## 7.0 STUDY PARAMETERS

### 7.1 Observations and Tests **(08/04/08) (06/22/09) (03/15/10) (10/01/12)**

The following observations and tests are to be performed and recorded on the appropriate form(s). **See Section 7.2 for the stained pathology slide requirements to confirm eligibility for GOG-0213 and Section 7.31 for the specimen requirements for translational research.**

| | Pre-Treatment | | During Chemotherapy Phase | | | During Maintenance/Surveillance Phase (**Patients on Arm II, IV, VI, and VIII only**) | | |
|---|---|---|---|---|---|---|---|---|
| Observations and Tests | Prior to Surgery | Prior to chemo-therapy | Weekly | Prior to Each Course (q 3 wks) | Prior to Every Other Course (q 6 weeks) | Prior to Every Course (q 3 wks) | Prior to Every Other Course (q 6 weeks) | Q 3 Months x 8 then q 6 Months **All Patients** |
| History & Physical | 1 | 1 | | X | | | X | |
| Blood pressure* | 1 | 1 | 2 | X | | X | X | |
| Toxicity Assessment | | | | X | | | X | |
| CBC/Differential/ Platelets | 3 | 3 | X | 4 | | 4 | | |
| Urine pregnancy test in women of child-bearing potential | 3 | | | | | | | |
| Urine Protein-Creatinine Ratio (UPCR)* | 3,5 | 3, 5 | | | 6 | | 6 | |
| Serum Creatinine | 3 | 3 | | 4 | | | 4 | |
| Bilirubin, SGOT/AST, Alkaline Phosphatase | 3 | 3 | | 4 | | | 4 | |
| Ca/PO4/Mg | | 3 | | 7 | | | 7 | |
| Serum CA-125 Level | 1 | 1 | | 4,13 | | | 4,13 | 13 |
| PT/PT INR/PTT* | 3 | 3 | | 8 | | | 8 | |
| Audiogram | | 9 | | | | | | |
| EKG | 1 | 1 | | | | | | |
| Radiographic Tumor Measurement | 1,10 | 1, 10 | | | See footnote 11c),d) | | | 11 |
| Chest X-Ray | 1,12 | 1, 12 | | | | | | |
| QOL Survey | X,14 | X, 14 | | | 14 | | 14 | 14 |
| Incision Check* | | X | 15 | | | | | |

* Required only for patients who were enrolled prior to August 29, 2011 as well as those enrolled after this date electing to receive bevacizumab.

1. Must be obtained within 28 days of first treatment. For those patients randomized to cytoreductive surgery, these observations are repeated prior to initiating chemotherapy.
2. Blood pressure should be assessed at least weekly during the first cycle of bevacizumab therapy. During the time between treatments, blood pressure assessment may be done at home by the patient at the investigator's discretion.
3. Must be obtained within 14 days prior to registration. For patients randomized to cytoreductive surgery, these observations are repeated within 14 days prior to initiating chemotherapy. **(06/22/09)**

