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 EDTAwill 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 **(09/29/14)**

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 Adverse Event Reporting System (CTEP-AERS). Submitting a report through CTEP-AERS 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 CTEP-AERS 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 CTEP-AERS 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 Hospitali-zation	Without Hospitali-zation	With Hospitali-zation	Without Hospitali-zation	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:

CTEP-AERS 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 CTEP-AERS 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 CTEP-AERS 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 CTEP-AERS Expedited Reporting Requirements for Surgical Trials:

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

10.14 Procedures for Expedited Adverse Event Reporting

10.141 CTEP-AERS Expedited Reports: Expedited reports are to be submitted using CTEP-AERS 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 CTEP-AERS (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 CTEP-AERS (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 CTEP-AERS 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 (CTEP-AERS). All CTEP-AERS submissions are reviewed by GOG before final submission to CTEP. Submitting a report through CTEP-AERS 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: CTEP-AERS 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 CTEP-AERS 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 CTEP-AERS 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:
CTEP-AERS 24-hour notification followed by complete report within 3 calendar days for:

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 7 calendar day report:

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

[2] Although an CTEP-AERS 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 CTEP-AERS 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 CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 3 calendar days of the initial 24-hour report.
  - "7 calendar days" - A complete CTEP-AERS 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 CTEP-AERS 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 CTEP-AERS 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 CTEP-AERS. 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 CTEP-AERS MD Help Desk at CTEP-AERSmd@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 CTEP-AERS Expedited Reports: Expedited reports are to be submitted using CTEP-AERS 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 CTEP-AERS (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 CTEP-AERS (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 CTEP-AERS 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 CTEP-AERS 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: CTEP-AERS 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 CTEP-AERS 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 CTEP-AERS 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 a commercial agent require reporting as follows:

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

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 7 calendar day report:

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

[2] Although an CTEP-AERS 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 the section entitled, "Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent." 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 CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 3 calendar days of the initial 24-hour report.

  "7 calendar days" – A complete CTEP-AERS 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) 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 to GOG via CTEP-AERS if the event occurs following treatment with a commercial agent.

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

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent:

The following events should be excluded from CTEP-AERS reporting, although they should still be reported to the routine AE CRFs:

- Grade 3 or 4 myelosuppression, with or without hospitalization **(12/19/11)**

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

10.32 Procedures for Expedited Adverse Event Reporting:

10.321 CTEP-AERS Expedited Reports: Expedited reports are to be submitted using CTEP-AERS 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.

AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v3.0, the event can be reported as: "Secondary malignancy-possibly related to cancer treatment (specify)".

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 CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

10.33 Automated CDUS reporting

For studies using commercial 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 CTEP-AERS will also be included with the quarterly CDUS data submissions.

10.4 GOG DATA MANAGEMENT FORMS (08/04/08) (06/22/09) (03/15/10)

The following forms must be completed and submitted to the GOG Statistical and Data Center (SDC) in accordance with the schedule below. All forms except: F-form, Pathology report, OP report and QOL forms should be submitted via the SDC Electronic Data Entry System (SEDES) which is available through the GOG website (www.gogstats.org). Quality of Life questionnaires are to be completed on Scantron forms and submitted by mail. Pathology material (F-form, path report and slides) should be submitted together via mail.

Form±	**Due within**		**Copies ***	**Comments**
	Weeks	**Event**		
Form R (Registration Form)	2	Registration	1	Mandatory Submission via SEDES
Form OSR (Recurrent Gynecologic Cancer - On Study Form)	2	Registration	1	Mandatory Submission via SEDES
Specimen Consent Application	1	Registration°	N/A	Complete Online
Form DR (Pretreatment Summary Form	2	Registration		Mandatory Submission via SEDES
Form D2M (Solid Tumor Evaluation Form) #	2	Registration	1	Mandatory Submission via SEDES
Primary Disease				
Form F (Pathology Form)	6	Registration	3	Submit together to the
Pathology Report	6	Registration	3	SDC via postal mail
Pathology Slides	6	Registration	**	
Secondary Cytoreductive Surgery				
Form F (Pathology Form	6	Surgery***	3	Submit together to the

