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 $\geq$ 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 $\geq$ 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

(either IV or PO), an anti-histamine H1 (diphenhydramine 25-50 mg IVP or orally, or an equivalent dose of an alternate H_1 blocker such as loratadine or fexofenadine), and a standard dose of anti-histamine H2 IVP (such as cimetidine, ranitidine, or famotidine).

In the event of a prior bevacizumab/placebo hypersensitivity reaction, the prophylactic regimen should be modified as suggested in 5.3232 below.

5.3232 Suggested Prophylaxis in Event of Prior Bevacizumab/ Placebo Infusion Reaction

In the event of a prior bevacizumab / placebo hypersensitivity reaction, subsequent infusions should be delivered over 90 minutes, and **(08/06/07)** the following prophylactic regimen is recommended upon re-exposure:

- H_1 blocker (diphenhydramine 25-50 mg IVP or orally one hour prior to injection; or an equivalent dose of an alternate H_1 blocker such as loratadine 10 mg or fexofenadine 60 mg).
- H_2 blocker (famotidine 20 mg IVP or orally one hour prior to injection; or an equivalent dose of an alternate H_2 blocker).
- Dexamethasone (10 mg administered PO 12 and 6 hours prior to bevacizumab injection).

5.3233 Docetaxel

For all courses 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 5.322, Section 6.51 and Section 6.62), **(06/26/06)** 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 H_1 blocker such as loratadine or fexofenadine) one hour prior to docetaxel.

In the event of a prior bevacizumab/placebo hypersensitivity reaction, the prophylactic regimen should be modified as suggested above in section 5.3232.

5.324 Antiemetic Regimens

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 10 mcg/kg IV (or 2 mg PO) 30 minutes prior to chemotherapy, with or without lorazepam 0.5-2.0 mg IV 30 minutes prior to chemotherapy.

5.325 Dosing of Carboplatin

The carboplatin dose will be calculated to reach a target area under the curve (AUC) of concentration x time according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Jelliffe formula.

The initial dose of carboplatin must be calculated using GFR. In the absence of new renal obstruction or other renal toxicity greater than or equal to CTC Grade 2 (serum creatinine >1.5 x ULN), the dose of carboplatin will not be recalculated for subsequent cycles, but will be subject to dose modification as noted.

In patients with an abnormally low serum creatinine (less than or equal to 0.6 mg/dl), due to reduced protein intake and/or low muscle mass, the creatinine clearance should be estimated using a minimum value of 0.6 mg/dl. If a more appropriate (higher) baseline creatinine value is available within 4 weeks of treatment, that value may also be used for the initial estimation of GFR. **(08/06/07)**

CALVERT FORMULA:

Carboplatin dose (mg) = target AUC x (GFR + 25)

For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance. The creatinine clearance is calculated by the method of Jelliffe using the following formula:

$$Ccr = 0.9 \times \frac{\{98 - [0.8\ (age - 20)]\}}{Scr}$$

Where: Ccr = creatinine clearance in ml/min
Age = patient's age in years (from 20-80)
Scr = serum creatinine in mg/dl

5.326 Dosing of bevacizumab/placebo

Bevacizumab will be administered at 15 mg/kg IV. Patient weight at screening will be used to determine the bevacizumab dose to be used for the duration of the study. If a patient's weight changes by ≥ 10% during

the course of the study, then the bevacizumab dose will be recalculated.

5.327 Supportive Care Guidelines for bevacizumab/placebo:

If an infusion-related adverse reaction occurs, the patient should be pre-medicated (if not already scheduled as described in Section 5.3232) for the next course; however, the infusion time for bevacizumab (or placebo) may not be decreased for the next infusion. If the next infusion is well tolerated with pre-medication, the infusion time for the next dose may then be decreased by 30 ± 10 minutes as long as the patient continues to be pre-medicated. If a patient experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90 ± 15 minutes. Similarly, if a patient experiences an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60 ± 10 minutes.

5.33 Prohibited Concomitant Therapeutic Modalities

Prior to documented disease progression, the following therapeutic modalities are prohibited:

5.331 Reassessment or cytoreductive surgery

5.332 Anti-neoplastic therapy not otherwise specified in the current protocol, including cytotoxic, biologic, hormonal, or radiation therapy, regardless of indication (treatment of measurable disease or consolidation therapy).

