(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.

6.64 Potential modifications for other non-hematologic toxicities with an impact on organ function of Grade 2 (or greater) require discussion with one of the study co-chairs except where noted below in Section 6.641. **(08/06/07)**

6.641 Special Modifications Study Treatment

6.6411 For any CTCAE Grade 3 non-hematologic adverse event (except controllable nausea/emesis) considered to be at least possibly related to study treatment, protocol directed treatment should be held until symptoms resolve to <= CTCAE Grade 1. If a CTCAE Grade 3 adverse event persists for > three weeks or recurs after resumption of therapy, the patient may be taken off protocol directed treatment after consulting with the Study Chair.**(08/06/07)**

6.6412 For any CTCAE Grade 4 non-hematologic adverse event (except controllable nausea/emesis), the patient may be taken off protocol directed treatment therapy after consulting with the Study Chair.. **(08/06/07)**

6.65 Unanticipated Major Surgical Procedures – For any unanticipated (emergent/urgent) major surgical procedure performed for reasons other than disease progression or CTCAE at least possibly related to bevacizumab/placebo, treatment should be held > 28 days post-operatively prior to resumption, so long as other criteria in sections 6.5 and 6.6 are met. **(06/26/06)** Treatment delay is **not** required for minor procedures including a) cystoscopy, b) the removal or insertion of a central venous catheter, nephrostomy tube, or ureteral stent or c) thoracentesis or paracentesis for symptom relief in the absence of disease progression according to section 8.3. NOTE: the performance of non-emergent abdominal surgery (such as ostomy reversal, interval or secondary cytoreductive surgery, or second look surgery) prior to documentation of disease progression according to section 8.3 is considered a major protocol violation. **(08/06/07)(10/14/08)**

6.7 Guidelines for Use of Cytotoxic Therapy During Phase A, After Discontinuation of Protocol Directed Cytotoxic Therapy and Prior to Disease Progression **(08/06/07)**

In this phase III trial, the primary analysis of all endpoints including progression-free survival and overall survival, will be made according to the assigned treatment arm (intent- to-treat analysis). From the standpoint of safety, all arms are monitored on an ongoing basis for toxicity, and are subject to consideration for amendment and/or termination in the event of excessive toxicity.

The intent-to-treat analysis is necessary to avoid introducing biases that can result from eliminating those patients who drop-out due to toxicity, noncompliance, illnesses, or other factors. Using this approach, all registered and randomized patients are included in the analysis. Thus, the management of every patient, regardless of whether they are able to receive study-directed therapy, will have an impact on the analysis.

Therefore, so long as a patient has not developed progressive cancer as per section 8.0 and has not yet received 6 cycles of carboplatin/taxane therapy, if a patient's cytotoxic therapy is continued despite discontinuation of protocol directed treatment for adverse events (as directed specifically in section 6.0), it is recommended that such cytotoxic therapy be administered according to best clinical practice standards, which is the use of a platinum, a taxane, or the combination for up to 6 cycles. There are no specific guidelines in this situation for dose modifications, laboratory testing, or use of growth factor support. **In such situations, treatment data should still be submitted using D2R forms.**

7.0 STUDY PARAMETERS

7.1 Observations and Tests **(1-16-06) (06/26/06)**

The following observations and tests are to be performed and recorded on the appropriate form(s). Specimen requirements for research are provided in Section 7.2

	Pre-Treatment	During Cytotoxic Chemotherapy and Bevacizumab/placebo Treatment			Following Cytotoxic Chemotherapy, During Bevacizumab/placebo Only Treatment		Post-Treatment
Observations and Tests	Prior to Initial Study Treatment	Weekly	Prior to Each Course	Prior to Every Other Course	Prior to Every Course	Prior to Every Other Course	Every 3 months for 2 years, every 6 months for 3 years, then annually
History & Physical	1		19,20			19,20	X
Blood pressure	1	2	19		19		X
Toxicity Assessment	3		X			X	X
CBC/Differential/ Platelets	3	X	4			4	5
Urine Protein-Creatinine Ratio (UPCR)	3, 6			7		7	18
Serum Creatinine	3		4			4	8
Bilirubin, SGOT, Alkaline Phosphatase	3		X			X	8
Ca/PO4/Mg	3		8			8	8
Serum Pregnancy Test (if childbearing potential exists)	3						
PT/INR, PTT	3		9			9	8
Audiogram	10						
EKG	1						
Radiographic Disease Assessment	1, 11			12,20		12,20	12
Chest X-Ray	1, 13						
Serum CA-125 Level	1, 14		15,20			15,20	X
QoL Survey	X, 16			16		16	16
Incision Check	X	17					

