- Granisetron 1 mg IV (or 2 mg PO) 30 minutes prior to chemotherapy plus dexamethasone 10 mg IV, with or without lorazepam 0.5 – 2.0 mg IV 30 minutes prior to chemotherapy.
- Be sure to give prescription(s) for prevention of delayed nausea/vomiting as per institutional guidelines/standards.

5.236Dosing of Paclitaxel**(06/22/09)**

The initial dose of paclitaxel will be 175 mg/m^2. Alterations in this dose are presented in Section 6.1612. As such, patients whose body weight changes by 10% or more should undergo recalculation based on the adjusted body surface area.

5.237Dosing of bevacizumab**(06/22/09)(08/29/11)**

Bevacizumab will be administered at 15 mg/kg IV. **For patients randomized to the chemotherapy arm, the** weight at screening will be used to determine the bevacizumab dose to be used for the duration of the study. For patients undergoing the second surgical procedure **the** baseline weight for calculating the bevacizumab dose should be post-op. If a patient's weight changes by ≥ 10% during the course of the study, the bevacizumab dose will be recalculated.

5.2371 Supportive Care Guidelines for Bevacizumab
If an infusion-related adverse reaction occurs, the patient should be pre-medicated prior to subsequent doses of bevacizumab (Section 5.234); however, the infusion time for bevacizumab may not be decreased for the next infusion. If a patient experiences an infusion-associated averse event with the 60-minute infusion, all subsequent doses should be given over 90 minutes ± 15 minutes.

5.238 Dosing of Carboplatin **(03/15/10) (08/23/10) (1/3/11)**

See Appendix V for current Carboplatin dose calculation instructions

5.239 Dosing of Gemcitabine (10/01/12)
See Section 5.233

5.24 Duration of treatment – Paclitaxel or Gemcitabine and Carboplatin (Arm I, Arm III, Arm V, and Arm VII): **(06/22/09)**

5.241 Patients with measurable disease achieving clinical complete response (negative physical exam, negative CT scan or MRI and normal CA-125) (CR; Section 8.131) during the chemotherapy phase will be treated with a minimum of 6 cycles of therapy or for 2 additional cycles following the CR designation (maximum of 8 cycles), whichever is greater.

5.242 If stable or partial regression is the maximum documented response, patients will continue their chemotherapy to a maximum of 8 cycles (see Section 8.15) or adverse effects (see Section 6.0). Patients will then be

followed off therapy until documented progression occurs. (See Section 8.14) **(08/04/08)(6/22/09)**

5.243 If progressive disease is observed while on therapy, patients will have study therapy discontinued and will be treated with appropriate alternative chemotherapy.

5.244 Patients without measurable lesions as determined by a CT scan prior to initiating study treatment will continue therapy for 6 cycles or if CA-125
normalizes for 2 cycles beyond CA-125 normalization, whichever is greater as long as: the criteria for progression (See Section 8.14); and the criteria for study termination by drug toxicity (See Section 6.0) have not been met. Patients with normal CA-125 at the start of therapy (without measurable lesions) will have chemotherapy stopped after six cycles. .

5.25 Duration of treatment – Carboplatin, Bevacizumab and Paclitaxel or Gemcitabine (Arm II Arm IV, Arm VI, and Arm VIII) **(06/22/09) (03/15/10)(10/01/12)**

5.251 Patients with measurable disease achieving clinical complete response (CR; Section 8.131) during the chemotherapy phase will be treated for a minimum of 6 cycles of therapy or for 2 additional cycles following the CR designation (maximum of 8 cycles) and then begin the maintenance regimen. The maintenance phase will be continued until progression or adverse effects preclude additional treatment.

5.252 If stable or partial regression is the maximum documented response, patients will receive up to 8 cycles (minimum of 6 cycles) of therapy and then begin the maintenance regimen. The maintenance phase will be continued until progression or adverse effects preclude additional treatment.**(08/04/08)**

5.253 If progressive disease is observed while on therapy, patients in all arms will have study therapy discontinued and will be treated with appropriate alternative chemotherapy.

