

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 = 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/m² IV over 3 hours followed by Carboplatin AUC 6 IV over 30 minutes (Note : docetaxel 75mg/m² 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 on any body weight change ≥ 10%.(08/06/07)

*** Bevacizumab / Placebo 15mg/kg IV. Doses of bevacizumab/placebo may be rounded to the nearest 5 mg. After initial treatment, doses of bevacizumab/placebo should be re-calculated based on any body weight change ≥ 10%.(08/06/07)

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

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

5.321 Biometric considerations in dose calculation

5.3211 Maximum body surface area used for Paclitaxel and Docetaxel dose calculations will be 2.0 m² 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:

- 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/m² 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. 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 H₁ 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:

- H₁ blocker (diphenhydramine 25-50 mg IVP or orally one hour prior to injection; or an equivalent dose of an alternate H₁ blocker such as loratadine 10 mg or fexofenadine 60 mg).
- H₂ blocker (famotidine 20 mg IVP or orally one hour prior to injection; or an equivalent dose of an alternate H₂ 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/m² 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 H₁ 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:

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

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 During 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)**
- 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 $\geq 1,500$ cells/mm³ (CTCAE Grade 1) and the platelet count is $\geq 100,000$ /mm³. 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 as otherwise specified, through completion of cycle 6 (Phase A) **and** after re-registration (Section 5.12), through completion of Phase B.

- Exceptions:

Patients who received G-CSF prior to the current cycle may begin with ANC ≥ 1000 cells/mm³, 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/mm³, 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 $\geq 1,000$ cells/mm³ (CTCAE Grade 1) and the platelet count is $\geq 75,000$ /mm³. 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 $>1000/\text{mm}^3$. Growth factors should be discontinued if the ANC exceeds $10,000/\text{mm}^3$ 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 /mm³ 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 ($<25,000/\text{mm}^3$) or bleeding associated with Grade 3 thrombocytopenia (25,000 to $<50,000/\text{mm}^3$). 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-CSF <u>and</u> maintain all current drug doses	Discontinue Protocol-Directed Cytotoxic Therapy**
Yes	Yes	Reduce carboplatin one AUC unit (and docetaxel one dose level*)	Add G-CSF <u>and</u> 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/mm³ (CTCAE Grade 2 or worse) within 24 hours prior to scheduled therapy, or less than 1,000 cells/mm³, 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/mm³ 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 substituted for paclitaxel unless medically contraindicated, according to Section 5.322. (08/06/07)

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 $\leq$ 150 mm Hg and diastolic $\leq$ 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 $\geq$ 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.
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- 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 $\geq$ CTCAE Grade 3 arterial thrombotic events (including cerebrovascular ischemia, transient ischemic attack, cardiac ischemia/infarction, peripheral or visceral arterial ischemia) or CTCAE Grade 2 arterial thrombotic events new or worsened since beginning bevacizumab/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 $\leq$ 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 than 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)

Treatment with bevacizumab/placebo will be modified in the event of wound disruption requiring medical or surgical intervention, bowel perforation or 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 $\leq$ 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)
- 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 $\leq$ 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) the removal or insertion of a central venous catheter, nephrostomy tube, or ureteral stent or b) 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)

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, 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 PARAMETERS7.1 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					