1. Must be obtained within 28 days prior to initiating protocol therapy.
2. Blood pressure should be assessed at least weekly during the first cycle (usually cycle 2 of protocol therapy unless contraindicated) **(06/26/06)** of bevacizumab/placebo therapy. During the time between treatments, blood pressure assessment may be done at home by the patient at the investigator's discretion, and the investigator or study nurse will be responsible for obtaining these results from the patient.
3. Must be obtained within 14 days prior to initiating protocol therapy.
4. Must be obtained within 4 days of re-treatment with protocol therapy.
5. Weekly until counts recover from nadir
6. Urine protein should be screened by UPCR (see Section 3.33 for details). Patients must have a UPCR < 1.0 to allow participation in the study.
7. 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.

8. When clinically indicated
9. For patients on prophylactic or therapeutic anticoagulation with warfarin, PT INR should be monitored before each treatment. Treatment should be held for PT INR of > 1.5 on prophylactic warfarin or > therapeutic range if on full-dose warfarin.**(10/14/08)**
10. For patients with a history of hearing loss; repeat as clinically indicated
11. An initial CT scan or MRI of at least the abdomen and pelvis is required to establish post-surgical baseline for the extent of residual disease within 4 weeks of registration and beginning treatment.
12. Follow-Up Radiographic Assessment of Disease. In the absence of disease progression by criteria in Section 8.3, imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation should be repeated with the following schedule, regardless of whether or not the patient had measurable disease on initial CT or MRI: **(08/06/07)**
    a) After cycle 3 (before cycle 4) of paclitaxel-carboplatin
    b) After cycle 6 of paclitaxel-carboplatin (before cycle 7, bevacizumab/placebo)
    c) After completion of carboplatin and paclitaxel (or docetaxel) chemotherapy, during treatment with bevacizumab/placebo as follows: cycle 10 (before cycle 11); cycle 14 (before cycle 15), cycle 18 (before cycle 19), cycle 22 (within 4 weeks as of day 1) **(06/26/06)**
    d) After completion of all protocol therapy, every 3 months for 2 years, then every 6 months for 3 years, then annually **(06/26/06)**
    e) During or after completion of all protocol therapy, as clinically indicated at any time for clinical suspicion of progressive disease, including rising serum CA-125 levels not meeting criteria for disease progression in and of themselves according to section 8.3

    If based on any of these evaluations a response (CR or PR) is documented, a same modality imaging study should be performed after more than 4 weeks but within 3 months in order to confirm persistence of response by RECIST criteria. Regardless of the level of response confirmed, imaging will be repeated according to the schedule above.

    Imaging assessments as part of this protocol should be discontinued if disease progression is confirmed according to guidelines in section 8.3, regardless of means of confirmation, except that when disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation should be obtained within two weeks that such progression is documented.
13. Not required if CT or MRI of chest already performed at pre-treatment baseline.
14. Baseline pre-chemotherapy value is required. When available, also include pre-surgical value.
15. Progression can be based upon serum CA-125, only during the period following completion of cytotoxic chemotherapy, if one of the three conditions are met: 1. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart or 2. Patients with elevated CA-125 pretreatment, which never normalizes must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart or 3. Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart. When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1).If the patient does not meet criteria for disease progression on the basis of CA-125 elevations, then CA-125 monitoring should be continued according to schedule.
16. See Sections 4.5 and 5.4. QoL surveys are to be obtained at 6 time points:
    - baseline, defined as prior to cycle 1;

- prior to cycle 4 of protocol directed chemotherapy (~ 9 weeks from day 1 of cycle 1 if no longer receiving protocol directed treatment);
- prior to cycle 7 (~18 weeks from day 1 of cycle 1 if no longer receiving protocol directed treatment);
- prior to cycle 13 (~ 36 weeks from day 1 of cycle 1 if no longer receiving protocol directed treatment)
- prior to cycle 22 (~60 weeks from day 1 of cycle 1 if no longer receiving protocol directed treatment)**(10/14/08)**
- six months after cessation of bevacizumab/placebo (~ 84 weeks from day 1 of cycle 1 if protocol directed treatment discontinued prior to treatment cycle 22).. **(06/26/06) (08/06/07)**