5.254 Patients without measurable lesions as determined by a CT scan prior to initiating study treatment will continue chemotherapy and the biologic agent for 6 cycles or if CA-125 normalizes for 2 cycles beyond CA-125 normalization, whichever is greater as long as: the criteria for progression (See Section 8.15); and the criteria for study termination by drug toxicity (See Section 6.0) have not been met. Patients with normal CA-125 at the start of therapy (without measurable disease) will have chemotherapy stopped after six cycles. The maintenance regimen will begin after completing chemotherapy and continue until progression or adverse effects preclude additional treatment.

5.26 Biometric considerations in dose calculation

Maximum body surface area used for dose calculations will be 2.0 m^2 as per GOG Chemotherapy Procedures Manual

5.3 Secondary Cytoreduction: **(06/22/09)**

The value of secondary surgical cytoreduction is being evaluated in this trial through a randomization of surgical candidates deemed appropriate by their treating physicians. Participation in the surgical randomization arm of this trial is **NOT** required for entry on this study. Patients with recurrent disease, meeting entry criteria but deemed not appropriate for surgical exploration are eligible to participate in the chemotherapy randomization. Those patients for whom their treating physicians consider appropriate for surgery will be randomized to either secondary cytoreduction or no surgery prior to a second randomization of chemotherapy. Surgical exploration should be undertaken within 28 days of registration onto this study.

5.31 Procedures and goals of secondary cytoreduction are outlined in Appendix II.

5.32 Please see Section 7.3 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.

6.0 TREATMENT MODIFICATIONS

6.1 Dose Modifications:

Since chemotherapy in the recurrent setting is largely palliative, infusion without routine use of growth factor support will be attempted. Certain chemotherapy combinations have additive hematologic toxicity and other combinations are characterized by differing hematologic toxicity. Therefore, dose modification will be based on dose-limiting toxicity (DLT) for either or both neutropenia (ANC) or thrombocytopenia (PLT) and conducted as outlined in the following table below.

If a dose reduction is indicated, recalculate chemotherapy dosages using the baseline weight and serum creatinine. **(03/15/10)**

6.11 Dose-limiting neutropenia (DLT-ANC) is defined as:

- Febrile neutropenia: febrile is defined as fever ≥ 38.5°C, with or without documented infection in the presence of an ANC of 1000 cells/mm^3 or less
- Prolonged Grade IV ANC persisting ≥ 7 days.
- Uncomplicated Grade IV ANC, < 7 days, is NOT a DLT.

6.12 Dose-limiting thrombocytopenia (DLT-PLT) is defined as:

- Grade IV thrombocytopenia (< 25,000/mm^3)
- Grade III thrombocytopenia (25,000 to 50,000/mm^3) complicated by bleeding, easy bruising, petechiae or requiring platelet transfusion (see Section 6.141)
- Uncomplicated Grade III thrombocytopenia is NOT a DLT

6.13 Guidelines for dose modification based on dose-limiting neutropenia and thrombocytopenia: (nadirs)

Table A

DLT ANC‡	DLT PLT§	First Occurrence	Second Occurrence	Third Occurrence
Yes	No	Reduce the **REGIMEN** drug doses by one level as in Table B-1 *	Add myeloid growth factor **AND** maintain all drug doses	Off Study Treatment, Follow-up Continued
Yes	Yes	Reduce the **REGIMEN** drug doses by one level as in Table B-1 *	Off Study Treatment, Follow-up Continued	
No	Yes	Decrease one AUC unit **AND** maintain other drug doses *	Off Study Treatment, Follow-up Continued	

‡ DLT-ANC: Neutropenic Dose-Limiting Toxicity (Section 6.11)

§ DLT-PLT: Thrombocytopenic Dose-Limiting Toxicity (Section 6.12)

* For patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Sections 6.161 and 6.167, dose modifications can be found in Table B-2.

