SUMMARY OF CHANGES

For Protocol Revision # 17 to:

NCI Protocol #: GOG-0213

Protocol Date: November 16, 2018

This amendment is being submitted in response to an RA from Dr. Helen Chen (helen.chen@nih.gov).

#	Section	Page(s)	Change
1	Title Page	1	NCI version date has been updated. Includes revisions #1-17. Revised footer has been added.
2	3.15		Language has been updated to reflect the use of CTCAE 4.0.

3	4.36	33-38	An updated and revised CAEPR for Bevacizumab has been inserted (Version 2.5, May 2, 2018), and includes the following changes:
			
			• The section below utilizes CTCAE 5.0 language unless otherwise noted.
			• The SPEER grades have been updated.
			• The footnotes have been reordered.
			
			• Increase in Risk Attribution:
			  • Changed to Rare but Serious from Also Reported on Bevacizumab Trials But With Insufficient Evidence for Attribution: Pulmonary hypertension
			
			• Provided Further Clarification
			  • Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy) is now reported as Hemolytic uremic syndrome.
			  • Acute coronary syndrome *(CTCAE 4.0 language)* is now reported as Chest pain - cardiac.
			  • Renal and urinary disorders - Other (nephrotic syndrome) *(CTCAE 4.0 language)* is now reported as Nephrotic syndrome.
			  • Vascular disorders - Other (arterial thromboembolic event) *(CTCAE 4.0 language)* is now reported as Arterial thromboembolism.
			  • Blood and lymphatic system disorders - Other (idiopathic thrombocytopenia purpura) *(CTCAE 4.0 language)* is now reported as Thrombotic thrombocytopenic purpura.
			  • Eye disorders - Other (floaters) is now reported as Floaters.
			  • Eye disorders - Other (vitreous hemorrhage) is now reported as Vitreous hemorrhage.

#	Section	Page(s)	Change
			• Musculoskeletal and connective tissue disorder - Other (aseptic necrotic bone) *(CTCAE 4.0 language)* is now reported as Osteonecrosis. • Renal and urinary disorders - Other (dysuria) *(CTCAE 4.0 language)* is now reported as Dysuria. • Musculoskeletal and connective tissue disorder - Other (myasthenia gravis), previously under the MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS SOC *(CTCAE 4.0 language),* is now reported as Myasthenia gravis under the NERVOUS SYSTEM DISORDERS SOC. • Infusion related reaction, previously under the GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS SOC *(CTCAE 4.0 language),* is now reported under the INJURY, POISONING AND PROCEDURAL COMPLICATIONS SOC.
4	4.37		Language has been updated to reflect the use of CTCAE 5.0.
5	6.0		Throughout section 6, language has been updated to reflect the use of CTCAE 4.0.
6	8.19		Language has been updated to reflect the use of CTCAE 4.0.
7	10.12		Expedited Reporting via CTEP-AERS has been changed to CTCAE 5.0.
8	10.13		Language has been added to reflect the use of CTCAE 5.0 for Expedited Reporting.
9	10.141		Language has been added to reflect the use of CTCAE 5.0 for Expedited Reporting.
10	10.23		Language has been added to reflect the use of CTCAE 5.0 for Expedited Reporting.
11	10.241		Language has been added to reflect the use of CTCAE 5.0 for Expedited Reporting.

#	Section	Page(s)	Change
12	10.31		Language has been added to reflect the use of CTCAE 5.0 for Expedited Reporting.
13	10.321		Language has been modified to reflect the use of CTCAE 5.0.
14	11.0		Throughout section 11, language has been updated to reflect the use of CTCAE 4.0.
15	IC		NCI Version Date has been updated.
16	IC		An updated and revised condensed risk profile for Bevacizumab has been inserted (Version 2.5, May 2, 2018), and includes the following changes: • Provided Further Clarification: • Damage to the organs which may cause loss of teeth or loss of motion (under Occasional) is now reported as part of Damage to the jawbone which may cause loss of teeth (under Occasional) and Damage to organs (bone, lungs, others) which may cause loss of motion (under Rare).