17. See Section 3.28. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection are eligible but require weekly wound examinations until complete closure. Any occurrence of fascial dehiscence or deterioration related to the incision should be addressed according to guidelines for treatment modification in Section 6.57 and Adverse Events reporting in Section 10.3.
18. Check UPCR at first post-treatment visit at the end of Phase B. Check the UPCR at subsequent post-treatment follow-up intervals only if the value is > 1.
19. Within one week before and as close to the beginning of the next applicable course as possible. **(08/06/07)**
20. Patients who have not experienced disease progression according to section 8.0, including those who discontinue protocol directed therapy per section 6.0, need to be followed in a consistent fashion to monitor tumor status. Therefore, the schedule of tumor assessment by physical examination, CA125 monitoring and imaging should be conducted according to the time line shown per the study calendar regardless. **(08/06/07)**

7.2 Translational Research (1-16-06) (06/26/06)

7.21 Specimen Requirements

Below is a summary of the specimen requirements for GOG-0218 patients who give permission for their specimens to be submitted and used for this research study. Refer to Appendix VI for a description of the Specimen Procedures for GOG-0218 including instructions for obtaining a GOG Bank ID, submitting SP Forms as well as preparing, shipping, banking and distributing and the GOG-0218 specimens for this protocol and future research. **(03/16/09)**

The banking of whole blood for future research will apply to all of the patients who provide consent regardless of randomization and treatment including those already enrolled on GOG-0218. **(03/16/09)**

Quick Scan Summary of the Specimen Requirements for GOG-0218

Required Specimens (Specimen Codes)[1]	**Form SP Label in Forms Tracking System[2]**	**Collection Time Points and Requirements***	**Deadlines and Recommendations[2]**
Archival Formalin-Fixed and Paraffin-Embedded Primary or Metastatic Tumor (FT01):[3] 1st choice: Block 2nd choice: Slides+Scroll - Slides: 15 unstained 10 micrometer sections on slides - Scroll: 50 micrometer scroll in tube/vial	SP-FT01-0218	Collected prior to initiating front-line chemotherapy. **Mandatory** for patients enrolled at GOG and CTSU Institutions within the United States who give consent. **Optional** for patients enrolled at Institutions outside the United States who give consent.	Ship FT01 to the GOG Tissue Bank using your own shipping container within 8 weeks of study entry. [3] Form SP for FT01 will need to be submitted to the GOG Statistical and Data Center (SDC) online using the SDC Electronic Data Entry System (SEDES) within 8 weeks of study entry.
Frozen Primary or Metastatic Tumor Tissue: snap-frozen or OCT-embedded and frozen (RT01) [4]	SP-RT01-0218	Collected prior to initiating front-line chemotherapy. **Optional** high priority requirement for all patients who give consent.	Ship RT01, SB01 and PB01 to the GOG Tissue Bank using a Single-Chamber Specimen Kit within 8 weeks of study entry. [4] SP Forms for RT01, SB01 and PB01 will need to be submitted to the SDC online using SEDES within 8 weeks of study entry.
Frozen Pre-Treatment Serum (SB01) [4] Draw 10 ml blood into your own plain red-top Vacutainer® tube	SP-SB01-0218	Collected prior to initiating front-line chemotherapy. **Optional** high priority requirement for all patients who give consent.	
Frozen Pre-Treatment Plasma (PB01) [4] Draw 10 ml blood into your own purple-top Vacutainer® tube with EDTA	SP-PB01-0218		
Whole Blood (WB01)[5] Draw 10 ml blood into your own purple-top Vacutainer® tube with EDTA.	SP-WB01-0218	Collected prior to or after initiating front-line chemotherapy, or at any time during follow up. **Optional** high priority requirement for all patients who give consent.	Ship WB01 to the GOG Tissue Bank at ambient temperature the day the blood is collected.[5] Form SP for WB01 must be submitted to the SDC online using SEDES the day the blood is collected.

* If the patient gives permission for some of her tumor and some of her blood to be submitted to the GOG Tissue Bank for this research study and/or future research.

[1] Label each specimen with the protocol number (GOG-0218), a GOG Bank ID (# # # # - # # – G # # #), a specimen code (see above) and the collection date (mm/dd/yyyy).

