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. Note: the procedure for submitting the optional biologic specimens for the translational science objectives of the study is describe in this section, The procedure for submitting the *required* stained slides to document the site and stage of disease is described in Section 10.2.

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** *for patients who give permission for their specimens to be submitted and used for GOG-0218*	**Deadlines and Recommendations**[2]
Archival Formalin-Fixed and Paraffin-Embedded Primary or Metastatic Tumor (FT01): 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. **Optional** for patients enrolled at Institutions outside the United States.	Ship FT01 to the GOG Tissue Bank using your own shipping container within 8 weeks of study entry. 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)	SP-RT01-0218	Collected prior to initiating front-line chemotherapy. **Optional** requirement for all patients.	Ship RT01 to the GOG Tissue Bank using a Single-Chamber Specimen Kit within 8 weeks of study entry. Form SP for RT01 will need to be submitted to the SDC online using SEDES within 8 weeks of study entry.
Frozen Pre-Treatment Serum (SB01)	SP-SB01-0218	Collected prior to initiating front-line chemotherapy. Blood must be drawn in a plain red-top tube (about 10 ml if possible) and serum prepared as described in Appendix VI. **Optional** requirement for all patients.	Ship SB01 to the GOG Tissue Bank using a Single-Chamber Specimen Kit within 8 weeks of study entry. Form SP for SB01 will need to be submitted to the SDC online using SEDES within 8 weeks of study entry.
Frozen Pre-Treatment Plasma (PB01)	SP-PB01-0218	Collected prior to initiating front-line chemotherapy. Blood must be drawn in a purple-top tube with EDTA (about 10 ml if possible) and plasma prepared as described in Appendix VI.	Ship PB01 to the GOG Tissue Bank using a Single-Chamber Specimen Kit within 8 weeks of study entry. Form SP for PB01 will need to be submitted to the SDC online using SEDES within 8 weeks of study entry.

		Optional requirement for all patients.	

[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)**

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

7.211 Tissue Specimens

7.2111 **Archival formalin-fixed and paraffin-embedded primary or metastatic tumor tissue** collected prior to initiating front-line chemotherapy will be:

- **a mandatory requirement** for patients who have given informed consent for their tumor tissue to be submitted and used for this research study and are enrolled at **GOG or CTSU Institutions within the United States.**
- **an optional requirement for** patients who have given informed consent for their tumor tissue to be submitted and used for this research study and are enrolled at Institutions **outside of the United States.**

Every attempt should be made to provide a tumor block. If it is not possible to provide a block on a permanent or temporary basis, the back-up option will be to provide "Slides+Scroll" that is fifteen unstained sections, 10 micrometers in thickness, on clean autoclaved glass slides suitable for laser capture microdissection, RNA extractions and genomic analysis, and a 50 micrometer thick scroll of tumor in a microfuge tube or cryovial suitable for RNA extraction and genomic analysis. **(06/26/06)**

If your institution cannot permanently provide a tumor block for this research study, please urge the Pathology Department to allow a tumor block to be submitted to the GOG Tissue Bank on a temporary basis. In this case, please state in field 15 on the SP Form for FT01 that the tumor block must be returned after the unstained sections and cores are obtained.

The type of specimen (block or sections) and the type of tumor tissue (primary or metastatic) must be specified on the specimen transmittal form (Form SP) submitted for FT01 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". **(06/26/06)**

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. **(06/26/06)**

7.2112 **Frozen primary or metastatic tumor** tissue collected prior to initiating front-line chemotherapy will be **an optional requirement** for patients who have given informed consent for their tumor tissue to be submitted and used for this research study. The frozen tumor specimen must be snap-frozen or OCT-embedded and frozen.