4. Must be obtained within 4 days of re-treatment with protocol therapy.
5. Urine protein should be assessed by UPCR (see Section 3.37 for details). Patients must have a UPCR < 1.0 to allow participation in the study.
6. Patients receiving bevacizumab should be monitored by urine analysis for urine protein: creatinine (UPC) ratio prior to every other dose of bevacizumab.
7. When clinically indicated.
8. For patients on prophylactic or therapeutic anticoagulation, 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.
9. For patients with a history of hearing loss; repeat as clinically indicated.
10. An initial CT scan (with intravenous and oral contrast, unless contraindicated) or MRI (with gadolinium, unless contraindicated and fat suppression sequence) of at least the abdomen and pelvis is required to establish post-surgical baseline for the extent of residual disease within28 days prior to initiating chemotherapy. **(06/22/09)** PET-CT imaging alone cannot be used to establish extent of post-operative disease residuum unless also performed with CT or MRI as described.
11. Follow-Up Radiographic Assessment of Disease (in patients with measurable and non-measurable disease). Imaging should use the same modality and encompass the same fields as in the initial pre-treatment evaluation should be repeated with the following schedule:
    a) Within 28 days of first treatment.
    b) If the patient was randomized to cytoreductive surgery, then repeat radiographic assessment within 14 days of initiating chemotherapy.
    c) **After cycle 3 (before cycle 4) of study treatment (06/22/09)**
    d) **After cycle 6 of study treatment (06/22/09)**
    e) **After cycle 8 of study treatment (03/15/10)**
    f) Every three months for two years and then every 6 months after completion of chemotherapy during the maintenance/surveillance phase.
    Imaging assessments as part of this protocol can be discontinued if disease progression is confirmed according to guidelines in section 8.14 and 8.15.. However, if disease progression is based only on rising CA-125 criteria, then radiographic imaging must be obtained within two weeks following the date CA-125 based progression was documented. **(08/29/11)**
12. Not required if CT or MRI of chest already performed at pre-treatment baseline.
13. Progression can be based upon serum CA-125, 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. **(06/22/09)**
14. See Section 7.3. QOL surveys are to be assessed for at most 6 time points:
    a) prior to surgery (for those randomized to cytoreductive surgery).
    b) prior to initiating chemotherapy.
    c) prior to cycle 3 (6 weeks after starting chemotherapy).
    d) prior to cycle 6 (15 weeks after staring chemotherapy).
    e) 6 months after starting chemotherapy.
    f) 12 months after starting chemotherapy.
15. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection may initiate therapy, 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 6.1512 and Adverse Events reporting in Section 10.3.

7.2 Stained Pathology Slide Requirements for Central Review to Confirm Protocol Eligibility **(06/22/09)**

Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility for the protocol. At least one representative H&E stained slide (or slides) demonstrating primary site, histologic cell type, and grade, and **one** H&E stained slide showing the most advanced stage of disease will be required. If the most advanced stage of disease is not documented by histology, the method of stage documentation needs to be stated (e.g. CT, MRI, etc.). If this protocol allows patients with recurrent or persistent disease, slides from recurrence and/or persistent disease will be required only if recurrence/persistent disease is confirmed by histology or cytology.

When submitting pathology material to the GOG Statistical and Data Center individual slides must be labeled with GOG Patient ID, patient initials and the surgical / pathology accession number (e.g., S08-2355) and block identifier (e.g., A6). Do not label the slides with disease site (e.g., right ovary) or procedure date.

Pack the labeled slides into plastic slide cassette(s). Tape plastic slide cassettes shut and wrap in bubble wrap or another type of padded material prior to shipping. Please include the GOG Patient ID, patient initials, and protocol number on all pages of the pathology report and black out the patient's name. Ship pathology slides, three copies of both the Pathology Form F (if required for the protocol) and the official pathology report in your own shipping containing using postal mail at your own expense directly to the **Pathology Materials Coordinator at the GOG Statistical and Data Center, Roswell Park Cancer Institute, Research Studies Center, Carlton and Elm Streets, Buffalo, New York, 14263**; phone (716) 845-5702. The GOG Upload Application in SEDES is an alternative method for submitting stained slides, pathology reports and Form F to the GOG Statistical and Data Center. Please see section 4.6 and 10.2 for additional requirements and instructions.

7.3 Translational Research

7.31 Specimen Requirements **(08/04/08) (06/22/09)**

A total of seven specimens will be sought from each GOG-0213 patient randomized to have secondary cytoreductive surgery. Three of these will be MANDATORY and four will be HIGH-PRIORITY OPTIONAL. Please see below for a summary of the specimen requirements and laboratory testing for this protocol. In addition, please carefully review Appendix III for a detailed description of the Specimen Procedures for GOG-0213. A copy of Form SP will need to be completed online and submitted to the GOG Statistical and Data Center (SDC) as specified in Section 10.2.

**The collection of a whole blood for DNA extraction and single nucleotide polymorphism (SNP) analysis will apply to all women on GOG-0213 who provide consent regardless of randomization and treatment including those already enrolled on protocol. Women who are already enrolled on GOG-0213 will need to be re-consented.**