5.4 Quality of Life Assessment Intervals

When determining the specific assessment times, the investigator must balance treatment toxicities, the natural history of the disease, and time since initiating therapy along with an acute awareness of the study objectives. The investigators for the proposed study recommend seven assessment points to include:

5.41 Baseline, defined as prior to cycle 1 (t = 0 weeks). This assessment allows a pre-treatment baseline against which to compare later results.

5.42 Prior to cycle 4 (t = 9 weeks, after three doses of chemotherapy and two doses bevacizumab/placebo), defined as second comparison point in which to compare short-term effects. Ideally, this assessment should be obtained *shortly before the administration of cycle 4*, but could occur up to one week prior to cycle 4. This third cycle comparison is justifiable given the anticipated continued early impact of anti-angiogenesis therapy on QoL, especially abdominal symptoms. Since this is also the first assessment of response, this will allow a correlation of QoL with response in this setting.

5.43 Prior to cycle 7 (t = 18 weeks, after six doses of chemotherapy and five doses bevacizumab/placebo), defined as final comparison point in which to compare short-term effects. Ideally, this assessment should be obtained *shortly before the*

administration of cycle 7, but could occur up to one week prior to cycle 7. This comparison is justifiable given the anticipated continued early impact of anti-angiogenesis therapy on QoL especially abdominal symptoms.

5.44 Prior to cycle 13 (t = 36 weeks, six months after completing cytotoxic chemotherapy), defined as the first assessment six months after the completion of carboplatin and paclitaxel. It is important to note that patients should continue to receive QOL assessments even if they stop the clinical trial early or are on other treatment regimens.

5.45 Prior to cycle 22 (t = 60 weeks), at the cessation of bevacizumab/placebo, approximately 15 months from initiation of all systemic therapy. It is important to note that patients should continue to receive QOL assessments even if they stop the clinical trial early or are on other treatment regimens. **(06/26/06) (10/14/08)**

5.46 Six months after cessation of bevacizumab/placebo (t = 84 weeks). This final QoL assessment will allow evaluation of the long term affects of therapy. It is important to note that patients should continue to receive QOL assessments even if they stop the clinical trial early or are on other treatment regimens.

6.0 TREATMENT MODIFICATIONS

In order to maintain dose-intensity and cumulative dose-delivery on this study, reasonable efforts will be made to minimize dose reduction and treatment delays as specified. Any patient whose treatment is delayed must be evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met. No dose escalation is planned for this study.

6.1 Individual Dose Modification Levels

All modifications are relative to the actual starting doses for the specific Regimen. For application of individual dose modifications, see specific guidelines below. Allowable drug dose levels and instructions are summarized in Tables A, B, C, and D.

- General Guidelines for Hematologic Toxicity (Section 6.2)
- Hematologic Nadirs, Table A (Section 6.3)
- Dose Levels for Docetaxel, Table B (Section 6.3)
- Delayed Hematologic Recovery, Table C (Section 6.4)
- Non-Hematologic Toxicity Table D (Section 6.5)

6.2 General Guidelines for Hematologic Toxicity

6.21 Initial treatment modifications will consist of cycle delay and/or dose reduction as directed.

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

6.23 Lower Limits for ANC and Platelet Count **(08/06/07)**

6.23.1 Phase A, With Cytotoxic Chemotherapy - Subsequent courses of treatment in Phase A which contains any cytotoxic chemotherapy (carboplatin, paclitaxel, docetaxel) will not begin until the ANC is ≥ 1,500 cells/mm^3 (CTCAE Grade 1) and the platelet count is ≥ **100,000**/mm^3. Such treatment during Phase A (including bevacizumab / placebo) will be delayed for a maximum of three weeks until these values are achieved. Patients who fail to recover adequate counts within a three-week delay will no longer receive protocol-directed cytotoxic chemotherapy, but **will** resume bevacizumab / placebo alone or non-protocol directed cytotoxic chemotherapy as described in Section 6.7 through completion of cycle 6 (Phase A) **and** after re-registration (Section 5.12), through completion of Phase B. **(10/14/08)**

- Exceptions:

  Patients who received G-CSF prior to the current cycle may begin with ANC ≥ 1000 cells/mm^3, if clinically appropriate, to allow for transient reductions in ANC after discontinuation of G-CSF.

