	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:

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,

the systemic therapy as well as surgery will be allocated with equal probability within blocks of treatments. The treatment assignment will remained concealed until after the patient has been successfully registered onto the study. All interim and final reports will include an accounting of all patients registered, regardless of compliance to the assigned treatment or eligibility to the study.**(08/29/11)**

11.2 Measures of Efficacy and safety

The principle observations for evaluating the therapeutic effects of treatment are:

11.21 Primary efficacy endpoint: Overall survival

11.22 Secondary efficacy endpoint: Progression-free survival (PFS)

11.23 Safety endpoints: frequency and severity of adverse events (Common Terminology Criteria for Adverse Events (CTCAE) – version 3.0).

11.3 Treatment efficacy

Overall type I error: This study includes two primary objectives. The first objective is to determine whether the addition of bevacizumab increases overall survival relative to carboplatin and paclitaxel alone. The second objective is to determine whether surgical cytoreduction increases overall survival. The study design will allocate 2.5% (one-tail) type I error to *each* of these two objectives accounting for interim analyses.

Expected median survival on the standard treatment: Previous studies indicate that the expected death rate for platinum-sensitive patients treated with a platinum-taxane regimen who do not undergo debulking surgery is approximately 0.378 $year^{-1}$ (median survival time = 22 months).

Accrual target for evaluating the efficacy of systemic therapy
The targeted accrual for this component of the study is 660 patients. It is anticipated that 240 eligible patients per year can be enrolled from GOG treatment centers. Therefore, the expected time to accrue the targeted sample size is 2.75 years. An additional 1.5 year post-accrual follow-up period is anticipated.

Statistical power for evaluating the efficacy of biologic therapy: The first objective of this study is to determine whether bevacizumab (CTB) reduces the overall death rate when compared to the standard treatment (CT). The null hypotheses: H_{01}: $\Delta_{01} = \lambda_{CTB} / \lambda_{CT} \geq 1$will be assessed, where $\lambda_{.}$is the death rate for the indicated treatment. The treatment regimens will be compared with a logrank procedure which includes ***all*** of the patients categorized by their randomly assigned treatment. This comparison will not include those patients who were enrolled after August 28, 2011 and hence selected their systemic treatment. The

type I error for this comparison will be limited to 2.5% (one-tail) accounting for the planned interim analyses. The logrank test will be stratified by the secondary surgical debulking status (randomized to undergo cytoreduction, vs randomized to not undergo secondary cytoreduction vs not a candidate or did not consent to secondary surgical cytoreduction) and the duration of treatment free-interval prior to enrolling onto this study (6-12 months vs > 12 months).**(08/29/11)(12/19/11)**

If the bevacizumab-containing regimen reduces the overall death rate 25% relative to the control regimen, then this is considered clinically significant. Assuming proportional hazards, this effect size is comparable to increasing the expected proportion surviving at least 22 months (median) 9.5% (50% vs 59.5%). In order to provide an 81% chance of detecting this effect size, the study will be considered sufficiently mature to permit a final analysis of the systemic regimens when there are at least 214 deaths (214/330=0.65) reported among those patients assigned to the standard regimen (CT). If the alternative hypothesis is true then the expected total number of deaths at the time of the final analyses is 394. The power curve for comparing the biologic-containing regimens to the control regimen is displayed in figure 1.

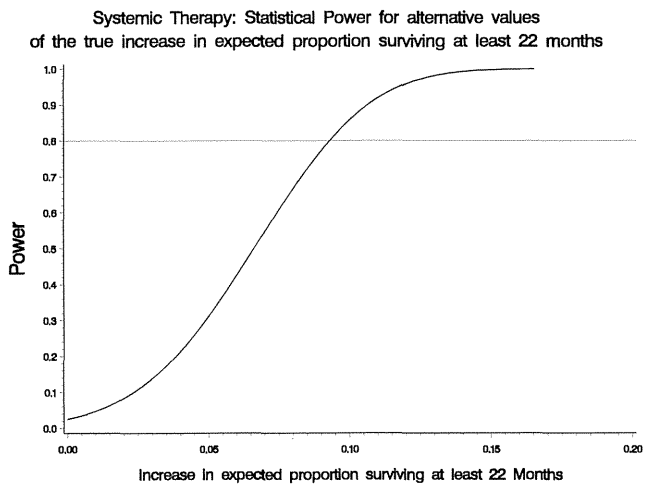

Figure 1.