## Quick Scan Summary of the Specimen Requirements for GOG-0213.

*(See Appendix III for detailed instructions for collecting, processing, storing, packing and shipping specimens for GOG-0213.)*

| 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 (FFPE) Primary or Metastatic Tumor (FT01) either<br>• 1st choice: Block<br>• 2nd choice: 16 Unstained Slides | SP-FT01-0213 | Archival primary or metastatic tumor left over from a previous surgery will be a mandatory requirement for **women who consent and undergo surgery** on GOG-0213. | Ship FT01 to the GOG Tissue Bank using your own shipping container within 8 weeks of study entry. FT01 could also be included in the dual chamber kit if available when the other specimens were ready to ship to the Bank.<br><br>Submit Form SP for FT01 to the SDC online within 8 weeks of study entry. |
| Pre-Op Serum (SB01)<br><br>Pre-Op Plasma (PB01) | SP-SB01-0213<br><br>SP-PB01-0213 | Pre-op serum and plasma will be an optional but high priority requirement for **women who consent and undergo surgery** on GOG-0213. The blood to prepare these specimens must be collected after providing consent for this research study but prior to undergoing secondary cytoreductive surgery. | Ship the FR01 and RR01 (mandatory requirement) and any of the optional specimens (SB01, PB01, FN01 and/or RN01) to the GOG Tissue Bank in the dual-chamber kit within 3 days of surgery when possible as described below [6] and in Appendix III.<br><br>Submit Form SP for each of these specimens to the SDC online within 7 days of surgery. |
| Fixed Recurrent Tumor (FR01) in a jar of formalin or embedded in a paraffin block [4]<br><br>Frozen Recurrent Tumor (RR01) snap frozen piece or frozen in OCT mold [4] | SP-FR01-0213<br><br>SP-RR01-0213 | Recurrent tumor will be a mandatory requirement for **women who consent and undergo surgery** on GOG-0213. Fixed and frozen tumor will need to be removed during secondary cytoreductive surgery. | |
| Fixed Normal Tissue[4,5] (FN01) in a jar of formalin or embedded in a paraffin block<br><br>Frozen Normal Tissue[4,5] (RN01) snap frozen piece of frozen in OCT mold | SP-FN01-0213<br><br>SP-RN01-0213 | Normal tissue will be an optional but high priority requirement for **women who consent and undergo surgery** on GOG-0213. Fixed and frozen normal tissue will need to be removed during secondary cytoreductive surgery. | |
| Whole Blood (WB01)[7] to extract DNA for SNP analysis.<br>• Draw 10 ml blood into your own purple-top Vacutainer® tube with EDTA. | SP-WB01-0213 | Collect prior to or after starting treatment on this phase III trial or at any time during follow up from **all women on protocol who provide consent regardless of randomization and treatment** including women already enrolled on GOG-0213. Collect on a Monday through Friday schedule. **Do not collect this blood the day before a holiday.** | Ship WB01 to the GOG Tissue Bank at ambient temperature the day the blood is collected.[7]<br><br>Form SP for WB01 must be submitted to the SDC online using SEDES the day the blood is collected. |

[1] Label each specimen with the protocol number (GOG-0213), a GOG Bank ID (# # # # - # # – G # # #), a specimen code (see above) and the collection date (mm/dd/yyyy).

[2] Please complete Form SP for EACH specimen and include a copy when the specimen is submitted to the GOG Tissue Bank as described in Appendix III.

[3] The block or 16 unstained slides of primary 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-0213, 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 III for important instructions for preparing and shipping the archival FFPE primary and/or metastatic tumor specimens to the GOG Tissue Bank for GOG-0213. 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 optional 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).

[4] **Quantity of tissue needed for research: Please submit as much tissue as possible for research. Gram quantities are ideal.** Visually, one gram of tissue is about the size of five quarters stacked on top of each other (i.e., one quarter in diameter and five stacked quarters in height). Please try to submit gram quantities whenever possible. Larger amounts of tissue will allow for replicate laboratory testing to be performed and will enable multiple assays to be run on the same specimen.

[5] **Normal tissue can be any normal epithelial tissue including non-involved ovary, Fallopian tube, uterus, cervix, or skin. When normal epithelium is not available, please submit non-involved peritoneal surface, residual omentum, or retroperitoneal muscle.** Please try to submit normal epithelium whenever possible as this type of tissue will serve as the most appropriate control for the laboratory testing to be preformed for this protocol. **Note for the pathologist,** in the unlikely event that any tumor tissue is subsequently identified within the normal tissue submitted for research, the Pathology Department at the treating institution will be informed and the material will be immediately returned for diagnostic purposes. Please try to submit as much normal tissue as possible. The larger the piece the better.