The GOG-0218 consent form does not cover the collection of frozen tumor tissue from the diagnostic and/or surgical staging procedures. Rather, individual institutions are given the flexibility to utilize whatever mechanism they choose for banking the frozen tumor tissue from their patients at the time of their diagnostic and/or surgical staging procedure(s) for research purposes. The GOG Specimen Banking protocol (GOG-0136) or an institutional banking protocol are among the acceptable mechanisms for banking frozen tumor tissue. These mechanisms require that the patient sign an Institutional Review Board (IRB) approved consent form prior to surgery allowing the patient's frozen tumor to be banked for research purposes. Once surgical staging is completed and a suitable candidate for GOG-0218 is identified, the patient will be asked to sign an informed consent document for this protocol and give specific permission for her frozen tumor banked from her previous surgery to be submitted and used for GOG-0218.

Specify whether or not you are able to submit the optional frozen tumor specimen on the Fast Fact Sheet for each patient you enroll on GOG-0218 to make sure the case is assigned to the proper form group. When frozen tumor is submitted, the type of specimen (piece of snap-frozen tissue or OCT-mold with embedded frozen tissue) must be specified on the specimen transmittal form (Form SP) submitted for RT01 for GOG-0218. In addition, indicate if the tumor is primary or metastatic in field 22 on Form SP and then whether the item being shipped is an OCT-mold or a piece of snap frozen tumor in field 9 on Form SP. If both are being submitted, select "Other" and enter "OCT-mold+piece" in the specify field.

If more than one type of frozen tumor will be submitted, please label the tumor specimens sequentially using RT01 for primary tumor tissue and RT02 for metastatic tumor and contact the GOG Statistical and Data Center to have the additional SP Form for RT02 added to the patient form schedule. **(06/26/06)**

7.212 Blood Specimens **(06/26/06)**

7.2121 Serum Specimen

A **pre-treatment serum specimen** collected prior to initiating front-line chemotherapy will be **an optional requirement** for all patients who have given informed consent for their blood to be drawn to prepare serum for use in this research study.

Blood must be drawn in a plain red-top tube (about 10 ml if possible) and serum prepared as described in Appendix VI. **(06/26/06)**

Specify whether or not you are able to submit the optional pre-treatment serum specimen on the Fast Fact Sheet for each patient you enroll on GOG-0218 to make sure the case is assigned to the proper form group.

7.2122 Plasma Specimen **(06/26/06)**

A **pre-treatment plasma specimen** collected prior to initiating front-line chemotherapy will be **an optional requirement** for all patients who have given informed consent for their blood to be drawn to prepare plasma for use in this research study.

Blood must be drawn in a purple-top tube with the anti-coagulant EDTA (about 10 ml if possible) and plasma prepared as described in Appendix VI.

Specify whether or not you are able to submit the optional pre-treatment plasma specimen on the Fast Fact Sheet for each patient you enroll on GOG-0218 to make sure the case is assigned to the proper form group.

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 outcome TMAs will be generated in two sets of quadruplicate core. Each TMA will contain 250 cores representing 200 individual cases and 50 controls. Each set will represent 200 independent (unique) cases with the same 50 controls. This will allow one set to be used for screening or exploratory analyses and the other for validation. Additional sets will be prepared if sufficient blocks associated with these clinical outcomes are available. Incorporation of the same controls on each of these TMAs will allow investigators to evaluate the performance of the individual arrays and allow inferences to be drawn across arrays when certain criteria are satisfied.

Creation of these clinical outcome TMAs for stage III-suboptimal and stage IV **(06/26/06)** epithelial ovarian or peritoneal primary carcinoma will leverage the value of the tumor blocks submitted for GOG-0218 and establish an enduring resource for ovarian cancer research to study biomarkers of tumor response and survival following the front-line treatment options included in GOG-0218.

7.23 Laboratory Testing **(06/26/06)**

Sections from standard blocks and the GOG-0218 TMAs will be used for **immunohistochemistry assays** and **genomic analysis**. Specifically, unstained sections on charged slides will be distributed to Dr. Robert Burger at the University of California Irvine Medical Center to compare the immunohistochemical expression of CD-31 and VEGF in conventional tumor tissue sections compared with TMAs. In addition, unstained sections on clean slides, 50 μm thick tumor scroll, and frozen primary or metastatic tumor tissue will be distributed in batches to Dr. Michael Birrer at the National Cancer Institute for genomic analysis. Frozen pre-treatment serum and frozen pre-treatment plasma will be distributed in batches to Dr. Robert Burger at the University of California Irvine Medical Center and an **immunoassay** will be used to quantify VEGF level.