Statistical Power- evaluating the efficacy of surgical cytoreduction: In order to assess the hypothesis that cytoreductive surgery does not improve overall survival (H_{02}: $\Delta_{02} = \lambda_{surgery} / \lambda_{No\ surgery} \geq 1$), only those patients who were considered candidates for surgery and consented to have their surgical treatment determined by randomization will be included in this analysis. In order to evaluate the efficacy of surgical cytoreduction, patients will be grouped by their randomly assigned surgical treatment regardless of compliance or the degree of actual tumor debulking. This hypothesis will be assessed with a logrank test stratified by their chemotherapeutic/biologic treatment (CT vs CTB vs. CG vs CGB) and the duration of the treatment-free interval prior to enrolling onto this study (6-12

months vs > 12 months). The type I error will be limited to 2.5% for a one-tail test including the error spent due to interim analyses. **(08/29/11)(10/01/12)**

This study will be considered sufficiently mature for an analysis of the surgical cytoreduction hypothesis, H_{02}, when there are at least 250 deaths reported among those enrolled (and randomized) onto the surgical component of this study. This target size provides 80% power, if surgical cytoreduction truly decreases the death rate 30%. This treatment effect size is comparable to increasing the percent surviving 22 months or longer 11.5% (50% to 61.5%). The power curve for this study objective is summarized in Figure 2. The anticipated total accrual for this component of the study is 360 patients.**(08/29/11)**

An addendum to the statistical considerations following the amendment to extend recruitment to the surgical component of the study. ***(12/19/2011)***

As of Nov-1-2011, there were 114 patients enrolled onto the surgical component of this study and 17 of these patients had died. The planned total number of patients to be enrolled onto the surgical component of this study is 360 patients. There were 35 patient enrolled during 2010, and 34 patients are projected to be enrolled during 2011. Therefore, assuming the future accrual is 35 patients per year, this study is expected to complete its targeted accrual in 7 years (Nov-2018). Patients enrolled after Aug-28-2011 will have their cytoreductive surgery determined by randomization. All of these patients will receive a standard carboplatin-paclitaxel regimen and permitted to choose whether to have bevacizumab supplement their treatment.

The data currently available from GOG-0213, indicates that the marginal hazard of death is approximately 0.021 $month^{-1}$. Assuming a constant hazard, the expected number of deaths when the accrual is completed among the 114 patients, who are already enrolled onto the surgical component of this study is 97.4. Assuming a similar death rate for all future patients, Simpson's rule (Schoenfeld, Biometrics 1983) can be used to estimate the number of patients among those who will be enrolled over the next 7 years and will have died when the accrual has been completed (130.1 deaths). Hence the expected total number deaths at the time when the target accrual is completed is 97.4+130.1 = 227.5. Likewise, the expected number of deaths reported 9 months after the targeted accrual is complete is 100.2+150.0=250.2, which is approximately the number required for the final analysis.

Therefore, the targeted date for completing the accrual to the surgical component of this study is Fall-2018. The required number of deaths required for the final analysis (250 deaths) is expected to occur nearly 1 year after the targeted accrual has been completed. In the event that the required number of deaths for the final analysis is observed before the targeted accrual is completed, then accrual will be stopped prior to attaining the targeted accrual. The planned analyses and the

power calculations provided above are unchanged by this revised recruitment plan.**(12/19/2011)**

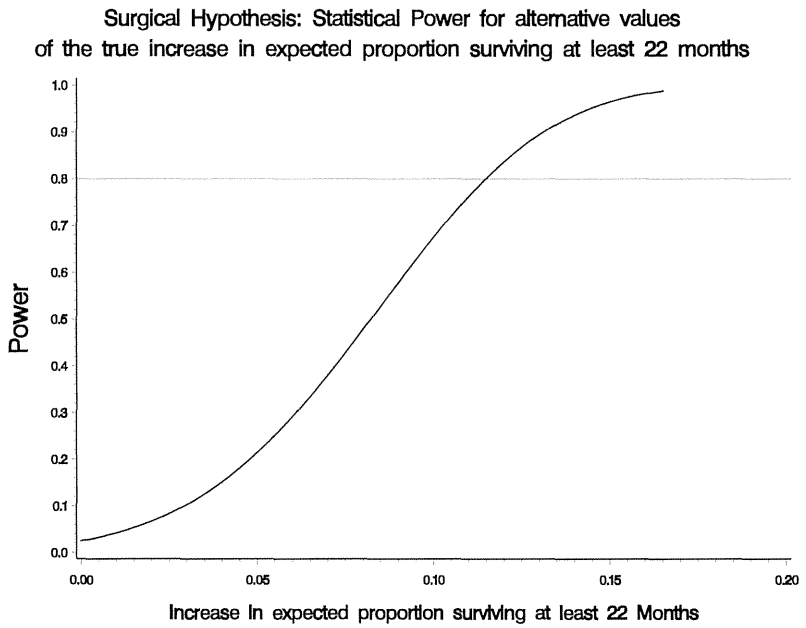

Figure 2.

