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

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

7.23 Preparation of Normal DNA from Whole Blood **(03/16/09)**

When whole blood is submitted for GOG-0218, the GOG Tissue Bank will extract normal DNA from each specimen upon receipt and bank the DNA for research including the haplotype tagging SNP (htSNP) analysis of WNK1, GRK4 and KLKB1 to study genetic predictors of bevacizumab-induced hypertension.

7.24 Laboratory Testing **(06/26/06) (03/16/09)**

Staff at the GOG Tissue Bank will coordinate with the Chairs of the GOG Committee for Experimental Medicine and the Tissue Utilization Subcommittee as well as staff in the GOG Statistical and Data Center to distribute appropriate specimens to approved investigators for testing for this trial (see Appendix VII and below for details). The study chair for GOG-0218 will coordinate study co-chairs, scientific collaborators and members of the GOG Statistical and Data Center as needed to perform appropriate statistical analysis and to prepare abstracts, presentations, reports and manuscripts.

7.241 Angiogenic Markers **(03/16/09)**

Sections from standard blocks and the GOG-0218 TMAs will be distributed to Dr. Robert Burger to examine the immunohistochemical expression of angiogenic markers including CD-31 and VEGF. Frozen pre-treatment serum and frozen pre-treatment plasma will also be distributed in batches to Dr. Robert Burger to quantify the concentration of angiogenic factors including VEGF-A in the circulation using an enzyme-linked immunosorbent assay. Dr. Burger will be responsible for: (a) supervising all steps in the angiogenic marker analyses, (b) providing an electronic copy of the angiogenic marker data in tumor, serum and plasma linked with accurate specimen identifiers (protocol code, Bank ID, specimen code and collection date) and relevant information regarding assay dates and controls to the GOG Statistical

and Data Center for analysis, and (c) returning any unused specimens with accurate identifiers to the GOG Tissue Bank.

7.242 Genomic Analysis **(03/16/09)**

FFPE tumor (unstained thick sections on clean glass slides and a 50 μm thick scroll) and frozen tumor specimens will be distributed to Dr. Michael Birrer for genomic analysis. Dr. Birrer will be responsible for: (a) supervising all of the genomic analyses, (b) providing an electronic copy of the genomic data in FFPE tumor and frozen tumor linked with accurate specimen identifiers (protocol code, Bank ID, specimen code and collection date) and relevant information regarding assay dates and controls to the GOG Statistical and Data Center for analysis, and (c) returning any unused specimens and by-products with accurate identifiers to the GOG Tissue Bank.

7.243 Haplotype Tagging SNP Analysis **(03/16/09)**

DNA from whole blood specimens with appropriate Q/C data and/or FFPE tumor will be distributed to Dr. Douglas Levine for DNA amplification by polymerase chain reaction (PCR) and genotyping in WNK1, GRK4 and KLKB1. To adequately determine the complete genetic variation in these three candidate genes, Sequenom MALDI-TOF mass spectroscopy or TaqMan allelic discrimination assays from Applied Biosystems will be used to genotype 46 haplotype tagging SNPs (htSNPs); 22 in WNK1, 16 in GRK4 and 8 in KLKB1. Dr. Levine will be responsible for: (a) supervising all steps in the htSNP analysis, (b) providing an electronic copy of the genotyping data linked with accurate specimen identifiers (protocol code, Bank ID, specimen code and collection date) and relevant information regarding assay dates and controls to the GOG Statistical and Data Center for analysis, and (c) returning any unused DNA with accurate identifiers to the GOG Tissue Bank.

7.25 Future Research **(03/16/09)**

See Section XII in Appendix VI for important details regarding the banking and distribution of residual tumor, serum, plasma and normal DNA remaining after completion of GOG-0218 for future research.