Pathology Report	6	Surgery***	3	SDC via postal mail
Cytoreductive Surgery: Form C (Surgical Reporting Form) Operative Report Discharge Summary	 6 6 6	Surgery***	 1 2 2	Mandatory Submission via SEDES Submit via postal mail Submit via postal mail
Form SP-FT01-0213 for archival formalin-fixed and paraffin-embedded (FFPE) primary or metastatic tumor (FT01): 1st choice: Block 2nd choice: 16 Unstained Slides	8	Registration		Submit via SEDES *f* Ship block or unstained slides for translational research with a copy of the SP Form for FT01 to the GOG Tissue Bank in Columbus Ohio†∇
Form SP-SB01-0213 for frozen pre-op serum in ten cryotubes	1	Surgery***		Submit via SEDES *f* Ship with a copy of appropriate SP Forms to the GOG Tissue Bank in Columbus Ohio‡∇
Form SP-PB01-0213 for frozen pre-op plasma in ten cryotubes	1	Surgery***		
Form SP-FR01-0213 for fixed recurrent tumor in formalin jar or paraffin block	1	Surgery***		
Form SP-RR01-0213 for frozen recurrent tumor	1	Surgery***		
Form SP-FN01-0213 for fixed normal tissue in formalin jar or paraffin block	1	Surgery***		
Form SP-RN01-0213 for frozen normal tissue	1	Surgery***		
Form SP-WB01-0213 for whole blood (WB01) to be shipped at ambient temperature the day the blood is collected ‡‡	26	Registration (except where noted in the patient form schedule)		Submit via SEDES.*f* Ship the whole blood with a copy of the SP Form for WB01 to the GOG Tissue Bank in Columbus Ohio‡‡
Form T (Common Toxicity Reporting Form) -post op**** #	2	Surgery***	1	Mandatory Submission via SEDES
Form D2R-Cycle Dose Drug Form #	2 2	Completion of each cycle of therapy	1	Mandatory Submission via SEDES
Form T (Common Toxicity Reporting Form) #	2	Beginning of each subsequent cycle	1	Mandatory Submission via SEDES
Form D2M (Solid Tumor Evaluation Form) #	2	Clinical response assessment	1	Mandatory Submission via SEDES
Form BMR (Biomarker Reporting Form) ±	2	Prior to surgery, prior to each cycle of therapy and during follow-up	1	Mandatory Submission via SEDES
FACT-O**** (Scantron Form)	2	Prior to surgery	1	If randomized to surgery submit the original

				Scantron form to the GOG SDC via postal mail
FACT-O**** (Scantron Form)	2	Prior to cycle 1, 3 and 6 and at 6 and 12 months after starting chemotherapy.	1	Submit the original Scantron form to the GOG SDC via postal mail
Form SRGSTAT (Surgical Status Form)	52	Registration	1	Mandatory Submission via SEDES
Form Q0 (Treatment Completion Form	2	Completion of study treatment	1	Mandatory Submission via SEDES
Form Q (Follow-up Form)	2	Disease progression, death, and post-treatment follow-up	1	Mandatory submission via SEDES quarterly for 2 years, semi-annually for 3 more years, yearly thereafter

* The number of required copies including the original form which must be sent to the Statistical and Data Center if the forms are not submitted via SEDES. No copies are required for forms submitted through SEDES. Forms submitted through SEDES should not be sent through postal mail or fax.

** Pathology slides are required for central review by the GOG Pathology Committee. See Section 7.4 for details.

*** Patients who are randomized to surgical cytoreduction, submit after surgery.

**** Submit original Scantron QOL forms and coversheet to the GOG Statistical and Data Center. The patients randomized to cytoreductive surgery undergo an assessment prior to surgery as well as prior to initiating chemotherapy.

