

**Hypersensitivity reaction to carboplatin:** The occurrence of a hypersensitivity reaction to carboplatin may occur in this previously treated population. Successful retreatment has been reported with a modified dilution and infusion schedule.<sup>45,46</sup> A suggested desensitization protocol that may be used in patients with a carboplatin hypersensitivity is reduced infusion dose of 1:1000 dilution (0.1cc in 100 ml) over 1 hour, followed by a 1:100 dilution (1.0 cc in 100 ml) over 1 hour, followed by a 1:10 dilution (10 cc in 100 ml) over 1 hour, followed by 1:1 concentration for the remaining infusion. Patients experiencing a significant hypersensitivity reaction to carboplatin may be removed at the discretion of the treating physician if it is felt to be unsafe to offer a desensitization program.(08/29/11)

- 6.168 **Hypertension:** Patients receiving bevacizumab should be monitored prior to each dose with measurement of blood pressure. Medication classes used for management of patients with Grade 3 hypertension receiving bevacizumab included ACE inhibitors, Beta blockers, diuretics, and calcium channel blockers.
- For controlled hypertension, defined as systolic  $\leq$  150 mm Hg and diastolic  $\leq$  90 mmHg, continue therapy;
  - For uncontrolled hypertension (systolic  $>$  150 mm Hg or diastolic  $>$  90) or symptomatic hypertension less than CTCAE V3.0 Grade 4, hold all therapy (carboplatin, paclitaxel, and bevacizumab) for one week with anti-hypertensive therapy initiated or continued. (03/15/10)
  - If hypertension is controlled and symptomatic hypertension has resolved by three weeks after holding treatment, continue all therapy.
  - If hypertension remains uncontrolled or symptomatic hypertension, less than CTCAE V3.0 Grade 4, persists after three weeks after holding treatment, the patient is removed from study.
  - Any patient developing CTCAE V3.0 Grade 4 hypertension will be removed from study.
- 6.169 **Wound disruption:** Patients will be removed from study in the event of a wound disruption requiring medical or surgical intervention.

6.1610 **Bowel perforation/obstruction/fistula/GI leak**: For new development of bowel perforation, bowel obstruction (partial or complete), fistula, or GI leak (any grade); the patient will be taken off study treatment.

6.1611 Potential modifications for other non-hematologic toxicities with an impact on organ function of Grade 2 (or greater) require discussion with one of the study co-chairs.

6.1612 **Weight loss**: If a patient's weight changes by  $\geq 10\%$  during the course of the study, the doses of paclitaxel (or docetaxel) and bevacizumab will be recalculated. For patients undergoing the second surgical procedure the baseline weight for calculating the carboplatin and bevacizumab should be the patient's postoperative weight. (08/04/08)

6.1613 **RPLS (Reversible Posterior Leukoencephalopathy Syndrome) or PRES (Posterior Reversible Encephalopathy Syndrome)**: Hold bevacizumab in patients with symptoms/ signs suggestion of RPLS/ PRES; subsequent management should include MRI scans and control of HTN. Discontinue bevacizumab upon diagnosis of RPLS/ PRES unless the patient meets the criteria below. (03/15/10)

Note: (06/22/09)

- Resumption of bevacizumab may be considered in patients who have documented benefit from the agent, provided that RPLS was mild and has completely resolved clinically and radiographically within 2-4 weeks; decision to resume bevacizumab in these patients must be discussed with the study chair and approved by the sponsor.
- Chemotherapy may continue if the patient is considered medically stable for infusion.

6.17 No dose-escalations are allowed on this study.

6.18 **Dose modifications for Gemcitabine/carboplatin (Arms V, VI, VII, VIII) (10/01/12)**

6.181 **Carboplatin and Gemcitabine (Day1)**

Carboplatin and gemcitabine dosing on Day 1 of each cycle should be held if ANC is  $<1500/\mu\text{L}$ , Hgb is  $<8.5$  g/dL, or platelets are  $<100,000/\mu\text{L}$  within 24 hours of the scheduled treatment. The chemotherapy can be delayed for a maximum of 3 weeks until these values are achieved. Patients who fail to recover adequate

counts(with or without growth factors) within the 3 weeks will no longer receive protocol- defined chemotherapy but will enter into the maintenance phase to receive the study drug (bevacizumab or observation) alone. Study drug can be held for up to 3 weeks if carboplatin and gemcitabine are held in order to allow for same-day administration of carboplatin and gemcitabine and study drug (if chosen).

