-CTC Grade 4 neutropenia was increased in patients with NSCLC receiving paclitaxel-carboplatin (PC) plus bevacizumab (26.2%) compared with patients receiving PC alone (17.2%). Febrile neutropenia was also increased (5.4% for PC plus bevacizumab vs. 1.8% for PC alone). There were 19 (4.5%) infections with NCI-CTC Grade 3 or 4 neutropenia in the PC plus bevacizumab arm of which 3 were fatal compared to 9 (2%) neutropenic infections in patients receiving PC alone, of which none were fatal. During the first 6 cycles of treatment the incidence of serious infections including pneumonia, febrile neutropenia, catheter infections and wound infections was increased in the PC plus bevacizumab arm [58 patients (13.6%)] compared to the PC alone arm [29 patients (6.6%)].**(08/06/07)**

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 Quality of Life Measures

The FACT-O TOI has been selected as the multidimensional, combined generic and disease-specific QOL questionnaire for use with ovarian cancer patients. The questionnaire is a 26-item self-report measure developed specifically for cancer patients and designed to be used in a variety of settings, including clinical trials.

FACT-O TOI displays the QOL measures in the following order, recognizing the need for ease of administration and scoring: (1) FACT-G, (2) Additional Concerns: Ovarian component, (3) Additional items: stomach pain (from Protocol GOG-0172).

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 Two Phase Registration / Randomization **(1-16-06)**

5.11 Phase A - Initial Registration / Randomization

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

5.111 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.

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

5.113 The Fast Fact Sheet data must be gathered.

5.114 The institution must register the patient to Phase A of the protocol using the web-based registration application or by phone if necessary (800-523-2917) and obtain a GOG patient study ID. 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 GOG Statistical and Data Center (SDC) by phone if necessary (800-523-2917).

5.115 The institution will enter the patient's initials (e.g. FML), GOG patient study ID number, and under "assigned regimen," the term "Phase A" in the appropriate place in their Log Book to verify the patient's entry into Phase A.

This is a randomized, double-blind trial. The web registration process for Phase A will allow the GOG SDC to automatically load the Drug Order / Re-order Application (DORA) for the patient and submit an electronic request for the blinded, patient-specific clinical supplies of bevacizumab / placebo for Phase A to the Pharmaceutical Management Branch (PMB), CTEP at the NCI at the time of the initial registration / randomization. Phase A supplies should arrive at the clinical site within approximately seven to ten days of randomization (see Section

4.3).

For institutions enrolling patients through CTSU, refer to Appendix VIII for special instructions for Phase A initial registration / randomization.

5.12 Phase B - Completion of Chemotherapy / Re-registration

After completing the administration of all drugs on day 1 of cycle 6 of treatment, utilize the SDC Electronic Data Entry System (SEDES) by going to the GOG Web Menu page, selecting "SEDES", selecting "DORA02" in the patient forms schedule, and then completing the Drug Order / Re-order Application (DORA).

This is a randomized, double-blind trial. This web re-registration process for Phase B will allow the GOG SDC to automatically submit an electronic request for the blinded patient-specific clinical supplies of bevacizumab / placebo for Phase B to the PMB at the time of the completion of chemotherapy / re-registration. Phase B supplies for cycles 7 through 10 should arrive at the clinical site within approximately seven to ten days of re-registration. The institution will need to re-order clinical supplies three times to complete Phase B. (see Section 4.372)

For institutions enrolling patients through CTSU, refer to Appendix VIII for special instructions for Phase B completion of chemotherapy / re-registration.

5.2 Procedures for International Collaborators

If this study is activated for international collaboration, an appropriate Appendix will be included to specify procedures that will be employed for patient registration and randomization.