  Patients who are delayed more than 7 days may begin with ANC ≥ 1000

cells/mm^3, if clinically appropriate; as they will receive G-CSF with subsequent therapy (see Section 6.241).

6.23.2 Phase A If Cytotoxic Chemotherapy Discontinued, or Phase B - Subsequent cycles of therapy with bevacizumab/placebo alone either during Phase A if cytotoxic chemotherapy has been discontinued or during Phase B will not begin until the ANC is ≥ 1,000 cells/mm^3 (CTCAE Grade 1) and the platelet count is ≥ **75,000**/mm^3. Treatment with bevacizumab/placebo will be delayed for a maximum of three weeks until these values are achieved. Patients who fail to recover adequate counts within a three-week delay will no longer receive any protocol-directed therapy. **(08/06/07)**

6.23.3 In cases where protocol directed cytotoxic (platinum/taxane) therapy has been discontinued during Phase A for reasons other than cancer progression, please see section 6.7 for guidelines. **(08/06/07)**

6.24 Use of Hematopoietic Cytokines and Protective Agents

The use of hematopoietic cytokines and protective reagents are restricted as noted:

6.241 In general, patients will NOT receive prophylactic filgrastim (G-CSF), PEG-filgrastim (Neulasta), or sargramostim (GM-CSF) unless they experience treatment delays or recurrent neutropenic complications after treatment modifications as specified. In particular, hematopoietic growth factors should not be used to avoid initial chemotherapy dose modifications as stipulated in the protocol. However, patients may also receive growth factors for management of neutropenic complications in accordance with clinical treatment guidelines. If required, it is recommended that growth factors be initiated the day after the last dose of chemotherapy and typically continuing for a minimum of 10 days or until the ANC is sustained above >1000/mm^3. Growth factors should be discontinued if the ANC exceeds 10,000/ mm^3 and should not be used within 72 hours of a subsequent dose of chemotherapy.

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

6.243 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) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival, and that these agents are administered only to avoid red blood cell transfusions. They

do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted.
http://www.fda.gov/Medwatch/safety/2007/safety07.htm **(08/06/07)**

6.244 Patients may NOT receive amifostine or other protective reagents, unless indicated in the study design.

6.25 Dose Modifications for Bevacizumab

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

6.26 Dose Modifications for Paclitaxel and Docetaxel **(08/06/07)**

There will be no dose modifications for paclitaxel based on hematologic toxicity. Dose modifications for docetaxel (if substituted for paclitaxel according to protocol guidelines) for hematologic toxicity should be made according to parameters below in Table A, Table B and Table C.

6.3 Modifications for Hematologic Toxicity (Nadirs)

6.31 Initial occurrence of dose-limiting neutropenia (defined in 6.32) or dose limiting thrombocytopenia (defined in 6.33) will be handled according to Table A, using the regimen modifications in Table B. **(06/26/06)**

6.32 Dose-Limiting Neutropenia (DLT-ANC) is defined by the occurrence of febrile neutropenia or prolonged Grade 4 neutropenia persisting ≥ 7 days. There will be no modifications for uncomplicated Grade 4 neutropenia lasting less than 7 days. Febrile neutropenia is defined within the CTCAE as fever **with or without** clinically or microbiologically documented infection with ANC less than 1,000 /mm^3 and fever greater than or equal to 38.5°C.

6.33 Dose-limiting thrombocytopenia (DLT-PLT) is defined by any occurrence of Grade 4 thrombocytopenia (<25,000/mm^3) or bleeding associated with Grade 3 thrombocytopenia (25,000 to <50,000/mm^3). There will be no modifications for uncomplicated Grade 3 thrombocytopenia.

Table A:		Modification Instructions for Dose-Limiting Hematologic Toxicity (In conjunction with Table B when docetaxel substituted for paclitaxel)		
DLT ANC	**DLT PLT**	**First Occurrence**	**Second Occurrence**	**Third Occurrence**
Yes	**No**	Reduce carboplatin one AUC unit (and docetaxel one dose level*)	Add G-GSF and maintain all current drug doses	Discontinue Protocol-Directed Cytotoxic Therapy**
Yes	**Yes**	Reduce carboplatin one AUC unit (and docetaxel one dose level*)	Add G-GSF and decrease carboplatin one AUC unit (and docetaxel one dose level*)	Discontinue Protocol-Directed Cytotoxic Therapy**
No	**Yes**	Reduce carboplatin one AUC unit (and docetaxel one dose level*)	Decrease carboplatin one AUC unit (and docetaxel one dose level*)	Discontinue Protocol-Directed Cytotoxic Therapy**