Dose adjustment for gemcitabine in combination with carboplatin for subsequent cycles is based on toxicity observed during the preceding cycle. The dose of gemcitabine should be permanently reduced to the 800 mg/m<sup>2</sup> on Days 1 and 8, in case of any of the following hematologic toxicities:

- Absolute granulocyte count <500 x 10<sup>6</sup>/L for more than 5 days
- Absolute granulocyte count <100 x 10<sup>6</sup>/L for more than 3 days
- Febrile neutropenia
- Platelets <25,000 x 10<sup>6</sup>/L
- Cycle delay of more than one week due to toxicity □If any of the above toxicities recur after the initial dose reduction for the subsequent cycles, gemcitabine should be given only on day 1 at 800□mg/m<sup>2</sup> (omit gemcitabine on Day 8).

#### **6.182 Gemcitabine Dose Modification within a Treatment Cycle (Day 8) □**

Gemcitabine dosage adjustments for hematologic toxicity within a cycle of treatment is based on the granulocyte and platelet counts taken on Day 8 of therapy, as shown in the Table.

**TABLE: Day 8, Gemcitabine Dose Modification for Hematological Toxicity □**

Absolute granulocyte count (/mm <sup>3</sup> )		Platelet count (/mm <sup>3</sup> )	Gemcitabine Dose
≥ 1500	and	≥100,000	100% D1 dose
1000–1499	and/or	75,000–99,999	50% D1 dose
<1000	and/or	<75,000	Omit D8 dose

If a patient experiences an HSR, platinum desensitization may be allowed after discussion with the Study Chair. For any other dose modifications for non-hematologic toxicity, please follow institutional practice and prescribing information (also outlined in Section 6.16). In general, for severe (Grade 3 or 4) non-hematological toxicities, except nausea/vomiting, therapy with gemcitabine should be held or decreased by 50% depending on the judgment of the treating physician. □ Patients who require discontinuation of either carboplatin or gemcitabine due to toxicity should continue receiving study drug with the non-discontinued chemotherapy to complete 6 cycles (7–10 cycles if deemed necessary by the investigator and approved by the Study Chair). Patients requiring discontinuation of both carboplatin and gemcitabine prior to disease progression should continue single-agent study drug until disease progression or unacceptable toxicity, as determined by the investigator.

7.0 STUDY PARAMETERS7.1 Observations and Tests(08/04/08) (06/22/09)(03/15/10)(10/01/12)

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

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

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

1. Must be obtained within 28 days of first treatment. For those patients randomized to cytoreductive surgery, these observations are repeated prior to initiating chemotherapy.

2. Blood pressure should be assessed at least weekly during the first cycle of bevacizumab therapy. During the time between treatments, blood pressure assessment may be done at home by the patient at the investigator's discretion.
3. Must be obtained within 14 days prior to registration. For patients randomized to cytoreductive surgery, these observations are repeated within 14 days prior to initiating chemotherapy. **(06/22/09)**
4. Must be obtained within 4 days of re-treatment with protocol therapy.
5. Urine protein should be assessed by UPCR (see Section 3.37 for details). Patients must have a UPCR < 1.0 to allow participation in the study.
6. Patients receiving bevacizumab should be monitored by urine analysis for urine protein: creatinine (UPC) ratio prior to every other dose of bevacizumab.
7. When clinically indicated.
8. For patients on prophylactic or therapeutic anticoagulation, PT INR should be monitored before each treatment. Treatment should be held for PT INR of > 1.5 on prophylactic warfarin or > therapeutic range if on full-dose warfarin.
9. For patients with a history of hearing loss; repeat as clinically indicated.
10. An initial CT scan (with intravenous and oral contrast, unless contraindicated) or MRI (with gadolinium, unless contraindicated and fat suppression sequence) of at least the abdomen and pelvis is required to establish post-surgical baseline for the extent of residual disease within 28 days prior to initiating chemotherapy. **(06/22/09)** PET-CT imaging alone cannot be used to establish extent of post-operative disease residuum unless also performed with CT or MRI as described.
11. Follow-Up Radiographic Assessment of Disease (in patients with measurable and non-measurable disease). Imaging should use the same modality and encompass the same fields as in the initial pre-treatment evaluation should be repeated with the following schedule:
  - a) Within 28 days of first treatment.
  - b) If the patient was randomized to cytoreductive surgery, then repeat radiographic assessment within 14 days of initiating chemotherapy.
  - c) **After cycle 3 (before cycle 4) of study treatment(06/22/09)**
  - d) **After cycle 6 of study treatment (06/22/09)**
  - e) **After cycle 8 of study treatment (03/15/10)**
  - f) Every three months for two years and then every 6 months after completion of chemotherapy during the maintenance/surveillance phase.