6.14 Adjustments for Hematologic Toxicity **(03/15/10)**

6.141 **Hemorrhage**: Patients receiving bevacizumab who develop a CTCAE V3.0 Grade 3 hemorrhage and receiving full-dose anticoagulation will be taken off study treatment. For all other patients with CTCAE V3.0

Grade 3 hemorrhage, bevacizumab should be held until ALL of the following criteria are met (continue carboplatin and paclitaxel):

- bleeding has resolved
- blood hemoglobin level is stable (serial measures with less than 10% change)
- there is no bleeding diathesis that would increase the risk of therapy
- there is no anatomical or pathologic condition that can increase the risk of hemorrhage recurrence.

Patients who experience delay of resolution according to the above criteria for greater than 3 weeks, recurrence of Grade 3 hemorrhage, or any CTCAE V3.0 Grade 4 hemorrhage will be taken off study treatment.

6.142 **Thrombosis:(03/15/10)**

Arterial Thrombosis
Patients will be taken off study treatment for ≥ CTCAE Grade 3 arterial thrombotic events (including cerebrovascular ischemia, transient ischemic attack, cardiac ischemia/infarction, peripheral or visceral arterial ischemia) or CTCAE Grade 2 arterial thrombotic events new or worsened since beginning bevacizumab therapy.

Venous Thrombosis
All therapy (carboplatin, paclitaxel, and bevacizumab)will be held for CTCAE Grade 3 or asymptomatic CTCAE Grade 4 venous thrombosis. For patients on therapeutic anticoagulation, PT INR or PTT (whichever appropriate) should be monitored closely during bevacizumab therapy. If the planned duration of full-dose anticoagulation is ≤ 3 weeks, treatment should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is > 3 weeks, treatment may be resumed

during the period of full dose anticoagulation if ALL of the following criteria are met (otherwise the patient will be taken off study treatment):

- The patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin (or other anticoagulant) or on stable dose of heparin prior to restarting treatment.
- The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels).
- The subject must not have had hemorrhagic events while on study.
- The patient is benefiting from treatment (no evidence of disease progression).

Patients with symptomatic CTCAE Grade 4, or recurrent/worsening thromboembolic events after resumption of bevacizumab, will be taken off study treatment.

6.143 **Coagulopathy**: For CTCAE V3.0 Grade 3 or 4 coagulopathy: hold all therapy (carboplatin, paclitaxel, and bevacizumab), until PT resolves to Grade 1. For patients with PT/INR > therapeutic range while on therapeutic warfarin, hold treatment until PT/INR within therapeutic range. Patients experiencing treatment delay >3 weeks because of failure to meet the above criteria will be taken off study. **(06/22/09) (03/15/10)**

Table B-1 Regimen modifications for DLTs (6.11-613), hematologic toxicities (6.141-6.143) and delayed hematologic toxicity (6.153)(03/15/10)

Arm	Drug	Level –1	Starting Dose
I and III	Paclitaxel *	135 mg/m^2	175 mg/m^2
	Carboplatin	AUC 4	AUC 5
II and IV	Paclitaxel *	135 mg/m^2	175 mg/m^2
	Bevacizumab	15 mg/kg	15 mg/kg
	Carboplatin	AUC 4	AUC 5

* See Table B-2 below, for patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Sections 6.161 and 6.167.

Table B-2 Dose Levels for Docetaxel*

Arm	Drug	Level –1	Starting Dose
I-IV	Docetaxel	65 mg/m^2	75 mg/m^2

* For patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Sections 6.161 and 6.167.