PROTOCOL GOG-0213

A PHASE III RANDOMIZED CONTROLLED CLINICAL TRIAL OF CARBOPLATIN AND PACLITAXEL (OR GEMCITABINE) ALONE OR IN COMBINATION WITH BEVACIZUMAB (NSC #704865,) FOLLOWED BY BEVACIZUMAB AND SECONDARY CYTOREDUCTIVE SURGERY IN PLATINUM-SENSITIVE, RECURRENT OVARIAN, PERITONEAL PRIMARY AND FALLOPIAN TUBE CANCER. NCI-SUPPLIED AGENTS: BEVACIZUMAB (NSC #704865) **(12/19/2011) (10/01/12) NCT# 00565851**

NCI Version 11/16/2018

Includes Revisions #1-17

POINTS:

PER CAPITA –14

MEMBERSHIP –6 and 6 additional if surgical candidate is randomized

TRANSLATIONAL RESEARCH PER CAPITA – Award based on specimen submission with 1 point for each FFPE tumor (primary, metastatic, recurrent), 1 point for frozen recurrent tumor, 0.5 point for frozen normal tissue, 0.5 point for FFPE normal tissue, 0.5 point for pre-op serum, 0.5 point for pre-op plasma, and 0.5 point for whole blood (MAX = 6.5 points). **(03/09/15)**

TRANSLATIONAL RESEARCH MEMBERSHIP - Bonus membership point will be awarded for **submission of satisfactory** fixed primary tumor, frozen recurrent tumor, fixed recurrent tumor, frozen serum and frozen plasma.