Imaging assessments as part of this protocol can be discontinued if disease progression is confirmed according to guidelines in section 8.14 and 8.15.. However, if disease progression is based only on rising CA-125 criteria, then radiographic imaging must be obtained within two weeks following the date CA-125 based progression was documented. **(08/29/11)**
12. Not required if CT or MRI of chest already performed at pre-treatment baseline.
13. Progression can be based upon serum CA-125, if one of the three conditions are met: 1. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart or 2. Patients with elevated CA-125 pretreatment, which never normalizes must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart or 3. Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart. When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1). If the patient does not meet criteria for disease progression on the basis of CA-125 elevations, then CA-125 monitoring should be continued according to schedule. **(06/22/09)**
14. See Section 7.3. QOL surveys are to be assessed for at most 6 time points:
  - a) prior to surgery (for those randomized to cytoreductive surgery).
  - b) prior to initiating chemotherapy.
  - c) prior to cycle 3 (6 weeks after starting chemotherapy).
  - d) prior to cycle 6 (15 weeks after starting chemotherapy).
  - e) 6 months after starting chemotherapy.
  - f) 12 months after starting chemotherapy.
15. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection may initiate therapy, but require weekly wound examinations until complete closure. Any occurrence of fascial dehiscence or deterioration related to the incision should be addressed according to guidelines for treatment modification in Section 6.1512 and Adverse Events reporting in Section 10.3.

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

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

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

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

## 7.3 Translational Research

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

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

submitted to the GOG Statistical and Data Center (SDC) as specified in Section 10.2.

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

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

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

Required Specimens (Specimen Codes) <sup>1</sup>	Form SP Label in Forms Tracking System <sup>2</sup>	Collection Time Points and Requirements	Deadlines and Recommendations <sup>2</sup>
Archival Formalin-Fixed and Paraffin-Embedded (FFPE) Primary or Metastatic Tumor (FT01) either <ul style="list-style-type: none"> <li>• 1<sup>st</sup> choice: Block</li> <li>• 2<sup>nd</sup> choice: 16 Unstained Slides</li> </ul>	SP-FT01-0213	Archival primary or metastatic tumor left over from a previous surgery will be a mandatory requirement for <b>women who consent and undergo surgery</b> on GOG-0213.	Ship FT01 to the <u>GOG Tissue Bank</u> using your own shipping container within 8 weeks of study entry. FT01 could also be included in the dual chamber kit if available when the other specimens were ready to ship to the Bank.  Submit Form SP for FT01 to the SDC online within 8 weeks of study entry.
Pre-Op Serum (SB01) Pre-Op Plasma (PB01)	SP-SB01-0213 SP-PB01-0213	Pre-op serum and plasma will be an optional but high priority requirement for <b>women who consent and undergo surgery</b> on GOG-0213. The blood to prepare these specimens must be collected after providing consent for this research study but prior to undergoing secondary cytoreductive surgery.	Ship the FR01 and RR01 (mandatory requirement) and any of the optional specimens (SB01, PB01, FN01 and/or RN01) to the <u>GOG Tissue Bank</u> in the dual-chamber kit within 3 days of surgery when possible as described below <sup>6</sup> and in Appendix III.
Fixed Recurrent Tumor (FR01) in a jar of formalin or embedded in a paraffin block <sup>4</sup>  Frozen Recurrent Tumor (RR01) snap frozen piece or frozen in OCT mold <sup>4</sup>	SP-FR01-0213  SP-RR01-0213	Recurrent tumor will be a mandatory requirement for <b>women who consent and undergo surgery</b> on GOG-0213. Fixed and frozen tumor will need to be removed during secondary cytoreductive surgery.	Submit Form SP for each of these specimens to the SDC online within 7 days of surgery.