7.3 Stained Pathology Materials for Central Review by the GOG Pathology Committee to Confirm Protocol Eligibility. **(03/16/09)**

Stained pathology slides are required for central review by the GOG Pathology Committee. At least one representative H&E stained slide (or slides) demonstrating primary site, histologic cell type, and grade, and **one** H&E stained slide showing the most advanced stage of disease will be required. When submitting H&E stained pathology material to the GOG Statistical and Data Center, individual **slides must** be labeled with GOG patient number, patient's initials as well as the surgical / pathology

accession number (e.g., S08-2355) and block identifier (e.g., A6). It is not necessary to label the slides with the source of tissue (e.g., right ovary, endometrium, cervix, left common iliac lymph node) or the date of collection. Please pack slides in a plastic slide cassette labeled with the GOG Patient number and the patient's initials. Tape the slide cassette shut and wrapped in bubble wrap or another type of padded material. Ship the stained pathology slides, two copies of both the Pathology Form F and the official pathology report in your own shipping containing using postal mail at your own expense to the Pathology Materials Coordinator at the GOG Statistical and Data Center, Roswell Park Cancer Institute, Research Studies Center, Carlton and Elm Streets, Buffalo, New York, 14263; phone (716) 845-5702. Please include the GOG Patient ID, patient initials, and protocol number in the upper right hand corner of all pages of the pathology report and black out the patient's name.

8.0 EVALUATION CRITERIA

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee.[111] Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

8.1 Definitions

8.11 Measurable Disease

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

8.12 Non-Measurable Disease

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

8.13 Target Lesions

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

8.14 Non-target lesions

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

8.2 Guidelines for Evaluation of Measurable Disease

8.21 Method of Measurement

8.211 General Aspects of Tumor Measurement

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

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

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

8.212 Specific Methods of Tumor Measurement

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

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

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

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

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

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

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

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

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

8.3 Response Criteria

8.31 Evaluation of Target Lesions

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

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

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

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

8.32 Evaluation of non-target lesions

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

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

8.322 Incomplete Response/

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

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

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

8.32221 Progression Based On Serum CA-125

Progression can be based upon serum CA-125, only during the period following completion of cytotoxic chemotherapy, if one of the three conditions are met:

1. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart

or

2. Patients with elevated CA-125 pretreatment, which never normalizes must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart

or

3. Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart

When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1).

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

8.33 Evaluation of Best Overall Response

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

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

Note:

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

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

- X In rare cases when there is evidence of disease on CT, MRI or physical examination, a discrepancy may exist between trends in CA125 levels and data from either imaging or physical examination. If there is evidence of disease on CT, MRI or physical examination, such disease is shrinking, and there is no evidence of new disease, then rising CA125 levels according to Section 8.32221 would be insufficient to determine disease progression. **(08/06/07) (06/01/09)**

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

8.4 Confirmatory Measurement/Duration of Response **(03/16/09)**

8.41 Confirmation (10/14/08) **(03/16/09)**

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

8.42 Duration of Overall Response **(03/16/09)**

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

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

8.5 Definitions Related to Evaluation Unrelated to Objective Response

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

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

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

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

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

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

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

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

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

9.0 DURATION OF STUDY

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

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

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

10.0 STUDY MONITORING AND REPORTING PROCEDURES

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

10.11 Definition of Adverse Events (AE)

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

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

10.12 Reporting Expedited Adverse Events

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

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

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

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

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

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

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

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

- Grade 4 and Grade 5 unexpected events

AdEERS 7 calendar day report:

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

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

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

March 2005

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

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

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

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

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

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

10.14 Procedures for Expedited Adverse Event Reporting:

10.141 AdEERS Expedited Reports: Expedited reports are to be submitted using AdEERS available at http://ctep.cancer.gov. The NCI guidelines for expedited adverse event reporting requirements are also available at this site. Please consult these guidelines for secondary malignancy (including AML, MDS) reporting requirements.

In the rare occurrence when Internet connectivity is lost, an AE report may be submitted using CTEP's Adverse Event Expedited Report-Single Agent or Multiple Agent paper template (available at http://ctep.cancer.gov) and faxed to 301-230-0159. A 24-hour notification is to be made to CTEP by telephone at 301-897-7497, only when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted on a paper template or a 24-hour notification phoned in must be entered electronically into AdEERS by the original submitter at the site. **(06/26/06)**

For the purposes of expedited reporting of adverse events to CTEP, unexpected events are those not listed in the Agent Specific Adverse Event List (ASAEL). The ASAEL is a subset of AEs within the Comprehensive Adverse Event and Potential Risks List (CAEPR). This list of events is based on CTEP's clinical experience with this agent and defines "expected" Grade 2 and 3 AEs not requiring hospitalization as exempt from expedited reporting. The CAEPR is a complete list of reported and/or potential AEs associated with an agent under a CTEP IND. For questions or comments regarding the ASAEL or CAEPR, please contact the AdEERS MD Help Desk at adeersmd@tech-res.com.