5.3 Treatment Plan

5.31 Therapeutic Program

Patients will be randomized to one of three treatment regimens in equal proportions:

Arm	Phase A Regimen*	Schedule		Phase B Regimen*	Schedule
I	**Chemotherapy****	q 21 days x 6 cycles	Then	**Placebo*****	q 21 days - cycles 7 through 22 **(06/26/06)**
	Placebo***	q 21 days x 5 cycles beginning with cycle 2 of Chemotherapy			
II	**Chemotherapy****	q 21 days x 6 cycles	Then	**Placebo*****	q 21 days - cycles 7 through 22 **(06/26/06)**
	Bevacizumab***	q 21 days x 5 cycles beginning with cycle 2 of Chemotherapy			
III	**Chemotherapy****	q 21 days x 6 cycles	Then	**Bevacizumab*****	q 21 days - cycles 7 through 22 **(06/26/06)**
	Bevacizumab***	q 21 days x 5 cycles beginning with cycle 2 of Chemotherapy			

NOTE: Cycle 1 treatment should be administered within 14 days after randomization. (10/14/08)
NOTE: Cycle = 21 days, including cycle 6 (08/06/07)
NOTE: Phase A ends at the beginning of cycle 7 (first cycle of Phase B) (08/06/07)
NOTE: In the absence of disease progression as defined in section 8.0 or limiting toxicity as defined in section 6.0, protocol directed therapy on Phase A and Phase B should proceed on schedule. This includes patients with evidence of persistent disease entering Phase B but who have not met the definition of disease progression as defined in section 8.0. (08/06/07)
NOTE: Patient re-registration required to move from "Phase A" to "Phase B" (see Section 5.1).
* All treatment doses on day 1 +/- 24 hours
** Paclitaxel 175 mg/m^2 IV over 3 hours followed by Carboplatin AUC 6 IV over 30 minutes (Note : docetaxel 75mg/m^2 IV over 1 hour may be substituted for paclitaxel **only under special circumstances** [see sections 2.65, 5.322, and 6.51].) Doses of paclitaxel or carboplatin may be rounded to the nearest 5 mg, while doses of docetaxel should be rounded to the nearest 1 mg. After initial treatment, doses of paclitaxel and docetaxel should be re-calculated based only on body weight change of ≥ 10%.**(08/06/07)(10/14/08)**
*** Bevacizumab / Placebo 15mg/kg IV. Doses of bevacizumab/placebo may be rounded to the nearest 5 mg. After initial treatment, doses of bevacizumab/placebo should be re-calculated based on any body weight change ≥ 10%.**(08/06/07)**

This is a randomized, double-blind trial. Blinded, phase and patient-specific clinical supplies of bevacizumab / placebo will be requested from the Pharmaceutical Management Branch, CTEP, NCI by the GOG Statistical and Data Center at the time of the initial registration / randomization (**Phase A**) AND at the time of the completion of chemotherapy / re-registration (**Phase B**) and should arrive at the clinical site within approximately seven to ten days (see Section 4.3).

5.32 Methods of Chemotherapy and Study Drug (Bevacizumab / Placebo) Administration

5.321 Biometric considerations in dose calculation

5.3211 Maximum body surface area used for Paclitaxel and Docetaxel dose calculations will be 2.0 m^2 as per GOG Chemotherapy Procedure Manual

5.3212 Bevacizumab / Placebo will be dosed at 15 **mg/kg**, with no maximum to total mg.

5.322 Sequence and timing of drug administration: (10/14/08)

- Paclitaxel will be infused over 3 hours. Due to the risk of immediate hypersensitivity reaction, paclitaxel should always be the first drug to be infused during any combination. (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/m^2 see Section 6.51. and Section 6.62)
  Carboplatin will be administered as a 30 minute infusion, following paclitaxel (or docetaxel) administration.

- Bevacizumab/placebo administration will be as a continuous intravenous infusion following carboplatin infusion. **DO NOT USE COMMERCIAL BEVACIZUMAB OR AVASTIN.**. Drug administration orders by the investigator should include patient name, patient GOG ID number, phase number (A or B) and cycle number. **PRIOR TO EACH INFUSION, VERIFY STUDY DRUG SUPPLY IS SPECIFIC FOR PROTOCOL NUMBER GOG-218, PATIENT ID NUMBER AND PHASE (A OR B)** Anaphylaxis precautions should be observed during bevacizumab/placebo administration (Appendix V). **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS**. The initial dose should be delivered over 90 minutes as an IV infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

5.323 Pre-Medication:

5.3231 Paclitaxel

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 to these drugs.

This regimen should include a standard dose of dexamethasone