6 Ship the surgical specimens including fixed recurrent tumor (FR01) and frozen recurrent tumor and any of the optional high priority specimens (fixed normal tissue [FN01], frozen normal tissue [RN01], serum [SB01] and plasma [PB01]) to the GOG Tissue Bank in the dual-chamber kit within 3 days of surgery when possible to the GOG Tissue Bank (address provided above) with a completed SP Form for each specimen. These specimens can be shipped on a Monday through Thursday schedule for Tuesday through Friday delivery using shipping labels obtained through the GOG Tissue Bank's Kit Management application. **(08/29/11)**

Refer to footnotes 4, 5 and 6 in the Quick Scan Summary of Specimen Requirements for GOG-0213 as well as Section V and Section IX in Appendix III for important instructions for preparing and shipping the surgical specimens to the GOG Tissue Bank for GOG-0213. Refer to Section VI and Section IX in Appendix III for important instructions for preparing and shipping the frozen serum to the GOG Tissue Bank for GOG-0213. In the event that it is not possible to submit any of these 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, tumor not present during surgery, not enough tumor or tissue for research).

[7] Whole blood specimen for GOG-0213 **MUST** be shipped to the GOG Tissue Bank (address provided above) with a completed SP Form for WB01. The blood must be shipped at ambient temperature 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 a shipping label obtained through the GOG Tissue Bank's Kit Management application. **Do not collect blood the day before a holiday** as staff will not be available at the Bank to receive or process the blood. Refer to Section VII and Section IX in Appendix III for important instructions for preparing and shipping the whole blood specimen to the GOG Tissue Bank for GOG-0213 as the GOG Tissue Bank cannot 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).

## 7.32 Creation of Tissue Microarrays (TMAs) for GOG-0213 **(06/22/09)**

The GOG Tissue Bank will collaborate with the GOG Statistical and Data Center and the GOG Tissue Utilization Subcommittee to design and create a series of TMAs for GOG-0213 to study markers of recurrence, survival and treatment response or resistance. The specific types of the TMAs that can be created will depend on the paraffin block submissions for this protocol and the clinical outcomes observed for these cases. For example, one TMA could contain matched cores of tumor collected prior to initiating first-line and second-line therapy with adjacent normal tissue from secondary cytoreductive surgery

whereas another TMA could represent tumor cores from patients who experienced short survival, intermediate survival or long survival or include tumor cores from patients treated on a specific treatment arm who experienced short, intermediate or long progression-free survival.

7.33 Laboratory Testing **(06/22/09)**

Staff at the GOG Tissue Bank will coordinate with the Chairs of the GOG Committee for Experimental Medicine and the Tissue Utilization Subcommittee as well as staff in the GOG Statistical and Data Center to distribute appropriate specimens to approved investigators for testing for this trial. Investigators will be responsible for completing the approved testing and transferring appropriate laboratory data with accurate specimen identifiers to the GOG Statistical and Data Center for analysis. The study chair for GOG-0213 will coordinate study co-chairs, scientific collaborators and members of the GOG Statistical and Data Center as needed to perform appropriate statistical analysis and to prepare abstracts, presentations, reports and manuscripts.

Appropriate unstained sections from conventional blocks and/or TMAs, aliquots of serum or plasma, and specified concentrations of DNA with appropriate Q/C data will be distributed to Dr. Michael Birrer at MGH Cancer Center and/or to investigators approved by the GOG Committee on Experimental Medicine for biomarker, genomic, proteomic and SNP analyses based on available funding and expertise. Laser-capture microdissection will be performed as need to examine cell type-specific expression profiles. The exact choice of the biomarkers and profiles to be evaluated and the assays to be performed in the GOG-0213 tissue specimens, serum, plasma and DNA from whole blood will be reevaluated based on evolving data in the field. All bioinformatics and statistics will be performed as a collaboration with the GOG Statistical and Data Center.

7.331 Light Microscopy

Light microscopy will be performed using formalin-fixed and paraffin-embedded tissue specimens to characterize the histopathologic features of the tissue specimens undergoing molecular and biochemical profiling, and to satisfy some of the specimen election criteria for gene expression profiling. Stained specimens will be reviewed by Dr William Rodgers (chair of the GOG Pathology Committee) and other members of the Pathology Committee.