The number of patients to be enrolled onto the surgical component of this study depends on the proportion of patients who are candidates for surgery and willing to have their surgical treatment determined through randomization. In the event that the targeted accrual for objective 1 (660 patients) is attained and there are too few patients enrolled who are either not candidates for surgery or do not consent to surgery (objective 2) then consideration will be given to continuing randomization to the surgical cytoreduction factor only. That is, accrual will be continued but randomization to the systemic therapies will be stopped, and only randomization to the surgical intervention will continue. Adjuvant chemotherapy will be determined at that time. In the event that the chemotherapy objectives are known, the choice of regimen will follow that finding the "winning arm". In the event that this is unknown, adjuvant therapy will be the control arm, paclitaxel and carboplatin with or without bevacizumab. It is anticipated that at least 360 patients will need to be enrolled onto the surgical component of this study.**(08/29/11)**

Interim Analyses: Interim analyses are planned when there are at least 110 deaths reported among all those patients randomly allocated (prior to August 29, 2011) to the CT regimen (approximately 50% of the full information of the systemic therapy component of this study), The actual time for the interim analyses will coincide with the nearest scheduled Data Monitoring Committee (DMC) meeting for which the required number of events has occurred. The semi-annual DMC meetings coincide with the GOG business meetings which are held in January and

July each year and the precise date of these meetings is set without confidential knowledge of the study results. **(10/01/12)**

The interim analyses will include an assessment of treatment efficacy. An alpha-spending function proposed by Lan and DeMets[82], which mimics the O'Brien and Fleming[83] group sequential boundary, will be used to calculate the critical values used for the interim analyses. The proportion of the total information available at the interim analysis will be calculated as the fraction: number of observed deaths among those randomly allocated to the CT regimen to the planned total number of deaths required for final analysis. For example, if the interim analysis occurs at 55% of the information time, H_{01} will be assessed using the previously described stratified logrank test and the critical p-value set to 0.0082 for the interim analysis and 0.0475 for final analysis. **(08/29/11)**

H_{02} will also be assessed at this interim analysis with a similar error spending function, but the critical values for this assessment will be based on the proportion of the total information calculated as the number of reported deaths among those enrolled into this component of the study relative to the total number of deaths required for the final analyses. Finally, a second interim analysis of H_{02} will occur when at least 50% of the planned number of deaths has been reported. The critical values for this assessment will be based on the error spending function, the type I error spent on the previously mentioned interim analysis, and the actual proportion of deaths reported at the time of this interim analysis.

The interim analysis that will occur at approximately the 50% of the total information time for H_{01} (or H_{02}) will also include futility analyses. Since the purpose of the study is to identify interventions that increase overall survival duration, consideration will be given to stopping randomization to the experimental interventions (CTB or cytoreductive surgery) if it exhibits poorer survival relative to its control treatment (CT or no surgical intervention, respectively) indicated by an adjusted hazard ratio, $\Delta_{01} > 1.0$ (or $\Delta_{02} > 1.0$) at the time of the interim analyses. This interim decision rule decreases the statistical power for each pair-wise comparison by less than 1%. The results of the interim analyses are reviewed by the GOG Data Monitoring Committee (DMC). The decision to terminate randomization to any particular regimen includes consideration of toxicities, treatment compliance, progression-free survival, and results from external studies.

Final analysis: The study will be considered sufficiently mature to permit a final assessment of H_{01} when there are at least 214 deaths reported among those patients assigned to the standard regimen (CT). The study will be considered sufficiently mature to permit an assessment of H_{02} when there at least 250 deaths reported among those enrolled (and randomized) onto the surgical component of this study. The previously described logrank test will be performed and the corresponding treatment hazard ratio will be estimated. The critical values for rejecting the null hypotheses will be adjusted for interim analyses, using the

O'Brien and Fleming-like type I error spending function proposed by Lan and DeMets (1986).