10.15 Automated CDUS reporting

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

10.2 GOG DATA MANAGEMENT FORMS **(06/26/06)**

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, BDR form, Pathology report, Operative report, Quality of Life forms and Quality of Life coversheet must 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 and OSO	4	Registration	1	Submit via SEDES
Form MEDH	4	Registration	1	Submit via SEDES
Form C	4	Registration	1	Submit via SEDES
Operative Report	4	Registration	2	Submit via postal mail
Form DR	4	Registration	1	Submit via SEDES
Form BDR	4	Registration	2	Submit via postal mail
Form D2M***	4	Registration	1	Submit via SEDES
Primary disease: Form F Pathology Report Pathology Slides	 6 6 6	 Registration Registration Registration	 3 3 **	Submit together to SDC via postal mail
Form D2R – cycle 1 Subsequent cycles	2 2	Completion of each cycle of therapy	1 1	Submit via SEDES
Form D2M***	2	Clinical response assessment	1	Submit via SEDES
Drug Order/Re-order Application (DORA)	20	Treatment Start	N/A	Complete online
Form T-PHRM1	2	Beginning of each subsequent cycle	1	Submit via SEDES
Form Q0	2	Completion of study Rx and change in Rx	1	Submit via SEDES
Form Q	2	Disease progression; death; normal follow-up	1	quarterly for 2 years, semi-annually for 3 more years, annually thereafter; Submit via SEDES
Quality of Life Form and Coversheet	2	Date Completed ****	1	Submit Coversheet and Scantron form via postal mail
Specimen Consent Application	1	Registration	N/A	Complete online
Form SP-FT01-0218 for archival formalin-fixed and paraffin-embedded primary or metastatic tumor (FT01): 1st choice: Block 2nd choice: Slides+Scroll	8	Registration	1	Submit via SEDES ƒ Ship block or slides+scroll for translational research with a copy of the SP Form for FT01 to the GOG Tissue Bank in Columbus Ohio † **(03/16/09)**
Form SP-RT01-0218 for frozen primary or metastatic tumor (piece of snap frozen tissue or frozen OCT mold)	8	Registration	1	Submit via SEDES ƒ Ship frozen serum with a copy of the SP Form for SB01 and SB02 to the GOG Tissue Bank in Columbus Ohio ‡ **(03/16/09)**
Form SP-SB01-0218 for frozen pre-treatment serum submitted in up to ten	8	Registration	1	

cryogenic vials				
Form SP-PB01-0218 for frozen pre-treatment plasma submitted in up to ten cryogenic vials	8	Registration	1	
Form SP-WB01-0218 for whole blood (WB01) to be shipped at ambient temperature the day the blood is collected ‡‡ **(03/16/09)**	26	Registration (except where noted in the patient form schedule) **(03/16/09)**		Submit via SEDES.*ƒ* Ship the whole blood with a copy of the SP Form for WB01 to the GOG Tissue Bank in Columbus Ohio ‡‡ **(03/16/09)**
Surgical CRF	8	30 days after any surgical procedure performed on patients while on study	2	Submit via SEDES

* The number of required copies including the original form which must be sent to the Statistical and Data Center, if not completed on-line through SEDES.

** Pathology slides are required for central review by the GOG Pathology Committee. At least one representative H&E stained pathology slide (or slides) demonstrating the primary tumor, histologic cell type, and grade, and **one** H&E stained pathology slide to show the most advanced stage of disease. See Section 7.3 for mailing instructions. **(06/26/06) (03/16/09)**

*** See footnote 12 in Section 7.1.

**** QOL is assessed at the following time points: prior to randomization, prior to cycle 4 (9 weeks after starting treatment), prior to cycle 7 (18 weeks after starting treatment), prior to cycle 13 (36 weeks after starting treatment), prior to cycle 21(60 weeks after starting treatment), and 6 months after completing study treatment (84 weeks after starting treatment). The time in parenthesis refer to patients removed from study treatment prior to completing the entire regimen. Use only Scantron forms with the header "GOG Protocol 0218". Additional QoL forms are be provided by the SDC upon request. Cover sheet must be submitted together with the Scantron form. If assessment is not performed, a cover sheet is still required and may be submitted via SEDES.