* See Table B below, for patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Section 6.51.
Applies to platinum/taxane therapy, not to bevacizumab/placebo. Please see section 6.231 for specific guidelines on maintaining bevacizumab/placebo under these circumstances. See also section 6.7 for general guidelines on non-protocol-directed cytotoxic therapy. **(08/06/07)

Table B: Dose Levels for Docetaxel*		
Starting Dose Level	**Dose Level -1**	**Dose Level -2**
75 mg/m^2	65 mg/m^2	55 mg/m^2

* For patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Section 6.51.

6.4 Modifications for Delayed Hematologic Recovery:

6.41 Delay on the basis of neutropenia (Delay-ANC) is defined if the ANC is less than 1,500 cells/mm^3 (CTCAE Grade 2 or worse) within 24 hours prior to scheduled therapy, or less than 1,000 cells/ mm^3, if the patient received G-CSF during the previous cycle.

6.42 Delay on the basis of thrombocytopenia (Delay-PLT) is defined if the platelet count is less than **100,000**/ mm^3 within 24 hours prior to scheduled therapy.

6.43 Modifications noted below are only required for management of delays in the absence of dose reductions stipulated by nadir DLT-ANC and/or DLT-PLT (as noted above). In other words, if the patient experiences DLT-ANC and Delay-ANC, make the modifications as indicated for the nadir counts without additional modifications based on delayed recovery.

Table C. Modifications for Delayed Hematologic Recovery		
Category	**Delay (days)**	**Modification**
Delay-ANC	**1-7**	No Change
	8-21	Add G-CSF with Next Cycle
	>21	Discontinue Protocol-Directed Cytotoxic Therapy**
Delay-PLT	**1-7**	No Change
	8-21	Decrease carboplatin one AUC unit (and docetaxel one dose level*)
	>21	Discontinue Protocol-Directed Cytotoxic Therapy**

* For patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Section 6.51.

Applies to platinum/taxane therapy, not to bevacizumab/placebo. Please see section 6.231 for specific guidelines on maintaining bevacizumab/placebo under these circumstances. See also section 6.7 for general guidelines on non-protocol-directed cytotoxic therapy. **(08/06/07)

6.5 Adjustments for Non-Hematologic Toxicity

Table D: Modifications for Non-Hematologic Toxicity			
Drug	**Regimen -2 Level**	**Regimen -1 Level**	**Regimen Starting Dose**
Paclitaxel	110 mg/m^2	135 mg/m^2	175 mg/m^2
Carboplatin	4.0	5.0	6.0
Bevacizumab/placebo	Not Applicable	Not Applicable	Not Applicable
Docetaxel	55 mg/m^2	65 mg/m^2	75 mg/m^2

Table D should be used for dose level modifications for non-hematologic toxicity only as indicated specifically in the sections below. **(08/06/07)**

6.51 Grade 2 (or greater) peripheral neuropathy requires reduction of one dose level in paclitaxel and delay in all subsequent protocol-directed therapy for a maximum of three weeks until recovered to Grade 1. If peripheral neuropathy fails to recover to Grade 1 by a maximum delay of three weeks from time therapy is due, then paclitaxel should be withheld from all subsequent chemotherapy cycles and docetaxel at the starting dose level of 75 mg/m^2 substituted for paclitaxel unless medically contraindicated, according to Section 5.322. **(08/06/07)(10/14/08)**

In such cases where docetaxel has been substituted for paclitaxel, if CTCAE Grade 3 or 4 peripheral neuropathy occurs during or after the first cycle of docetaxel substitution then subsequent doses of docetaxel will be delayed for a maximum of three weeks until recovered to CTCAE Grade ≤ 2. If peripheral neuropathy fails to recover to Grade ≤ 2 by a maximum delay of three weeks from time therapy is due, then all docetaxel should be withheld from all subsequent chemotherapy cycles.