7.332 Biomarker Analysis **(06/22/09)**

Multiple types of biomarker analyses will be performed to expand our current understanding of the biology, progression, metastasis and responsiveness of recurrent ovarian and peritoneal primary cancer. Immunohistochemistry assays will be performed as needed in sections from conventional paraffin blocks and the GOG-0213 TMAs in Dr Michael Birrer's laboratory at the MGH Cancer Center, the GOG Receptor Core Laboratory, and/or by investigators approved by the

Committee on Experimental Medicine based on available funding and expertise. Reverse phase array and conventional immunoblot analyses

will be performed as needed in lysates from frozen recurrent tumor tissue, microdissected recurrent tumor cells and normal tissue. Quantitative RT-PCR will be performed as needed using specific primers

in RNA extracted from the appropriate type of tissue specimens. These assays will be used to identify and/or validate prognostic or predictive markers of recurrent, survival and treatment response or resistance. In addition, these assays will be used to validate individual markers identified in gene expression microarray studies (see below).

7.333 Genomic Profiling **(06/22/09)**

Gene expression microarray analysis will be undertaken using RNA isolated from frozen recurrent tumor and normal tissue to define gene expression patterns associated with disease progression, spread of disease, response to treatment or patient outcome. These studies will utilize an Affymetrix platform or an appropriate alternative and will be performed in Dr Michael Birrer's laboratory at the MGH Cancer Center and by investigators approved by the Committee on Experimental Medicine based on available funding and expertise.

7.334 Proteomic Profiling **(08/04/08) (06/22/09)**

Proteomic profiling will be performed in pre-op serum specimens to define protein/peptide fragment patterns that are associated with disease progression, spread of disease, and response to treatment or patient outcome. All proteomic studies will be performed by a Proteomic Group approved by the GOG Committee on Experimental Medicine based on available funding and expertise.

7.335 SNP Analysis **(06/22/09)**

The 10 ml of whole blood (WB01) drawn into a standard purple-top Vacutainer® tube with EDTA will be shipped to the GOG Tissue Bank in Columbus, OH for immediate processing, extraction of DNA and Q/C assessments. Staff at the GOG Tissue Bank will be responsible for shipping an appropriate quantity of DNA with corresponding Q/C data to Dr. Michael Birrer at MGH Cancer Center and/or investigators approved by the Committee on Experimental Medicine based on available funding and expertise for whole genome SNP-associations studies and/or evaluation of individual SNPs.

7.34 Future Research **(06/22/09)**

See Section XII in Appendix III for important details regarding the banking and distribution of the residual tumor specimens, normal tissue, serum, plasma and normal DNA from blood still remaining after completion of GOG-0213 for future research.

7.4 Quality of Life: **(08/04/08)**

7.41 Patients in the secondary cytoreduction arm will complete the quality of life questionnaire packet (which includes the FACT-O and the RAND SF-36 physical functioning questionnaire) before surgery and before the first cycle of chemotherapy. The FACT-O is available in Spanish and French. Requests should be submitted to the GOG Statistical and Data Center. Patients in the no surgery arm will complete the quality of life questionnaire packet before the first cycle of chemotherapy. Follow-up questionnaires will be completed prior to beginning of the third cycle (approximately six weeks from the start of treatment) and prior to beginning of the sixth cycle (or approximately 15 weeks from the start of treatment). Additional quality of life assessments will be done at six and twelve months after initiating chemotherapy. If a patient progresses or is removed from the study treatment, continue to follow the schedule of QOL assessments when possible regardless of subsequent treatments. Whenever possible, QOL questionnaires should be administered at the clinic visit before the patient is seen by the physician and before evaluations (e.g., results of CA-125 or scans) are shared with her. In the event that the questionnaires are not administered at the clinic visit, the QOL data can be collected by telephone or mail as back-up methods, with telephone data collection being the preferred back-up method.

7.42 The Quality of Life Liaison (Nurse\Data Manager) at each institution has overall responsibility for the administration of the study questionnaire.

7.43 The Nurse\Data Manager should read the instructions printed on the questionnaire to the patient and ensure the patient understands the instructions. It is important to assure the patient that all material on the questionnaire is confidential and will not be shared with the health care team and that it will not become part of the medical record.