The exact choice of the biomarkers and profiles to be evaluated and assays to be performed in the tumor tissue specimens (fixed and frozen tumor tissue) and blood specimens (serum and plasma) will be reevaluated based on evolving data in the field.

8.0 EVALUATION CRITERIA

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee.[91] Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

8.1 Definitions

8.11 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

8.12 Non-Measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

8.13 Target Lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

8.14 Non-target lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum numbers per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required but the presence or absence of each should be noted throughout follow-up.

8.2 Guidelines for Evaluation of Measurable Disease

8.21 Method of Measurement

8.211 General Aspects of Tumor Measurement

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

8.212 Specific Methods of Tumor Measurement

8.2121 Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

8.2122 Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

8.2123 Conventional CT and MRI. These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

PET scanning information will not be evidence of disease progression or measurable disease. PET CT Fusion studies may not meet technical requirements. Any CT used must use criteria for assessing according to RECIST.

8.2124 Ultrasound (US). When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

8.2125 Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained.

8.2126 Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

8.2127 Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

8.3 Response Criteria

8.31 Evaluation of Target Lesions

8.311 Complete Response (CR): Disappearance of all target lesions

8.312 Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

8.313 Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

8.314 Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

8.32 Evaluation of non-target lesions

8.321 Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level

Note: If serum CA-125 levels are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

8.322 Incomplete Response/

8.3221 Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

8.3222 Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of "non-target" lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the review panel (or study chair).

8.32221 Progression Based On Serum CA-125

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).

8.32222 Progression Based on Development or Worsening of Ascites or Pleural Effusions Suspected progression based solely on developing or worsening ascites or pleural effusions must be verified cytologically

8.33 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Sections 8.31 and 8.41).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:

X Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." **Every effort should be made to document the objective progression, even after discontinuation of treatment.**

X In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (e.g., fine needle aspirate/biopsy) before confirming the complete response status.

X In some cases a discrepancy may exist between trends in CA125 levels and data from either imaging or physical examination. In such cases, disease status by CT or MRI (and physical examination) should take precedence over CA125. For example, if there is evidence of disease on CT, MRI or physical examination, and none of the areas demonstrate any progression then rising CA125 levels according to Section 8.32221 would be insufficient to determine disease progression. **(08/06/07)**

X Patients who are not evaluated for response will be classified as either: having no target lesions at the time of enrollment onto the study, not re-assessed due to early death, or unknown (not assessable, or insufficient data),

8.4 Confirmatory Measurement/Duration of Response

8.41 Confirmation (10/14/08)

In order for a patient to be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met

8.42 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

8.5 Definitions Related to Evaluation Unrelated to Objective Response

8.51 Overall Survival is the observed length of life from entry into the study to death, regardless of cause or the date of last contact.**(10/14/08)**

8.52 Progression-Free Survival is the period from study entry until disease progression, death or date of last contact.

The time to progression will be determined by the clinical investigator and separately by an independent review of radiology studies. The independent review will occur at the Independent Review Facility (IRF) and will consist of the blinded review of radiology studies and other relevant clinical information by radiologists and oncologists. Details are provided in a separate charter.**(10/14/08)**

The defined date of disease progression will depend on the method of determination as follows:

8.521 For disease progression defined by imaging or palpation of at least a 20% increase in the sum of the LD of target lesions, the appearance of one or more new lesions, or unequivocal progression of existing non-target lesions, the date of progression will be defined as the date such lesions were first found to be progressed by imaging or palpation.

8.522 For disease progression defined by development or worsening of ascites or pleural effusions, the date of progression will be defined as the date of cytologic verification.

8.523 For disease progression defined by CA125 criteria alone, the date of progression will be defined as the first date of the initial CA125 of greater than or equal to two times the nadir value or upper limit of normal, whichever of these is applicable. Given that imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation is required within 2 weeks of the confirmatory (second) CA125 value, if imaging criteria are met for progression, then the date of progression would be defined as the date of the imaging study (as in 8.521).