Fixed Normal Tissue <sup>4,5</sup> (FN01) in a jar of formalin or embedded in a paraffin block	SP-FN01-0213	Normal tissue will be an optional but high priority requirement for <b>women who consent and undergo surgery</b> on GOG-0213. Fixed and frozen normal tissue will need to be removed during secondary cytoreductive surgery.	
Frozen Normal Tissue <sup>4,5</sup> (RN01) snap frozen piece of frozen in OCT mold	SP-RN01-0213		
Whole Blood (WB01) <sup>7</sup> to extract DNA for SNP analysis. <ul style="list-style-type: none"> <li>• Draw 10 ml blood into your own purple-top Vacutainer® tube with EDTA.</li> </ul>	SP-WB01-0213	Collect prior to or after starting treatment on this phase III trial or at any time during follow up from <b>all women on protocol who provide consent regardless of randomization and treatment</b> including women already enrolled on GOG-0213. Collect on a Monday through Friday schedule. <b>Do not collect this blood the day before a holiday.</b>	Ship WB01 to the <u>GOG Tissue Bank</u> at ambient temperature the day the blood is collected. <sup>7</sup>  Form SP for WB01 must be submitted to the SDC online using SEDES the day the blood is collected.

- <sup>1</sup> Label each specimen with the protocol number (GOG-0213), a GOG Bank ID (### - ## - G ###), a specimen code (see above) and the collection date (mm/dd/yyyy).
- <sup>2</sup> Please complete Form SP for EACH specimen and include a copy when the specimen is submitted to the GOG Tissue Bank as described in Appendix III.
- <sup>3</sup> The block or 16 unstained slides of primary tumor (FT01) must be shipped to the GOG Tissue Bank in your own shipping container using the US Postal Service at your expense. GOG Tissue Bank / Protocol GOG-0213, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, E-mail: [gogbank@nationwidechildrens.org](mailto:gogbank@nationwidechildrens.org). Refer to Section IV and Section IX in Appendix III for important instructions for preparing and shipping the archival FFPE primary and/or metastatic tumor specimens to the GOG Tissue Bank for GOG-0213. If more than one type of fixed tumor will be submitted, please label the tumor specimens sequentially using FT01 for primary tumor tissue and FT02 for metastatic tumor, and contact the GOG Statistical and Data Center to have the optional SP Form for FT02 added to the patient form schedule. In the event that it is not possible to submit the archival FFPE tumor specimen, submit the SP form via SEDES with the reason the specimen was not collected in item 5 (e.g., patient refused, not enough tumor for research, referring site won't release tumor).
- <sup>4</sup> **Quantity of tissue needed for research: Please submit as much tissue as possible for research. Gram quantities are ideal.** Visually, one gram of tissue is about the size of five quarters stacked on top of each other (i.e., one quarter in diameter and five stacked quarters in height). Please try to submit gram quantities whenever possible. Larger amounts of tissue will allow for replicate laboratory testing to be performed and will enable multiple assays to be run on the same specimen.
- <sup>5</sup> **Normal tissue can be any normal epithelial tissue including non-involved ovary, Fallopian tube, uterus, cervix, or skin. When normal epithelium is not available, please submit non-involved peritoneal surface, residual omentum, or retroperitoneal muscle.** Please try to submit normal epithelium whenever possible as this type of tissue will serve as the most appropriate control for the laboratory testing to be performed for this protocol. **Note for the pathologist**, in the unlikely event that any tumor tissue is subsequently identified within the normal tissue submitted for research, the Pathology Department at the treating institution will be informed and the material will be immediately returned for diagnostic purposes. Please try to submit as much normal tissue as possible. The larger the piece the better.
- <sup>6</sup> Ship the surgical specimens including fixed recurrent tumor (FR01) and frozen recurrent tumor and any of the optional high priority specimens (fixed normal tissue [FN01], frozen normal tissue [RN01], serum [SB01] and plasma [PB01]) to the GOG Tissue Bank in the dual-chamber kit within 3 days of surgery when possible to the GOG Tissue Bank (address provided above) with a completed SP Form for each specimen. These specimens can be shipped on a Monday through Thursday schedule for Tuesday through Friday delivery using shipping labels obtained through the GOG Tissue Bank's Kit Management application. **(08/29/11)** Refer to footnotes 4, 5 and 6 in the Quick Scan Summary of Specimen Requirements for GOG-0213 as well as Section V and Section IX in Appendix III for important instructions for preparing and shipping the surgical specimens to the GOG Tissue Bank for GOG-

0213. Refer to Section VI and Section IX in Appendix III for important instructions for preparing and shipping the frozen serum to the GOG Tissue Bank for GOG-0213. In the event that it is not possible to submit any of these specimens, submit the SP form via SEDES with the reason the specimen was not collected in item 5 (e.g., patient refused, tried but not able to draw blood or non-US site logistically infeasible, tumor not present during surgery, not enough tumor or tissue for research).