7.44 Assistance in reading the questionnaire is permitted if the patient is unable to complete the questionnaire on her own (e.g., difficulty in reading, elderly). It is important not to influence the response of the patient. Note why the patient required assistance and what assistance was given.

7.45 Patients should be instructed to answer all the questions regardless of whether the symptoms or conditions asked about are related to cancer or cancer treatment. Discourage family members from being present during questionnaire completion or from influencing patient's response.

7.46 Review the questionnaire for completeness before the patient leaves.

7.47 If the patient has marked more than one answer per question, ask the patient which answer best reflects how she is feeling.

7.48 If the patient has skipped a question or questions, assure that she noted in the space provided that she has chosen not to answer those questions.

7.49 It is essential that questionnaires be completed according to the schedule described in Section 7.1.

7.410 If the patient refuses or cannot complete the questionnaire at any time point, she should be asked to do so at the next scheduled administration time.

7.411 The patient may withdraw from the quality of life section of the protocol for any reason. The reason must be documented on the form.

7.412 The Quality of Life Liaison may attend a training session held at a biannual GOG meeting.

## 8.0 EVALUATION CRITERIA

### 8.1 Parameters of Response – GOG RECIST Criteria

8.11 Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be ≥ 20 mm when measured by conventional techniques, including palpation, plain x-ray, CT, and MRI, or ≥ 10 mm when measured by spiral CT.

8.12 Baseline documentation of "Target" and "Non-Target" lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest dimension) and their suitability for accurate repetitive measurements by one consistent method of assessment (either by imaging techniques or clinically). A sum of the longest dimension (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as *non-target* lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent".

All baseline evaluations of disease status should be performed as close as possible to the start of treatment and never more than 4 weeks before the beginning of treatment.

8.13 Best Response

Measurement of the longest dimension of each lesion size is required for follow-up. Change in the sum of these dimensions affords some estimate of change in tumor size and hence therapeutic efficacy. All disease must be assessed using the same technique as baseline. *Reporting of these changes in an individual case should be in terms of the* ***best response*** *achieved by that case since entering the study.*

8.131 Complete Response (CR) is disappearance of all *target* and *non-target* lesions and no evidence of new lesions documented by two disease assessments at least 4 weeks apart. Normalization of CA125, if elevated at baseline, is required for ovarian carcinoma studies.

8.132 Partial Response (PR) is at least a 30% decrease in the sum of longest dimensions (LD) of all *target* measurable lesions taking as reference the baseline sum of LD. There can be no unequivocal progression of *non-target* lesions and no new lesions. Documentation by two disease assessments at least 4 weeks apart is required. In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam, which is not radiographically measurable, a 50% decrease in the LD is required.

8.133 Increasing Disease is at least a 20% increase in the sum of LD of *target* lesions taking as references the smallest sum LD or the appearance of new lesions **within 8 weeks of study entry**. Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician within 8 weeks of study entry is also considered increasing disease (in this circumstance an explanation must be provided). In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam, which is not radiographically measurable, a 50% increase in the LD is required.

8.134 Symptomatic deterioration is defined as a global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression.

8.135 Stable Disease is any condition not meeting the above criteria.

8.136 Inevaluable for response is defined as having **no** repeat tumor assessments following initiation of study therapy *for reasons unrelated to symptoms or signs of disease.*

8.14 Progression (measurable disease studies) is defined as ANY of the following:

- At least a 20% increase in the sum of LD target lesions taking as reference the smallest sum LD recorded since study entry
- In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam which is not radiographically measurable, a 50% increase in the LD is required taking as reference the smallest LD recorded since study entry
- The appearance of one or more new lesions
- Death due to disease without prior objective documentation of progression
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression
- Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician (in this circumstance an explanation must be provided) **(06/22/09)**
- Progression based on serum CA-125:
    - Patients with elevated CA-125 pretreatment with normalization of CA-125 must show evidence of CA-125 during study treatment

greater than or equal to two times the upper normal limit on two occasions at least one week apart

- or -

- Patients with elevated CA-125 pretreatment, which never normalized during study treatment 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 -