± Serial CA-125 values should be reported on Form BMR

In the event that it becomes necessary to modify the dose or stop individual study agents for either protocol directed reasons or other reasons, continue to submit D2R, T and D2M forms until all study agents are stopped or another anti-cancer therapy is initiated.

o Required only for patients randomized to undergo secondary cytoreduction surgery.

▽ Required for patients randomized to undergo secondary cytoreductive surgery Appendix III**(08/04/08)**

f Form SP **must be submitted online** to the GOG SDC using SEDES regardless of whether the specimen is submitted for research.

† See footnote 3 in the Quick Scan Summary in Section 7.31 of the protocol and Section IX of Appendix III for important details for shipping FT01 to the GOG Tissue Bank with a completed SP Form, and for instructions for how to have an optional SP Form for FT02 loaded to the patient form schedule.

‡ See footnote 6 in the Quick Scan Summary in Section 7.21 of the protocol and Section IX of Appendix III for important details for shipping the surgical specimens including FR01 and RR01 and any of the optional high priority specimens (FN01, RN01, SB01 and PB01) to the GOG Tissue Bank with the corresponding SP Forms.

‡‡ See footnote 7 in the Quick Scan Summary in Section 7.21 of the protocol and Section IX of Appendix III for important details for shipping WB01 to the GOG Tissue Bank with the corresponding SP Form.

This study will be monitored by the **Abbreviated** Clinical Data System (CDUS) Version 3.0 CDUS data will be submitted quarterly to CTEP by electronic means.

This study utilizes the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) for defining and grading adverse events to be reported on GOG case report forms. A GOG CTCAE v3.0 Manual is 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.**(09/26/11)**

11.0 STATISTICAL CONSIDERATIONS

11.1 Randomization**(10/01/12)**

The individuals enrolled into this study will have one of two systemic treatments assigned and a subset of the enrolled patients will have surgical intervention assigned through randomization. That is, all patients will be randomized to one of the following systemic therapies: (All patients enrolled after August 28, 2011 will have their surgical cytoreductive treatment determined through randomization. These patients will select one of the following systemic treatments and declare their selection prior to enrollment onto the study) **(08/29/11)(12/19/11)**

11.11 **CT**: A standard regimen consisting of carboplatin (AUC 5) and paclitaxel (175 mg/m2) every 21 days for up to 8 cycles unless toxicity or progression necessitates discontinuing treatment early.

11.12 GC: A standard regimen consisting of carboplatin (AUC 4) day 1 and gemcitabine (1000 mg/m^2) day 1 and 8 for up to 8 cycles unless toxicity or progression necessitates discontinuing treatment early.

11.13**CTB**: The standard regimen combined with bevacizumab for up to 8 cycles followed by maintenance bevacizumab until disease progression or toxicity precludes further treatment.

11.14 GCB: The standard regimen combined with bevacizumab for up to 8 cycles followed by maintenance bevacizumab until toxicity or progression necessitates discontinuing treatment early.

Also, consenting individuals, who are candidates for secondary cytoreduction, will have surgery determined through randomization:

11.15 No cytoreductive surgery

11.16 Cytoreductive surgery performed prior to initiating systemic therapy.

A procedure that tends to allocate the treatments equally across prognostic categories will be used. The prognostic categories for this study will be defined with respect to the time from completing first-line chemotherapy to registration onto this study (6-12 months vs greater than 12 months). Specifically, for those individuals who are not candidates for surgery or refuse surgery, one of the two systemic regimens will be allocated with equal probability within blocks of treatments (this sentence applies only to patients enrolled prior to Aug 29, 2011, thereafter patients select either CT, GC, GCB or CTB as their systemic treatment.). For those who consent to have cytoreductive surgery determined through randomization,