- <sup>7</sup> Whole blood specimen for GOG-0213 **MUST** be shipped to the GOG Tissue Bank (address provided above) with a completed SP Form for WB01. The blood must be shipped at ambient temperature the day it is collected as the blood will be immediately processed upon receipt at the GOG Tissue Bank. Whole blood will need to be shipped to the GOG Tissue Bank *FedEx Priority Overnight* on a Monday through Friday schedule for Tuesday through Saturday delivery using the a shipping label obtained through the GOG Tissue Bank's Kit Management application. **Do not collect blood the day before a holiday** as staff will not be available at the Bank to receive or process the blood. Refer to Section VII and Section IX in Appendix III for important instructions for preparing and shipping the whole blood specimen to the GOG Tissue Bank for GOG-0213 as the GOG Tissue Bank cannot provide Shipping Kits for submitting the whole blood specimen for this protocol. In the event that it is not possible to submit the whole blood specimens, submit the SP form via SEDES with the reason the specimen was not collected in item 5 (e.g., patient refused, tried but not able to draw blood or non-US site logistically infeasible).

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

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

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

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

Appropriate unstained sections from conventional blocks and/or TMAs, aliquots of serum or plasma, and specified concentrations of DNA with

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

#### 7.331 Light Microscopy

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

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

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

Committee on Experimental Medicine based on available funding and expertise. Reverse phase array and conventional immunoblot analyses will be performed as needed in lysates from frozen recurrent tumor tissue, microdissected recurrent tumor cells and normal tissue. Quantitative RT-PCR will be performed as needed using specific primers in RNA extracted from the appropriate type of tissue specimens. These assays will be used to identify and/or validate prognostic or predictive markers of recurrent, survival and treatment response or resistance. In addition, these assays will be used to validate individual markers identified in gene expression microarray studies (see below).

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

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

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

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

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

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

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

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

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

7.41 Patients in the secondary cytoreduction arm will complete the quality of life questionnaire packet (which includes the FACT-O and the RAND SF-36 physical functioning questionnaire) before surgery and before the first

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

- 7.42 The Quality of Life Liaison (Nurse\Data Manager) at each institution has overall responsibility for the administration of the study questionnaire.
- 7.43 The Nurse\Data Manager should read the instructions printed on the questionnaire to the patient and ensure the patient understands the instructions. It is important to assure the patient that all material on the questionnaire is confidential and will not be shared with the health care team and that it will not become part of the medical record.
- 7.44 Assistance in reading the questionnaire is permitted if the patient is unable to complete the questionnaire on her own (e.g., difficulty in reading, elderly). It is important not to influence the response of the patient. Note why the patient required assistance and what assistance was given.
- 7.45 Patients should be instructed to answer all the questions regardless of whether the symptoms or conditions asked about are related to cancer or cancer treatment. Discourage family members from being present during questionnaire completion or from influencing patient's response.
- 7.46 Review the questionnaire for completeness before the patient leaves.
- 7.47 If the patient has marked more than one answer per question, ask the patient which answer best reflects how she is feeling.
- 7.48 If the patient has skipped a question or questions, assure that she noted in the space provided that she has chosen not to answer those questions.

- 7.49 It is essential that questionnaires be completed according to the schedule described in Section 7.1.
- 7.410 If the patient refuses or cannot complete the questionnaire at any time point, she should be asked to do so at the next scheduled administration time.
- 7.411 The patient may withdraw from the quality of life section of the protocol for any reason. The reason must be documented on the form.
- 7.412 The Quality of Life Liaison may attend a training session held at a biannual GOG meeting.