- Patients with CA-125 in the normal range 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 pretreatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1). If the disease progression is noted on imaging, then the date of progression will be the date of the imaging studies. Otherwise, the date of progression will be the date of the first CA-125 level that indicates progression. **(08/23/10)**

Progression (non-measurable disease) is defined as **ANY** of the following:

- Appearance of any new clinical, radiological or histological evidence of disease since study entry
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of recurrence
- Death due to disease without prior objective documentation of recurrence
- Progression based on serum CA-125:
  - Patients with elevated CA-125 pretreatment with normalization of CA-125 must show evidence of CA-125 during study treatment greater than or equal to two times the upper normal limit on two occasions at least one week apart

    - or -

  - Patients with elevated CA-125 pretreatment, which never normalized during study treatment 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 -

  - Patients with CA-125 in the normal range 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 pretreatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1). If the disease progression is noted on imaging, then the date of progression

will be the date of the imaging studies. Otherwise, the date of progression will be the date of the first CA-125 level that indicates progression. **(08/23/10)**

8.15 Recurrence (following CR) is defined as **ANY** of the following:

- Appearance of any new clinical, radiological or histological evidence of disease since study entry
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of recurrence
- Death due to disease without prior objective documentation of recurrence
- Increase in serum CA-125 levels as follows:
  - Patients with CA-125 in the normal range 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 pretreatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1). If the disease progression is noted on imaging, then the date of progression will be the date of the imaging studies. Otherwise, the date of progression will be the date of the first CA-125 level that indicates progression. **(08/23/10)**

8.16 Survival is the observed length of life from entry into the study to death or the date of last contact

8.17 Progression-Free Survival (measurable disease studies) is the period from study entry until disease progression, death or date of last contact.

8.18 Recurrence-Free Survival (non-measurable disease studies) is the period from study entry until disease recurrence, death or date of last contact.

8.19 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 remain on the designated study regimen until disease progression or toxicity precludes further treatment or the patient refuses study treatment.

9.2 All patients will be followed (with completion of all required case report forms) until disease progression, or the patient withdraws consent. In addition, following disease progression, patients will be monitored for delayed toxicity and survival for a period of 10 years with Q forms submitted to the GOG Statistical and Data Center, unless patient's consent is withdrawn.

# 10.0 STUDY MONITORING AND REPORTING PROCEDURES

## 10.1 ADVERSE EVENT REPORTING FOR A TRIAL EVALUATING A SURGICAL PROCEDURE

### 10.11 Definition of Adverse Events (AE)

An adverse event (AE) is any unfavorable and unintended sign, symptom, or disease that occurs in a patient administered a pharmaceutical product or protocol procedure, whether the event is considered related or unrelated to the study treatment.

### 10.12 Reporting Expedited Adverse Events

All CTCAE v3.0 expedited AEs must be reported to the GOG. All expedited AE reports should be submitted by using the CTEP automated system for expedited reporting (AdEERS). Submitting a report through ADEERS serves as notification to GOG, and satisfies the GOG requirements for expedited AE reporting.

### 10.13 Expedited Reporting of Adverse Events occurring within 30 Days of the Study Procedure

The following table summarizes the GOG requirements for expedited reporting of AEs that occur **within** 30 days of the surgical procedure.

Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Study Procedure:

From the period of protocol activation through September 30, 2011, Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (CTCAE v3.0) are utilized for defining and grading specific adverse events reported through the AdEERS system. **(09/26/11)**

*Beginning October 1, 2011,* the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will be utilized for AE reporting through the AdEERS system. CTCAE v 4.0 is located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of this Version of CTCAE. CTCAE v 4.0 definition is also available on the GOG member web site (https://gogmember.gog.org under MANUALS). **(09/26/11)**

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

| | 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 Days | Not Required | 7 Days | Not Required | 7 Days | 7 Days |
| **Possible Probable Definite** | Not Required | Not Required | Not Required | 7 Days | Not Required | 7 Days | Not Required | 7 Days | 7 Days |

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after surgery require reporting as follows:

AdEERS 7 calendar day report:
- At least Grade 3 with hospitalization or prolongation of hospitalization, or
- Persistent causes, significant disabilities/incapacities

[2] **Grade 5:** All deaths within 30 days of the surgical procedure must be reported within 7 calendar days using expedited reporting regardless of causality.