ƒ Form SP **must be submitted online** to the GOG SDC using SEDES regardless of whether the specimen is submitted for research. **(03/16/09)**

† See footnote 3 in the Quick Scan Summary in Section 7.21 of the protocol and Section IX of Appendix VI for important details for shipping FT01 to the GOG Tissue Bank with the corresponding SP Form. **(03/16/09)**

‡ See footnote 4 in the Quick Scan Summary in Section 7.21 of the protocol and Section IX of Appendix VI for important details for shipping the RT01, SB01 and PB01 specimens to the GOG Tissue Bank with the corresponding SP Forms. **(03/16/09)**

‡‡ See footnote 5 in the Quick Scan Summary in Section 7.21 of the protocol and Section IX of Appendix VI for important details for shipping WB01 to the GOG Tissue Bank and for completing the corresponding SP Form. **(10/14/08)** **(03/16/09)**

For institutions enrolling patients through CTSU, refer to Appendix VIII for special instructions for submitting data for the Specimen Consent Application and submitting SP Forms for FT01, RT01, SB01, PB01 and WB01 **(03/16/09)** to the GOG SDC. **(06/26/06)**

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.

11.0 STATISTICAL CONSIDERATIONS

11.1 **Randomization:** This study is a three-arm, double-blind, placebo-controlled randomized clinical trial. All individuals enrolled onto the study will receive standard treatment consisting of 6 cycles of carboplatin and paclitaxel (CT). The two experimental regimens will consist of standard therapy combined with either bevacizumab for 5 cycles (CTB5) or bevacizumab for 5 cycles followed by an additional 16 cycles for a total treatment time of approximately 15 months (CTB+)**(06/26/06)**. A dynamic allocation procedure will be used that tends to allocate CT, CTB5 and CTB+ in the ratio of 1:1:1 within the following stratification factors:

11.11 Stage of disease:
- 11.11.1 Stage III with maximum diameters of all gross residual disease $\leq$ 1 cm.
- 11.11.2 Stage III with maximum diameter of any gross residual disease > 1 cm.
- 11.11.3 Stage IV **(08/06/07)**

11.12 Initial performance status (0 vs 1 or 2).

Interim and final reports will include an accounting of all patients registered onto the study, regardless of their eligibility status or compliance to the assigned study treatment.

11.2 **Efficacy and toxicity measures:** (See Section 8 for definitions.) For this study the term PFS event rate will involve determining each patient's first failure event which may be due to progression, recurrence or death due to any cause. The duration a patient survives progression-free will be determined once by the clinical investigator and separately by an independent and blinded review of radiograms, and clinical data. Details concerning the independent review are contained in a separate charter. The principle observations for evaluating the therapeutic effects of treatment are:

11.21 Primary efficacy endpoint: Progression-free survival (PFS) as it is determined by the clinical investigator.
11.22 Secondary efficacy endpoint: Overall survival (OS)
11.23 Exploratory endpoint: PFS as it is determined by the independent and blinded reviewers.
11.24 Safety endpoints: frequency and severity of adverse effects (Common Terminology Criteria for Adverse Events -version 3.0).**(10/14/08)**

11.3 **Accrual goal, accrual rate and study duration: (08/06/07)(10/14/08)** The targeted accrual is 1800 patients (approximately 600 patients in each treatment group). It is anticipated that at least 250 patients per year with stage IV or suboptimal debulked stage III disease and 250 patients per year with stage III optimally debulked gross residual disease can be enrolled from GOG treatment centers. The anticipated time to accrue the targeted sample size is approximately 4.5 years from the start of the study, or approximately 2.7 years from the activation of the amendment to broaden the eligibility criteria to include patients with macroscopic optimally debulked residual (gross residual disease with the largest diameter of all residua less than or equal to 1 cm) stage III disease.

The first objective of this study is to compare each of the experimental regimens to the standard regimen. Assuming a constant PFS event rate and uniform accrual rates,

within each stratum, the anticipated time from initiating the study until PFS matures sufficiently for these two comparisons is slightly less than 5 years.