[2] Please complete Form SP for EACH of these four specimens and include a copy when the specimen is submitted to the GOG Tissue Bank as described in Appendix VI. **(06/26/06)**

[3] Archival FFPE primary or metastatic tumor (FT01) must be shipped to the GOG Tissue Bank in your own shipping container using the US Postal Service at your expense. GOG Tissue Bank / Protocol GOG-0218, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, E-mail: gogbank@nationwidechildrens.org. Refer to Section IV and Section IX in Appendix VI for important instructions for preparing and shipping the archival FFPE primary tumor specimens to the GOG Tissue Bank for GOG-0218. If you are submitting sections and scrolls to satisfy the FT01 requirement, be aware that "sections and scrolls" is not one of the choices provided for Items shipped (field 9 on Form SP), please select "Other" and specify "Slides+Scroll". If more than one type of fixed tumor will be submitted, please label the tumor specimens sequentially using FT01 for primary tumor tissue and FT02 for metastatic tumor, and contact the GOG Statistical and Data Center to have the additional SP Form for FT02 added to the patient form schedule. In the event that it is not possible to submit the archival FFPE tumor specimen, submit the SP form via SEDES with the reason the specimen was not collected in item 5 (e.g., patient refused, not enough tumor for research, referring site won't release tumor). **(03/16/09)**

[4] Frozen primary or metastatic tumor (RT01), serum (SB01) and plasma (PB01) for GOG-0218 **MUST** be shipped to the GOG Tissue Bank (address provided above) with corresponding SP Forms using a Single-Chamber Specimen Kit with excess dry ice on a Monday through Thursday schedule for Tuesday through Friday delivery using the GOG Tissue Bank's Federal Express Account Number (1290-2562-0). Refer to Sections V, VI and IX in Appendix VI for important instructions for preparing and shipping the frozen tumor, serum and plasma specimens to the GOG Tissue Bank for GOG-0218. In the event that it is not possible to submit any of theses specimens, submit the SP form via SEDES with the reason the specimen was not collected in item 5 (e.g., patient refused, tried but not able to draw blood, no frozen tumor available for research, or non-US site logistically infeasible). **(03/16/09)**

[5] An amendment has been approved to collect a whole blood specimen from new patients on GOG-0218 as well as women who were previously enrolled on GOG-0218. The whole blood specimen for GOG-0218 **MUST** be shipped to the GOG Tissue Bank (address provided above) at ambient temperature with a completed SP Form for WB01 the day it is collected as the blood will be immediately processed upon receipt at the GOG Tissue Bank. Whole blood will need to be shipped to the GOG Tissue Bank *FedEx Priority Overnight* on a Monday through Friday schedule for Tuesday through Saturday delivery using the GOG Tissue Bank's Federal Express Account Number (1290-2562-0). Refer to Section VII and Section IX in Appendix VI for important instructions for preparing and shipping the whole blood specimen to the GOG Tissue Bank for GOG-0218 as the GOG Tissue Bank can not provide Shipping Kits for submitting the whole blood specimen for this protocol. In the event that it is not possible to submit the whole blood specimens, submit the SP form via SEDES with the reason the specimen was not collected in item 5 (e.g., patient refused, tried but not able to draw blood, or non-US site logistically infeasible). **(03/16/09)**

For institutions enrolling patients through CTSU, refer to Appendix VIII for special instructions regarding the submission of SP Forms for FT01, RT01, SB01, PB01(06/26/06) and WB01. (03/16/09)

7.22 Creation of Tissue Microarrays

When a paraffin block is submitted, the GOG Tissue Bank will prepare appropriate standard unstained sections and thick sections on slides as well as a 50 μm thick scroll in an autoclaved microfuge tube or sterile cryovial. The GOG Tissue Bank will also take cores from appropriate tumor blocks to create a series of tissue microarrays (TMAs) for this study. The plan will be to create two types of clinical outcome TMAs for this protocol. The first will contain tumor cores from patients who experienced a clinical response (complete or partial response), stable disease or increasing disease. The second will contain tumor cores from patients who experienced short survival, intermediate survival or long survival. The specific types of the TMAs that can be created will depend on the tumor blocks that are submitted for this protocol and the clinical outcomes observed for these cases. Since three to four cores from the same paraffin block are needed to reflect staining in a conventional tissue section, both of the clinical