6.52 Hypertension. Patients receiving bevacizumab /placebo should be monitored prior to each dose with measurement of blood pressure (see Section 7.0 Study Parameters). Medication classes used for management of patients with Grade 3 hypertension receiving bevacizumab/placebo included angiotensin-converting enzyme inhibitors, beta blockers, diuretics, and calcium channel blockers. The use of anxiolytics in conjunction with specific anti-hypertensive agents is not prohibited. **(08/06/07)** The goal for blood pressure control should be consistent with general medical practice guidelines (i.e. < 140/90 mmHg in general and < 130/80 mmHg for patients with diabetes).

For controlled hypertension, defined as systolic ≤ 150 mm Hg and diastolic ≤ 90 mm Hg, continue bevacizumab/placebo therapy.

6.521 For uncontrolled hypertension (systolic > 150 mm Hg or diastolic > 90) or symptomatic hypertension less than CTCAE Grade 4, hold bevacizumab/placebo treatment (and cytotoxic chemotherapy in Phase A for up to 1 week if indicated, see below) **(08/06/07)**, with anti-hypertensive therapy initiated or continued, as in 6.52.

- During the period of combination chemotherapy with bevacizumab/placebo, if hypertension is controlled and symptomatic hypertension has resolved by one week after holding treatment, continue all therapy.

- During the period of combination chemotherapy with bevacizumab/placebo, if hypertension remains uncontrolled or symptomatic hypertension, less than CTCAE Grade 4, persists one week after holding treatment, the next treatment cycle should contain paclitaxel and Carboplatin only, if applicable, as otherwise indicated in the protocol, with bevacizumab/placebo **omitted**.

- During the period after completion of chemotherapy, if uncontrolled or symptomatic hypertension has not resolved by three weeks after holding treatment with bevacizumab/placebo, treatment with bevacizumab/placebo should be discontinued for the remainder of the study.

- Bevacizumab/placebo should be discontinued for the remainder of the study in any patient developing CTCAE Grade 4 hypertension.

6.53 Proteinuria. Patients receiving bevacizumab/placebo should be monitored by urine analysis for urine protein: creatinine (UPC) ratio prior to every other dose of bevacizumab / placebo:

UPC ratio < 3.5	Continue bevacizumab / placebo.
UPC ratio ≥ 3.5	Hold bevacizumab / placebo until UPC ratio recovers to < 3.5. If therapy is held for > 2 months due to proteinuria, discontinue bevacizumab / placebo.

Grade 4 or nephrotic syndrome	Discontinue bevacizumab / placebo.

6.54 Hemorrhage. Bevacizumab/placebo will be discontinued in patients with CTCAE Grade 3 hemorrhage and receiving full-dose anticoagulation. For all other patients with CTCAE Grade 3 hemorrhage, bevacizumab/placebo should be held until ALL of the following criteria are met:

6.541 bleeding has resolved
6.542 blood hemoglobin level is stable
6.543 there is no bleeding diathesis that would increase the risk of therapy
6.544 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 >3 weeks, recurrence of Grade 3 hemorrhage, or any CTCAE Grade 4 hemorrhage will be taken off bevacizumab/placebo therapy.

6.55 Thrombosis.

6.551 Arterial Thrombosis

Bevacizumab/placebo will be discontinued for ≥ 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/placebo therapy.

6.552 Venous Thrombosis

Treatment with bevacizumab/placebo will be held for CTCAE Grade 3 or asymptomatic CTCAE Grade 4 (including pulmonary embolism) **(08/06/07)** venous thrombosis. For patients on therapeutic anticoagulation, PT INR or PTT (whichever appropriate) should be monitored closely during bevacizumab/placebo therapy. If the planned duration of full-dose anticoagulation is ≤ 3 weeks, bevacizumab/placebo should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 3 weeks, bevacizumab/placebo may be resumed during the period of full-dose anticoagulation if ALL of the following criteria are met (otherwise such patients will be taken off bevacizumab/placebo therapy):

6.5521 The patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin (or other anticoagulant) or on stable dose of heparin prior to restarting treatment.

6.5522 The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels).

6.5523 The subject must not have had hemorrhagic events while on study.

6.5524 The patient is benefiting from treatment (no evidence of disease progression).

Patients with symptomatic Grade 4 thromboembolic events after study enrollment but prior to course 2 should be managed according to the above guidelines in section 6.552. However, patients with symptomatic CTCAE Grade 4 after receiving any bevacizumab/placebo, or recurrent/worsening venous thromboembolic events after resumption of bevacizumab/placebo treatment, will be taken off bevacizumab/placebo therapy. **(08/06/07)**

6.56 Coagulopathy. Bevacizumab/placebo should be held if the coagulation parameters are higher then the intended therapeutic range or for coagulopathy as follows. For CTCAE Grade 3 or 4 coagulopathy: hold treatment, until PT/PTT resolve to Grade 1. For patients with PT/INR > therapeutic range while on therapeutic warfarin, treatment with bevacizumab/placebo will be held until PT/INR is within the therapeutic range. Patients experiencing treatment delay >three weeks because of failure to meet the above criteria will be taken off bevacizumab/placebo therapy.