If both of the experimental regimens are superior to the standard regimen, then a second study objective is to compare the two experimental regimens to each other. The anticipated time from initiating the study until progression-free survival matures sufficiently for this comparison is approximately 6 years.

Expected median duration of survival and PFS on standard treatment
The expected median duration of overall survival and PFS for women with newly diagnosed, stage III or stage IV epithelial ovarian or primary peritoneal cancer treated with a standard platinum-taxane regimen is summarized in the following table.

Patient stratum	**Expected median PFS (months)**	**Expected median survival (months)**
Stage III gross disease > 1 cm or stage IV	13	31
Stage III with macroscopic residual disease ≤ 1 cm	16	42

Treatment efficacy: Primary hypotheses, overall type I error and power
The primary analyses of progression-free survival will include all patients enrolled onto the study regardless of eligibility or compliance to their assigned study regimen. Patients will be grouped by their randomized treatment for intention-to-treat analyses (ITT).

The first objective of this study is to determine whether bevacizumab (CTB5 or CTB+) reduces the PFS event rate when compared to the standard treatment (CT). Each of the null hypotheses: H_{01}: $\Delta_{01} = \lambda_{CT} / \lambda_{CTB5} \leq 1$ and H_{02}: $\Delta_{02} = \lambda_{CT}/\lambda_{CTB+} \leq 1$, will be assessed separately, where $\lambda_{\cdot}$ is the PFS event rate for the indicated treatment. The treatment regimens will be compared with two distinct logrank tests each of which include ***all*** of the patients enrolled into the study stratified by stage of disease (Stage III with all gross or macroscopic residual disease ≤ 1 cm vs Stage III with any gross residual >1 cm vs Stage IV) and initial performance status (0 vs 1 or 2). Since the CTB5 and CTB+ treatment regimens are equivalent over the first six cycles of therapy (initial 4.5 months) these two treatment groups can be combined during this interval and share information in order to increase the statistical power of each experimental-to-standard treatment comparison. Specifically, all of the patients will be included in the analysis of H_{01} however, the times at risk for those patients, who are randomized to receive CTB+ and survive progression-free longer than 4.5 months, will be censored at 4.5 months. Similarly, while assessing H_{02} the times at risk for those patients who are randomized to receive CTB5 and survive progression-free longer than 4.5 months, will be censored at 4.5 months. The study design will limit the overall type I error to 2.5% (one-tail) for these two comparisons accounting for the planned interim analyses and the correlation between these comparisons induced by using a common reference. Using 0.50 for the correlation between estimated hazard ratios, the one-tail type I error allocated to *each* of these comparisons is 1.35% including the error spent due to interim analyses [92]. If one of these experimental regimens truly decreases the PFS event rate 23%, this study design provides approximately a 90% chance of correctly classifying that regimen superior to the standard regimen (CT).

In the event that both experimental regimens are deemed superior to the standard regimen, the two experimental regimens (CTB5 and CTB+) will be compared to each other. In order to ensure adequate statistical power, additional patient follow-up following the evaluation of H_{01} and H_{02} will be required. The null hypothesis (H_{03}: $\Delta_{03} = \lambda_{CTB5} / \lambda_{CTB+} \leq 1$) will be assessed with a logrank test stratified by stage of disease (Stage III with all gross residual disease $\leq$ 1 cm vs Stage III with any gross residual disease > 1 cm vs Stage IV) and initial performance status (0 vs 1 and 2). Only those patients randomized to receive CTB5 or CTB+ and survive progression-free longer than 4.5 months will be included in this comparison. The type I error for testing this hypothesis will be limited to 0.05 (one-tail test). If the prolonged regimen of bevacizumab (CTB+) reduces the PFS event rate 20% relative to the shorter-duration bevacizumab regimen (CTB5) then the study design provides approximately 90% chance of declaring the CTB+ regimen more effective than the CTB5 regimen.