**Please see exceptions below under the section entitled, "Additional Instructions or Exceptions to Expedited Reporting Requirements for Surgical Trials."**

**March 2005**

- Expedited AE reporting timelines defined:
  "7 calendar days" – A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grades 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.

- Any event that results in persistent or significant disabilities and/or incapacities must be reported via AdEERS if the event occurs following a protocol procedure.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Surgical Trials:

- There are no additional instructions or exceptions to AdEERS expedited reporting requirements for this protocol.

10.14 Procedures for Expedited Adverse Event Reporting

10.141 AdEERS Expedited Reports: Expedited reports are to be submitted using AdEERS available at http://ctep.cancer.gov. The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.

Up until September 30, 2011, AML/MDS events must be reported via AdEERS (in addition to your routine AE reporting mechanisms). In CTCAE v3.0, the event can be reported as: "Secondary malignancy-Other (specify)". **(09/26/11)**

Starting October 1, 2011 when use of CTCAE v4.0 begins: AML/MDS events must be reported via AdEERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment related secondary malignancy. **(09/26/11)**

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to GOG by telephone at: 215-854-0770. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted.

10.2 ADVERSE EVENT REPORTING FOR AN INVESTIGATIONAL AGENT (TO USE FOR PATIENTS WHO SELECT BEVACIZUMAB AFTER AUGUST 28, 2011) **(12/19/11)**

10.21 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.

10.22 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.

10.23 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

From the period of protocol activation through September 30, 2011, Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (CTCAE v3.0) are utilized for defining and grading specific adverse events reported through the AdEERS system. **(09/26/11)**

*Beginning October 1, 2011,* the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will be utilized for AE reporting through the AdEERS system. CTCAE v 4.0 is located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of this Version of CTCAE. CTCAE v 4.0 definition is also available on the GOG member web site (https://gogmember.gog.org under MANUALS). **(09/26/11)**

| | 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."**

March 2005

**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 7 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) with the exception as listed below (grade 2-4 myelosuppression) 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.

- 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.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND:

- Reference the SPEER (Specific Protocol Exceptions to Expedited Report) for the subset of AEs that are protocol specific exceptions to expedited reporting via AdEERS. Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If the CAEPR for a protocol agent is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required. For questions or comments regarding the SPEER or CAEPR, please contact the AdEERS MD Help Desk at adeersmd@tech-res.com **(12/19/11)**

- *"All Grades 2, 3 and 4 myelosuppression (including neutropenia, anemia, and thrombocytopenia) regardless of the need for hospitalization is exempt from expedited reporting."*

10.24 Procedures for Expedited Adverse Event Reporting: **(12/19/11)**

10.241 AdEERS Expedited Reports: Expedited reports are to be submitted using AdEERS available at http://ctep.cancer.gov. The NCI

guidelines for expedited adverse event reporting requirements are also available at this site.

Up until September 30, 2011, AML/MDS events must be reported via AdEERS (in addition to your routine AE reporting mechanisms). In CTCAE v3.0, the event can be reported as: "Secondary malignancy-Other (specify)". **(09/26/11)**

Starting October 1, 2011 when use of CTCAE v4.0 begins: AML/MDS events must be reported via AdEERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment related secondary malignancy. **(09/26/11)**

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted.

10.25 Automated CDUS reporting

For studies using investigational agents, the GOG Statistical and Data Center (SDC) routinely reports adverse events electronically to the CTEP Clinical Data Update System (CDUS Version 3.0). The SDC submits this data quarterly. The AEs reported through AdEERS will also be included with the quarterly CDUS data submissions.

10.3 ADVERSE EVENT REPORTING FOR A COMMERICIAL AGENT (TO BE USED FOR PATIENTS NOT TAKING BEVACIZUMAB AFTER AUGUST 28, 2011) **(08/29/11) (12/19/11)**

10.31 Phase 2 and 3 Trials Utilizing a Commercial Agent: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of Any Commercial Study Agent

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

From the period of protocol activation through September 30, 2011, Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (CTCAE v3.0) are utilized for defining and grading specific adverse events reported through the AdEERS system. **(09/26/11)**

*Beginning October 1, 2011,* the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will be utilized for AE reporting through the AdEERS system. CTCAE v 4.0 is located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.