6.57 Wound Disruption/Bowel Perforation, Fistula, or GI Leak: **(06/26/06) (10/14/08)**

Treatment with bevacizumab/placebo will be modified in the event of wound disruption requiring medical or surgical intervention, bowel perforation or fistula (including tracheo-esophageal fistula) as follows:

6.571 Prior to Initiation of bevacizumab/placebo – For Grade 3 or 4 events, follow section 6.641 **(08/06/07)** (Special Modifications Study Treatment). In the event of superficial wound separations healing by secondary intention with no evidence of fascial dehiscence or infection, therapy with bevacizumab/placebo may be initiated with weekly wound examinations until complete closure, as specified in section 7.0.

6.572 After Initiation of bevacizumab/placebo – bevacizumab/placebo will be discontinued for any new event, regardless of Grade. **(1-16-06)**

6.58 Renal toxicity (associated with reduction in GFR) is not expected as a direct complication of chemotherapy in this untreated patient population using the prescribed dose and schedule of each regimen. As such, there are no specific dose modifications for renal toxicity. However, the target AUC dose of carboplatin must be recalculated each cycle in any patient who develops renal insufficiency, **(08/06/07)** defined by serum creatinine greater than 1.5 x

institutional upper limit normal (ULN), CTCAE Grade ≥ 2.

6.59 Intestinal obstruction. Bevacizumab/placebo will be held for occurrence of CTCAE Grade 3 toxicity, until resolution to ≤CTCAE Grade 1 and will be permanently discontinued for occurrence of CTCAE Grade 4 toxicity. Since the development of intestinal obstruction could be a result of cancer progression, the investigator should take steps to evaluate such patients for the possibility of disease progression according to section 8.0, using clinical, laboratory and radiographic information as clinically indicated; in the event of disease progression as per section 8.0, all protocol-directed therapy would be discontinued. **(08/06/07)**

6.60 Hepatic toxicity is not expected as a direct complication of chemotherapy in this untreated patient population using the prescribed dose and schedule for each regimen. However, the development of Grade 3 (or greater) elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin requires reduction of one dose level in paclitaxel and delay in subsequent therapy for a maximum of three weeks until recovered to Grade 1.**(08-06-07) (10/14/08)**

6.61 There will be no dose modifications for alopecia, nausea, constipation, or diarrhea. It is recommended that routine medical measures be employed to manage nausea, constipation, and diarrhea.

6.62 Treatment Guidelines for Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Bevacizumab should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure. Bevacizumab should be discontinued upon diagnosis of RPLS.

Note: Resumption of bevacizumab may be considered in patients who have documented benefit from the agent, provided that RPLS was mild and has completely resolved clinically and radiographically within 2-4 weeks; decision to resume bevacizumab in these patients must be discussed with the study chair and approved by the sponsor. **(Date 2006)**

6.63 In general, the occurrence of a hypersensitivity reaction to paclitaxel, carboplatin, bevacizumab/placebo or docetaxel is not considered a dose-limiting toxicity. Patients may be retreated at full doses after administration of medication to prevent hypersensitivity reactions, and adjustments in infusion rates should be made (see guidelines for re-treatment with bevacizumab/placebo in section 5.3232). **(08/06/07)** However, if despite these safety measures repeat attempt at infusion of the inciting drug results in a recurrent hypersensitivity reaction, the inciting drug should be discontinued for the remainder of the study. In the event of any CTCAE Grade 3 or 4 allergic or infusion reaction to bevacizumab / placebo, bevacizumab / placebo will be permanently discontinued. In the event of recurrent hypersensitivity reaction to paclitaxel, docetaxel should be substituted for paclitaxel, according to guidelines in Sections 5.322 and 6.51. Also, please see Appendix V for management of suspected hypersensitivity reactions to bevacizumab/placebo.