Supplemental final analyses: A proportional hazards model will be fitted to the survival data. Apart from the randomized therapy, other factors such as: prior exposure to bevacizumab, histologic cell type, initial performance status, and age will be included in the model as potential confounders because there exists evidence that these factors may have an effect on survival in these patients. Race and ethnicity will also be assessed, but there is no specific hypothesis concerning an interaction between these factors and treatment proposed.

Due to the lack of knowledge concerning interactions between treatments and these confounders, prior to assessing the main effects of the treatment, the homogeneity of the treatment effects will be assessed by testing the null hypothesis of no interactions. The likelihood ratio test will be performed by comparing models with and without interaction terms. Rejecting the null hypothesis of homogeneity at the 5% significance level will be considered sufficient evidence to warrant reporting the relative treatment effects within each factor and a cautious interpretation of the pooled estimates.

Safety Analyses: The GOG Data Safety and Monitoring Board (DSMB) reviews accumulating summaries of toxicities, serious adverse event (SAE) reports and deaths in which study treatment may have been a contributing cause. This committee does not review efficacy results. The DSMB may recommend study amendments pertaining to patient safety.

Grading and classification of adverse events will follow the CTCAE v. 3.0 toxicity criteria. The primary analysis will consist of comparing the relative odds of grade 3 or worse toxicities occurring during and following study treatment that are reported to be at least possibly related to study treatment. Specific attention will be given to the frequency of neutropenia, anemia, thrombocytopenia, hypertension, proteinuria, rash and gastrointestinal toxicities, which are unintended but not infrequent side effects from the study treatments. The safety analysis will focus on those patients who at least initiated study therapy. A logistic model will permit an estimate of the relative odds of grade 3 or worse adverse treatment effects for both randomized factors while adjusting for potential confounders like age. Deaths considered to be at least partially attributable to treatment will be reported and summarized. Reasons for stopping study treatment (e.g. patient refusal, toxicity, progression or death) will be reported.

11.4 Quality of Life

There are primarily three quality of life issues of interest:

11.41 Patients undergoing secondary cytoreduction may initially experience a decrease in QOL after the surgery.

11.42 Patients undergoing secondary cytoreduction may have better QOL compared to patients without surgery, after surgical healing.

11.43 Patients receiving carboplatin and paclitaxel only may experience a better QOL relative to those who receive these agents combined with bevacizumab.

The primary measures used in this study to assess the quality of life (QOL) are the self-administered FACT-O TOI for ovarian cancer patients and the Physical Functioning (PF) subscale of the Rand-SF 36. Each patient will be asked to complete these questionnaires at the following time points during their participation in the study:

i. Prior to surgery (only those undergoing surgical cytoreduction),
ii. Prior to cycle 1
iii. Prior to cycle 3 (6 weeks after staring systemic therapy),
iv. Prior to cycle 6 (12 weeks after starting systemic therapy),
v. 6 months after starting systemic therapy,
vi. 12 months after starting systemic therapy.

The times in parentheses indicate the assessment points for those patients who do not complete the entire study regimen.

Construct and content
The Functional Assessment of Cancer Therapy scale developed for ovarian cancer (FACT-O TOI) is a tool that provides a general QOL score. It consists of 3 subscales: physical well being (7 items), functional well being (7 items) and the Ovarian Cancer subscale (12 items) [43]. The Physical Functioning (PF) subscale of the Rand-SF 36 is the 10-item subscale of this general quality of life questionnaire[44].

Descriptive analyses of baseline QOL scores
Descriptive statistics from the baseline QOL data will be calculated. These will include descriptions of the distribution of QOL scores (mean, standard deviation, median, etc.). For all patients the baseline scores will be calculated using the questionnaire completed prior to treatment cycle 1, except for those undergoing cytoreductive surgery. In that case, the baseline score is calculated using the questionnaire completed prior to surgery. Therefore, comparisons involving the patients who were allocated to surgery, the effects of time are confounded with effects of surgery.

Differences in FACT-TOI scores between patients receiving CT and CTB: Data available from GOG-172 provides some estimates that can be used for planning the current study. In that study women with advanced ovarian cancer received 6 cycles of a platinum-taxane based treatment. The mean and variance of the baseline FACT-TOI scores were 67.2 and 15.9, respectively. The correlation

between the baseline FACT-TOI score and the same score reported 3 to 6 weeks after the sixth cycle of treatment was 0.36. The target sample size for this study is based on study objective 1 and is 660 patients (330 patients in each arm). It is anticipated that 90% of the patients will report FACT-TOI scores prior to initiating treatment and prior to treatment cycle 6. If bevacizumab truly changes patients' FACT-TOI scores 4.0 units after 6 cycles of treatment, the targeted sample size has about 91% power for an analysis of covariance, when the type I error is limited to 5% for a two tail test. However, a linear mixed model will be used for the final analysis of this data since this approach is more efficient, accommodates missing data, and accounts for correlations due to repeated measurements from the same individual. The actual power for this analysis, however, depends on the unknown pattern of missing values.