6.15 General Guidelines for **Delayed Hematologic Toxicity**

6.151 No subsequent chemotherapy cycle shall begin until the absolute neutrophil count (ANC) ≥ 1,500/mcl and platelets ≥ 100,000/mcl. No subsequent cycle of maintenance bevacizumab shall begin until the ANC is ≥ 1000/mcl and platelets are ≥ 75,000/mcl. **(03/15/10)**

6.152 Failure of the counts to recover appropriately by day 21 will require delay of the subsequent treatment until adequate count recovery.

6.153 Patients who require a delay of greater than 1 but ≤ 2 weeks for adequate count recovery (with or without growth factors) will have subsequent treatment with a one level dose reduction. Patients who have a second delay of greater than 7 days will require the use of myeloid growth factors in all subsequent cycles. Patients who have a delay of > 2 weeks will have a one level dose reduction and the addition of myeloid growth factors in all subsequent cycles. **(03/15/10)**

6.154 Patients who require a delay of greater than 3 weeks for adequate count recovery (with or without growth factors) will be removed from study treatment, but follow-up will continue.

6.155 There will be no dose modification on the basis of uncomplicated WBC or ANC nadirs.

6.156 Patients will NOT receive prophylactic thrombopoietic agents on this study.

6.1561 Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia.

6.1562 Patients may not receive amifostine or other protective reagents, unless indicated in the study design.

6.16 Adjustments for Non-hematologic Toxicity

Individual agents may be associated with specific non-hematological toxicity which warrants dose modification. Allowable dosing modifications are presented in the following table:

Table C Regimen modifications for non-hematologic toxicities (see dose adjustments per toxicity type as outlined below

Agent	-2 Level	-1 Level	Starting Dose Level
Carboplatin	Off study treatment	AUC 4	AUC 5
Paclitaxel	110 mg/m^2	135 mg/m^2	175 mg/m^2
Bevacizumab	Off study treatment	15 mg/kg	15 mg/kg
Docetaxel *	55 mg/m^2	65 mg/m^2	75 mg/m^2

* For patients in whom docetaxel has been substituted for paclitaxel according to guidelines in Sections 6.161 and 6.167.

6.161 **Neurologic toxicity:** Grade 2 (or greater) peripheral neuropathy requires reduction of one dose level in paclitaxel and delay in subsequent therapy (all agents) for a maximum of 3 weeks until recovered to grade 1. If peripheral neuropathy fails to recover to Grade 1 by a maximum delay of three weeks from time therapy is due then paclitaxel should be withheld from all subsequent chemotherapy cycles. For patients with persistent Grade 2 neurotoxicity, substitute docetaxel, unless medically contraindicated, according to Section 5.233.**(03/15/10)** Patients with persistent Grade 3-4 neurotoxicity should be removed from study.

In such cases where docetaxel has been substituted for paclitaxel, if CTCAE Grade 3 or 4 peripheral neuropathy occurs during or after the first cycle of docetaxel substitution then subsequent doses of docetaxel will be delayed for a maximum of three weeks until recovered to CTCAE Grade ≤ 2. If peripheral neuropathy fails to recover to Grade ≤ 2 by a maximum delay of three weeks from time therapy is due, then the patient is removed from study. **(08/23/10)**

6.162 **Gastrointestinal toxicity:** There will be no dose modifications for nausea, diarrhea, or constipation. It is recommended that routine medical measures be employed to manage nausea and constipation.

6.163 **Renal toxicity:** If renal function worsens on therapy, an investigation for underlying causes should be undertaken. Calculated or measured creatinine clearance under 40 ml/min or significant worsening of the renal function (50% reduction in calculated CrCl) requires withholding treatment until a cause is identified or renal function improves. In particular, disease progression should be ruled out. In these patients creatinine clearance should be evaluated weekly. If calculated or measured CrCl is less than 40 ml/min after a two-week delay, the Study Chair must be notified. No treatment is to be given to a patient with a calculated or measured CrCl less than 40 ml/min.

6.164 **Proteinuria:(06/22/09)** Patients receiving bevacizumab should be monitored by urine analysis for urine protein: creatinine (UPC) ratio prior to every other dose of bevacizumab.