8.53 Recurrence-Free Survival (patients with no measurable disease) is the period from study entry until disease recurrence, death or date of last contact.**(10/14/08)**

8.54 Subjective Parameters including performance status, specific symptoms, and side effects are graded according to the CTCAE v3.0.

9.0 DURATION OF STUDY

9.1 Patients will receive treatment until disease progression, the development of adverse events requiring discontinuation of protocol treatment, or completion of phase B bevacizumab/placebo therapy, whichever comes first. This includes patients who have completed phase A of treatment and have evidence of persistent disease which has not progressed according to section 8.0. The patient may voluntarily withdraw from the study at any time. No form of therapy targeted against a patient's cancer other than that specified in this protocol will be administered until disease progression. **(06/26/06)** Assigned treatment arm can be revealed to patients with progressive disease, at the time such disease progression is confirmed by the Study Chair or the GOG Statistical & Data Center (SDC). The information will be transmitted confidentially by way of the study site investigator of record for that patient. **(10/14/08)**

9.2 All patients will be followed for disease status and toxicity (with completion of all required case report forms) until death or voluntary withdrawal from study. In addition, following study therapy, patients will be monitored for delayed toxicity every three months for the first two years, every six months for the next three years, and then annually (or at disease progression or death) with Q forms submitted to the GOG Statistical and Data Center, unless consent is withdrawn. **(1-16-06)**

9.3 Adequate Duration of Study to Evaluate Toxicity. The minimal length of trial to evaluate toxicity is defined as receiving one course of therapy and receiving any follow-up information for evaluation of toxicity.

10.0 STUDY MONITORING AND REPORTING PROCEDURES

10.1 ADVERSE EVENT REPORTING FOR AN INVESTIGATIONAL AGENT **(1-16-06)**

10.11 Definition of Adverse Events (AE)

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs in a patient administered a medical treatment, whether the event is considered related or unrelated to the medical treatment.

This study will utilize the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) for defining and grading specific adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page at http://ctep.cancer.gov/reporting/ctc.html. A GOG CTCAE v3.0 Manual is also available on the GOG member web site (http://www.gog.org under MANUALS) and can be mailed to the institution registering a patient to this study if requested.

10.12 Reporting Expedited Adverse Events

Depending on the phase of the study, use of investigational agents, and role of the pharmaceutical sponsor, an expedited AE report may need to reach multiple destinations. For patients participating on a GOG trial, all expedited AE reports should be submitted by using the CTEP automated system for expedited reporting (AdEERS). All AdEERS submissions are reviewed by GOG before final submission to CTEP. Submitting a report through AdEERS serves as notification to GOG, and satisfies the GOG requirements for expedited AE reporting. All adverse reactions will be immediately directed to the Study Chair for further action.

The requirement for timely reporting of AEs to the study sponsor is specified in the Statement of Investigator, Form FDA-1572. In signing the FDA-1572, the investigator assumes the responsibility for reporting AEs to the NCI. In compliance with FDA regulations, as contained in 21 CFR 312.64, AEs should be reported by the investigator.

In the Description of any expedited AdEERS report, refer to the investigational agent as "bevacizumab/placebo." **(08/06/07)**

10.13 Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of the Investigational Agent

Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days
Possible Probable Definite	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days	7 Calendar Days	Not Required	24-Hrs; 3 Calendar Days	7 Calendar Days

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:

AdEERS 24-hour notification followed by complete report within 3 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 7 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under section entitled "Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND."

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Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.
  - "7 calendar days" - A complete AdEERS report on the AE must be submitted within calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions. Exception: All grade 3 or 4 myelosuppression (including neutropenia, anemia and thrombocytopenia), that DOES or DOES NOT require hospitalization is exempt from expedited reporting. However, THESE EVENTS SHOULD STILL BE INCLUDED IN THE ROUTINE TOXICITY CASE REPORT FORMS. **(08/06/07)**

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.