Difference in Rand SF-36 Physical Functioning (PF) subscale after surgery: This analysis will include those patients who were candidates for surgery and consented to have their surgical intervention determined through randomization. A paired t-test will be used to test the null hypothesis that there is no difference between baseline PF scores and the PF scores prior to cycle 1 for those patients randomized to cytoreductive surgery. The paired t-test is generally robust for moderate sample sizes when the distribution of PF scores is not normal. Data from GOG-2222 can be used for planning purposes. In that study, patients with newly diagnosed endometrial cancer completed the SF-36 PF subscale prior to initiating study treatment. When the scores are rescaled (0-100), the mean and standard deviation were 75.9 and 27.8, respectively. Assuming that at least 360 patients will be eligible and consent to participate in this component of the study, this sample size has 87% power for detecting a true difference of 9 units, when type I error is limited to 5% for a two-tail test.

Differences in FACT-TOI scores between patients undergoing cytoreductive surgery and patients not undergoing cytoreductive surgery. This analysis will include those patients who were candidates for surgery and consented to have their surgical intervention determined through randomization. There will be up to 5 or 6 time points for patients to report their FACT-TOI scores, depending on whether the patient was randomized to the secondary cytoreductive surgery arm of the study. There are no specific hypotheses being posited for how the treatment groups will differ in their mean QOL scores over time. Therefore, a linear mixed model will be used to model the difference in mean QOL scores over time. That is, the mean QOL scores will be modeled in order to compare those patients randomized to secondary cytoreductive surgery vs no surgery, as well as, the differences in mean QOL scores among the three types of systemic therapy. The model will assess whether there is evidence of a treatment-time interaction as well as whether differences in mean QOL scores between treatment groups varies as a linear or possibly a quadratic function of time.

11.5 Translational Research Statistical Considerations

Overview
The overall goal for the translational research component of this study is to discover molecular and/or biochemical profiles that may be useful for determining which patients from this patient population are likely to respond or experience longer survival. There are no specific up-front hypotheses proposed. The primary challenges related to this component of the study are the practicality of finding useful biomarker profiles from among potentially tens of thousands of biomarkers, as in the case of a gene microarray experiment. This challenge is further exasperated due to the limited number of available biologic specimens. In order to address these challenges, this study will utilize a training dataset to develop a prognostic index from the biomarker measurements and a separate and distinct validation dataset to assess the predicative value of the index. The steps to be used in this study for developing a molecular/biochemical profile are:

a) Identifying those individuals to be included in the training data set.
b) Developing an index from the molecular marker data and outcome data contained in the training set.
c) Assess reliability of the putative prognostic index.
d) Validate the putative prognostic index.

Anticipated sample size for translational objectives
The targeted accrual for the randomized systemic treatment component of this study is 660 patients. It is anticipated that 30% - 50% (approximately 198-330 patients) of these individuals will be candidates for and consent to secondary surgical cytoreduction. Only half of these individuals (99-165 patients) will be randomized to cytoreductive surgery. It is expected that viable tissue collected during cytoreductive surgery will be available in most of these cases. Also, a serum sample, which is drawn prior to surgery, will be available. The ratio of the size of the training dataset to the size of the validation dataset will range from 1:1 to 3:1.

Therefore, assuming that a biologic specimen is available from 130 eligible and evaluable patients who were treated with a randomized systemic treatment and undergoing surgery, the size of the training set is expected to range from 65-98 patients and the size of the validation dataset is expected to range from 32-65 patients.

Training and validation set
In order to establish a training dataset for the primary translational research objectives a sample of sequentially enrolled eligible and evaluable patients will be established in which at least 50 deaths have been reported. This requirement may need to be relaxed for follow-up studies since samples will eventually become depleted. A validation cohort will be derived in a similar fashion as the training cohort. That is, the training and validation cohorts will consist of sequentially enrolled eligible and evaluable patients. Individuals will not be permitted to be members of both the training and the validation cohorts.