UPC ratio ≤ 3.5 (CTCAE, v3.0 Grade 0-2) Continue bevacizumab. UPC ratio > 3.5 hold bevacizumab until UPC ratio recovers to ≤3.5. If bevacizumab is held for > 3 weeks, the patient is removed from study. Grade 4 or nephrotic syndrome: Patient is removed from study.
*** Please note chemotherapy may be administered if bevacizumab is held for Grade 3 proteinuria.**

6.165 **Hepatic toxicity:** Hepatic toxicity is not expected as a direct complication of chemotherapy in this population using the prescribed dose and schedule for each regimen. However, the development of grade 3 (or greater) elevations in SGOT (AST), alkaline phosphatase or bilirubin requires reduction of one dose level in all study drugs with the exception of carboplatin and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1. If therapy is held for > 3 weeks the patient is removed from study.

6.166 There will be no dose modifications for alopecia.

6.167 **Hypersensitivity reaction to paclitaxel or bevacizumab:** The occurrence of a hypersensitivity reaction to paclitaxel or bevacizumab is **not** considered a dose-limiting toxicity. Patients may be retreated at full doses after administration of medication (such as decadron 20 mg IV and diphenhydramine 50 mg IV 30 minutes prior to reinfusion) to prevent hypersensitivity reaction and may utilize a slow initial infusion rate of the suspected agent which is gradually increased to the standard infusion rate in the absence of reaction (such as 1 cc of the original IV solution diluted in 100 ml over 10 minutes, then 5 cc in 100 ml over 10 minutes then 10 cc in 100 ml over 10 minutes and finally, the original solution at the original speed). However, if despite these safety measures repeat attempt at infusion of the inciting drug results in a recurrent hypersensitivity reaction, the inciting drug should be discontinued for the remainder of the study. In the event of any CTCAE Grade 3 or 4 allergic or infusional reactions to bevacizumab, the patient is removed from study. In the event of recurrent hypersensitivity reaction to paclitaxel, docetaxel should be substituted for paclitaxel, according to guidelines in Sections 5.233 and 6.161.

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.[45,46] 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 ≥ 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/μL, Hgb is <8.5 g/dL, or platelets are <100,000/μL 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^2 on Days 1 and 8, in case of any of the following hematologic toxicities:

- Absolute granulocyte count <500 x 10^6/L for more than 5 days
- Absolute granulocyte count <100 x 10^6/L for more than 3 days
- Febrile neutropenia
- Platelets <25,000 x 10^6/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^2 (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^3)		Platelet count (/mm^3)	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 PARAMETERS