Interim analysis - (experimental regimens vs standard regimen)
An interim analysis of progression-free survival is scheduled to occur when there are at least 281 patients experiencing either progression or death reported among those randomized to receive the standard regimen. This time point is expected to be approximately 75% of the full information time (1045 PFS events on all three arms) for the PFS analyses when the alternative hypothesis, that both experimental regimens reduce the PFS event rate 23%, is true. Assuming a constant failure rate within each stratum and uniform accrual before (250 patients per year) and after the amendment (500 patients per year) to expand eligibility the interim analysis is expected to occur approximately 4 years after initiating the study (2.5 years after the amendment to expand eligibility criteria) depending on the actual accrual rate. An O'Brien and Fleming-like α-spending function as described by Lan and Demets (1983) will be used with the information fraction calculated as the number PFS events at the interim analysis among those patients randomized to the standard regimen to the full information of 375 PFS events on the standard regimen.

The interim analyses will include an assessment of treatment efficacy. For example, provided the interim analysis occurs at precisely 75% of the information time, each experimental regimen will be compared to the standard regimen with the previously described stratified logrank test and one-sided alpha set to 0.0044. If the study is in the accrual phase and either of these null hypotheses is rejected, then consideration will be given to terminating accrual to the standard regimen.

The interim analyses will also include futility assessments. If the previously described stratified logrank procedure indicates that the PFS event rate on an experimental arm exceeds the PFS event rate on the standard arm then consideration will be given to terminating accrual to that experimental arm. This futility analysis increases the overall type II error slightly.

Interim analysis - (short vs prolonged treatment with bevacizumab)
Only if *both* of the experimental arms are deemed superior to the standard arm with regard to the PFS event rates (H_{01} and H_{02} are rejected), then the two experimental regimens will be compared to each other. The previously described logrank test will be used to assess the null hypothesis, H_{03}. An O'Brien and Fleming-like α-spending

function as described by Lan and Demets (1983) will be used. The information fraction will be calculated as the number of patients on either the CTB5 or CTB+ arms with uncensored PFS events times greater than 4.5 months divided by the number of events required for the final analysis (710 PFS events). The interim assessment of H_{03} will coincide with either the interim assessment of H_{01} and H_{02} or the final assessment of H_{01} and H_{02} and only in the event that both of these hypotheses are rejected.

The stratified logrank procedure for assessing H_{03} will include those patients randomized to receive either CTB5 or CTB+, but exclude those patients who experienced either progression or death within 4.5 months of entering the study. If H_{01}, H_{02} and H_{03} are rejected, then consideration will be given to terminating enrollment into the study.

The interim analysis will also include a futility assessment. If the stratified logrank procedure indicates that the observed PFS event rate among those patients randomized to the CTB+ regimen is greater than the PFS event rate for those randomized to the CTB5 regimen then terminating accrual onto the CTB+ arm will be considered.

The interim analyses will also include an exploratory analysis which censors the time at risk of progression for those individuals who were considered to have experienced disease progression based *only* on rising CA-125. The time at risk for these individuals will be censored at the time of their most recent disease assessment prior progression based on CA-125.

The results of interim analyses are scheduled to be reviewed by the GOG Data Monitoring Committee (DMC) at its Semi-annual meetings. This committee meets in January and July each year. Additionally, the GOG DMC can schedule meetings that coincide with the GOG's Interim Meetings on an as needed basis. These later meetings are held in March and October each year. The precise dates for all of these meetings are set more than one year in advance by individuals who have no knowledge of efficacy results. Approximately eight weeks prior to each of the Semi-annual meetings, the study database is locked in order to prepare a progress report. If the prerequisite number of events has been attained, an interim analysis is also prepared and presented to the DMC at their next scheduled meeting. If the pre-requisite number of PFS events for an interim analysis first occurs at least eight weeks prior to the Group's Interim Meeting, then an interim analysis will be prepared and presented to the DMC in conjunction to the Group's upcoming Interim Meeting. The decision to terminate accrual to any particular regimen includes consideration of toxicities, treatment compliance, overall survival and results from external studies. Additionally, the GOG Data Safety and Monitoring Board (DSMB) reviews accumulating summaries of toxicities and all serious adverse event (SAE) reports on an ongoing basis (not efficacy results). This committee also reviews those deaths in which study treatment may have been a contributing cause. The DSMB reports to the DMC and it may recommend study amendments pertaining to patient safety.

The boundaries for assessing statistical significance will not be altered by the DMC's decision to terminate the accrual onto a particular study regimen,

Final analysis – (experimental regimens vs standard regimen)