## 8.0 EVALUATION CRITERIA

### 8.1 Parameters of Response – GOG RECIST Criteria

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

### 8.12 Baseline documentation of “Target” and “Non-Target” lesions

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

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

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

### 8.13 Best Response

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

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

- 8.132 Partial Response (PR) is at least a 30% decrease in the sum of longest dimensions (LD) of all *target* measurable lesions taking as reference the baseline sum of LD. There can be no unequivocal progression of *non-target* lesions and no new lesions. Documentation by two disease assessments at least 4 weeks apart is required. In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam, which is not radiographically measurable, a 50% decrease in the LD is required.
- 8.133 Increasing Disease is at least a 20% increase in the sum of LD of *target* lesions taking as references the smallest sum LD or the appearance of new lesions **within 8 weeks of study entry**. Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician within 8 weeks of study entry is also considered increasing disease (in this circumstance an explanation must be provided). In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam, which is not radiographically measurable, a 50% increase in the LD is required.
- 8.134 Symptomatic deterioration is defined as a global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression.
- 8.135 Stable Disease is any condition not meeting the above criteria.
- 8.136 Inevaluable for response is defined as having **no** repeat tumor assessments following initiation of study therapy *for reasons unrelated to symptoms or signs of disease*.
- 8.14 Progression (measurable disease studies) is defined as ANY of the following:
- At least a 20% increase in the sum of LD target lesions taking as reference the smallest sum LD recorded since study entry
  - In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam which is not radiographically measurable, a 50% increase in the LD is required taking as reference the smallest LD recorded since study entry
  - The appearance of one or more new lesions
  - Death due to disease without prior objective documentation of progression
  - Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression



- Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician (in this circumstance an explanation must be provided) **(06/22/09)**
- Progression based on serum CA-125:
  - Patients with elevated CA-125 pretreatment with normalization of CA-125 must show evidence of CA-125 during study treatment greater than or equal to two times the upper normal limit on two occasions at least one week apart  
- or -
  - Patients with elevated CA-125 pretreatment, which never normalized during study treatment must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart  
- or -
  - Patients with CA-125 in the normal range must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart

When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pretreatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1). If the disease progression is noted on imaging, then the date of progression will be the date of the imaging studies. Otherwise, the date of progression will be the date of the first CA-125 level that indicates progression. **(08/23/10)**

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

- Appearance of any new clinical, radiological or histological evidence of disease since study entry
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of recurrence
- Death due to disease without prior objective documentation of recurrence
- Progression based on serum CA-125:
  - Patients with elevated CA-125 pretreatment with normalization of CA-125 must show evidence of CA-125 during study treatment greater than or equal to two times the upper normal limit on two occasions at least one week apart  
- or -
  - Patients with elevated CA-125 pretreatment, which never normalized during study treatment must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart

- or -

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

When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pretreatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1). If the disease progression is noted on imaging, then the date of progression will be the date of the imaging studies. Otherwise, the date of progression will be the date of the first CA-125 level that indicates progression. **(08/23/10)**

- 8.15 Recurrence (following CR) is defined as ANY of the following:
- Appearance of any new clinical, radiological or histological evidence of disease since study entry
  - Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of recurrence
  - Death due to disease without prior objective documentation of recurrence
  - Increase in serum CA-125 levels as follows:
    - Patients with CA-125 in the normal range must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart. When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pretreatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1). If the disease progression is noted on imaging, then the date of progression will be the date of the imaging studies. Otherwise, the date of progression will be the date of the first CA-125 level that indicates progression. **(08/23/10)**
- 8.16 Survival is the observed length of life from entry into the study to death or the date of last contact.
- 8.17 Progression-Free Survival (measurable disease studies) is the period from study entry until disease progression, death or date of last contact.
- 8.18 Recurrence-Free Survival (non-measurable disease studies) is the period from study entry until disease recurrence, death or date of last contact.
- 8.19 Subjective Parameters including performance status, specific symptoms, and side effects are graded according to the CTCAE v3.0.

## 9.0 DURATION OF STUDY

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

## 10.0 STUDY MONITORING AND REPORTING PROCEDURES

### 10.1 ADVERSE EVENT REPORTING FOR A TRIAL EVALUATING A SURGICAL PROCEDURE (09/29/14)

#### 10.11 Definition of Adverse Events (AE)

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

#### 10.12 Reporting Expedited Adverse Events

All CTCAE v3.0 expedited AEs must be reported to the GOG. All expedited AE reports should be submitted by using the CTEP Adverse Event Reporting System (CTEP-AERS). Submitting a report through CTEP-AERS serves as notification to GOG, and satisfies the GOG requirements for expedited AE reporting.

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

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

Reporting Requirements for Adverse Events that occur within 30 Days<sup>1</sup> of the Study Procedure:

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

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

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