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

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

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

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

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

2. Blood pressure should be assessed at least weekly during the first cycle of bevacizumab therapy. During the time between treatments, blood pressure assessment may be done at home by the patient at the investigator's discretion.
3. Must be obtained within 14 days prior to registration. For patients randomized to cytoreductive surgery, these observations are repeated within 14 days prior to initiating chemotherapy. **(06/22/09)**
4. Must be obtained within 4 days of re-treatment with protocol therapy.
5. Urine protein should be assessed by UPCR (see Section 3.37 for details). Patients must have a UPCR < 1.0 to allow participation in the study.
6. Patients receiving bevacizumab should be monitored by urine analysis for urine protein: creatinine (UPC) ratio prior to every other dose of bevacizumab.
7. When clinically indicated.
8. For patients on prophylactic or therapeutic anticoagulation, PT INR should be monitored before each treatment. Treatment should be held for PT INR of > 1.5 on prophylactic warfarin or > therapeutic range if on full-dose warfarin.
9. For patients with a history of hearing loss; repeat as clinically indicated.
10. An initial CT scan (with intravenous and oral contrast, unless contraindicated) or MRI (with gadolinium, unless contraindicated and fat suppression sequence) of at least the abdomen and pelvis is required to establish post-surgical baseline for the extent of residual disease within28 days prior to initiating chemotherapy.**(06/22/09)** PET-CT imaging alone cannot be used to establish extent of post-operative disease residuum unless also performed with CT or MRI as described.
11. Follow-Up Radiographic Assessment of Disease (in patients with measurable and non-measurable disease). Imaging should use the same modality and encompass the same fields as in the initial pre-treatment evaluation should be repeated with the following schedule:
    a) Within 28 days of first treatment.
    b) If the patient was randomized to cytoreductive surgery, then repeat radiographic assessment within 14 days of initiating chemotherapy.
    c) **After cycle 3 (before cycle 4) of study treatment(06/22/09)**
    d) **After cycle 6 of study treatment (06/22/09)**
    e) **After cycle 8 of study treatment (03/15/10)**
    f) Every three months for two years and then every 6 months after completion of chemotherapy during the maintenance/surveillance phase.
    Imaging assessments as part of this protocol can be discontinued if disease progression is confirmed according to guidelines in section 8.14 and 8.15.. However, if disease progression is based only on rising CA-125 criteria, then radiographic imaging must be obtained within two weeks following the date CA-125 based progression was documented.**(08/29/11)**
12. Not required if CT or MRI of chest already performed at pre-treatment baseline.
13. Progression can be based upon serum CA-125, if one of the three conditions are met: 1. Patients with elevated CA-125 pretreatment and normalization of CA-125 must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart or 2. Patients with elevated CA-125 pretreatment, which never normalizes must show evidence of CA-125 greater than or equal to two times the nadir value on two occasions at least one week apart or 3. Patients with CA-125 in the normal range pretreatment must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart. When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1).If the patient does not meet criteria for disease progression on the basis of CA-125 elevations, then CA-125 monitoring should be continued according to schedule. **(06/22/09)**
14. See Section 7.3. QOL surveys are to be assessed for at most 6 time points:
    a) prior to surgery (for those randomized to cytoreductive surgery).
    b) prior to initiating chemotherapy.
    c) prior to cycle 3 (6 weeks after starting chemotherapy).
    d) prior to cycle 6 (15 weeks after staring chemotherapy).
    e) 6 months after starting chemotherapy.
    f) 12 months after starting chemotherapy.
15. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection may initiate therapy, but require weekly wound examinations until complete closure. Any occurrence of fascial dehiscence or deterioration related to the incision should be addressed according to guidelines for treatment modification in Section 6.1512 and Adverse Events reporting in Section 10.3.

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

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

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

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

7.3 Translational Research

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

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

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

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

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

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

Required Specimens (Specimen Codes)[1]	**Form SP Label** in Forms Tracking System[2]	**Collection Time Points and Requirements**	**Deadlines and Recommendations** [2]
Archival Formalin-Fixed and Paraffin-Embedded (FFPE) Primary or Metastatic Tumor (FT01) either • 1st choice: Block • 2nd choice: 16 Unstained Slides	SP-FT01-0213	Archival primary or metastatic tumor left over from a previous surgery will be a mandatory requirement for **women who consent and undergo surgery** on GOG-0213.	Ship FT01 to the GOG Tissue Bank using your own shipping container within 8 weeks of study entry. FT01 could also be included in the dual chamber kit if available when the other specimens were ready to ship to the Bank. 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 **women who consent and undergo surgery** on GOG-0213. The blood to prepare these specimens must be collected after providing consent for this research study but prior to undergoing secondary cytoreductive surgery.	Ship the FR01 and RR01 (mandatory requirement) and any of the optional specimens (SB01, PB01, FN01 and/or RN01) to the GOG Tissue Bank in the dual-chamber kit within 3 days of surgery when possible as described below [6] and in Appendix III. Submit Form SP for each of these specimens to the SDC online within 7 days of surgery.
Fixed Recurrent Tumor (FR01) in a jar of formalin or embedded in a paraffin block [4] Frozen Recurrent Tumor (RR01) snap frozen piece or frozen in OCT mold [4]	SP-FR01-0213 SP-RR01-0213	Recurrent tumor will be a mandatory requirement for **women who consent and undergo surgery** on GOG-0213. Fixed and frozen tumor will need to be removed during secondary cytoreductive surgery.	

Fixed Normal Tissue[4,5](FN01) in a jar of formalin or embedded in a paraffin block Frozen Normal Tissue[4,5](RN01) snap frozen piece of frozen in OCT mold	SP-FN01-0213 SP-RN01-0213	Normal tissue will be an optional but high priority requirement for **women who consent and undergo surgery** on GOG-0213. Fixed and frozen normal tissue will need to be removed during secondary cytoreductive surgery.	
Whole Blood (WB01)[7] to extract DNA for SNP analysis. • Draw 10 ml blood into your own purple-top Vacutainer® tube with EDTA.	SP-WB01-0213	Collect prior to or after starting treatment on this phase III trial or at any time during follow up from **all women on protocol who provide consent regardless of randomization and treatment** including women already enrolled on GOG-0213. Collect on a Monday through Friday schedule. **Do not collect this blood the day before a holiday.**	Ship WB01 to the GOG Tissue Bank at ambient temperature the day the blood is collected.[7] Form SP for WB01 must be submitted to the SDC online using SEDES the day the blood is collected.

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

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

[3] The block or 16 unstained slides of primary tumor (FT01) must be shipped to the GOG Tissue Bank in your own shipping container using the US Postal Service at your expense. GOG Tissue Bank / Protocol GOG-0213, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, E-mail: gogbank@nationwidechildrens.org.Refer to Section IV and Section IX in Appendix III for important instructions for preparing and shipping the archival FFPE primary and/or metastatic tumor specimens to the GOG Tissue Bank for GOG-0213.If more than one type of fixed tumor will be submitted, please label the tumor specimens sequentially using FT01 for primary tumor tissue and FT02 for metastatic tumor, and contact the GOG Statistical and Data Center to have the optional SP Form for FT02 added to the patient form schedule. In the event that it is not possible to submit the archival FFPE tumor specimen, submit the SP form via SEDES with the reason the specimen was not collected in item 5 (e.g., patient refused, not enough tumor for research, referring site won't release tumor).

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

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

6 Ship the surgical specimens including fixed recurrent tumor (FR01) and frozen recurrent tumor and any of the optional high priority specimens (fixed normal tissue [FN01], frozen normal tissue [RN01], serum [SB01] and plasma [PB01]) to the GOG Tissue Bank in the dual-chamber kit within 3 days of surgery when possible to the GOG Tissue Bank (address provided above) with a completed SP Form for each specimen. These specimens can be shipped on a Monday through Thursday schedule for Tuesday through Friday delivery using shipping labels obtained through the GOG Tissue Bank's Kit Management application.**(08/29/11)** Refer to footnotes 4, 5 and 6 in the Quick Scan Summary of Specimen Requirements for GOG-0213 as well as Section V and Section IX in Appendix III for important instructions for preparing and shipping the surgical specimens to the GOG Tissue Bank for GOG-

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

[7] Whole blood specimen for GOG-0213 **MUST** be shipped to the GOG Tissue Bank (address provided above) with a completed SP Form for WB01. The blood must be shipped at ambient temperature the day it is collected as the blood will be immediately processed upon receipt at the GOG Tissue Bank. Whole blood will need to be shipped to the GOG Tissue Bank *FedEx Priority Overnight* on a Monday through Friday schedule for Tuesday through Saturday delivery using the a shipping label obtained through the GOG Tissue Bank's Kit Management application. **Do not collect blood the day before a holiday** as staff will not be available at the Bank to receive or process the blood. Refer to Section VII and Section IX in Appendix III for important instructions for preparing and shipping the whole blood specimen to the GOG Tissue Bank for GOG-0213as 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).