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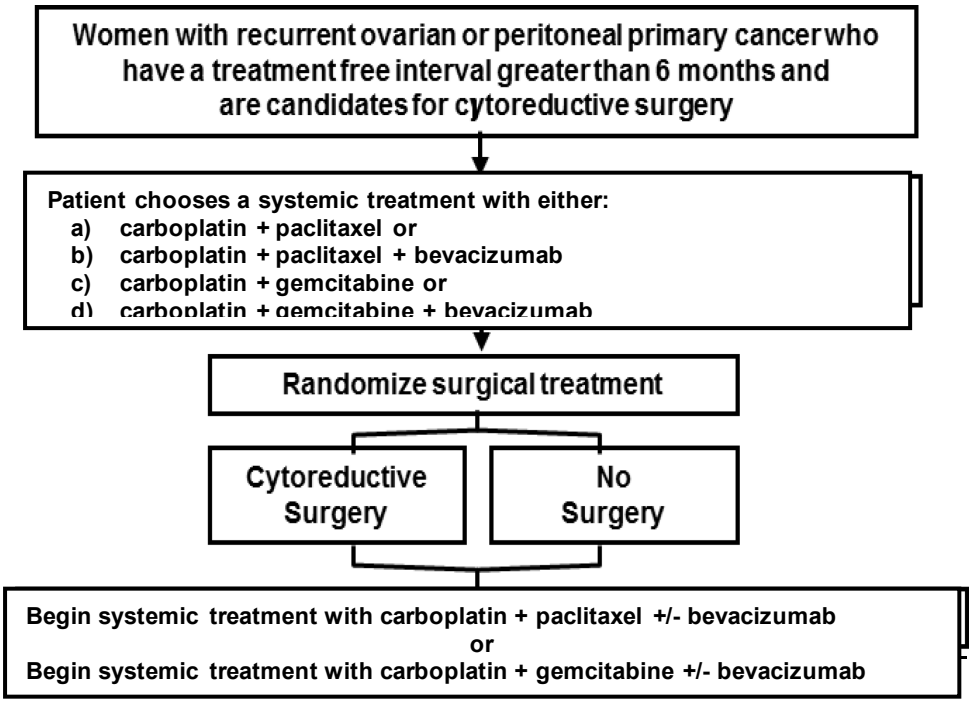
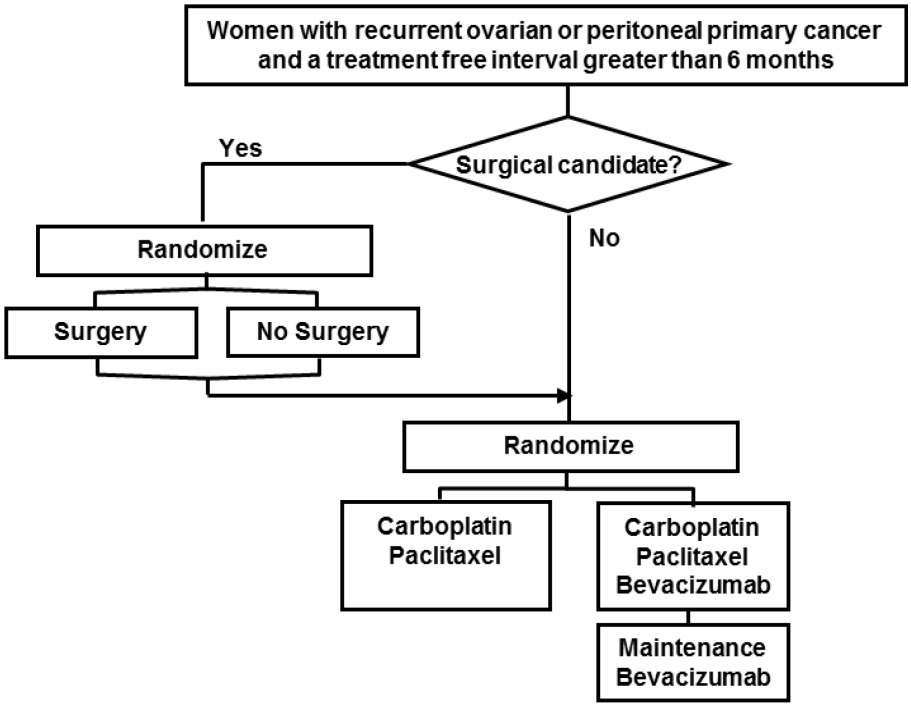
OPEN TO PATIENT ENTRY DECEMBER 06, 2007; REVISED AUGUST 4, 2008; REVISED JUNE 22, 2009; REVISED MARCH 15, 2010; REVISED AUGUST 23, 2010; REVISED JANUARY 3, 2011 REVISED AUGUST 29, 2011; REVISED SEPTEMBER 26, 2011; REVISED DECEMBER 19, 2011, REVISED OCTOBER 1, 2012; REVISED AUGUST 19, 2013; REVISED SEPTEMBER 29, 2014; REVISED MARCH 9, 2015; REVISED JUNE 15, 2015; REVISED OCTOBER 13, 2015; REVISED OCTOBER 3, 2016; REVISED

SCHEMA beginning 8/29/2011(08/29/11) (12/19/11) (10/01/12)



The following schema was in effect between 12/6/2007 to 8/28/2011. Once the accrual goal for evaluating the chemotherapy regimens was attained, that randomization was eliminated and only the surgical randomization remains (see the schema above) .**(08/29/11)(12/19/11)**

SCHEMA **(06/22/09)**



Post-surgical randomization treatment options now include either paclitaxel or gemcitabine in combination with carboplatin. Either chemotherapy doublet may be administered with bevacizumab at the discretion of the investigator. If chosen, bevacizumab maintenance is given until disease progression or unacceptable toxicity. **(10/01/12) (03/09/15)**

TABLE OF CONTENTS (08/04/08) (06/22/09)

1.0 OBJECTIVES

1.1 Specific Hypotheses: **(08/04/08)**

Two principle hypotheses will be directly addressed in this randomized, phase III clinical trial in recurrent platinum-sensitive ovarian, peritoneal primary or Fallopian tube cancer patients.

1.11 Surgical secondary cytoreduction prior to adjuvant chemotherapy increases the duration of overall survival in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer.

1.12 The addition of bevacizumab to second-line paclitaxel and carboplatin and maintenance phases of treatment increases the duration of overall survival relative to second-line chemotherapy alone in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary, or Fallopian tube cancer.

1.2 Primary Objectives:

1.21 To determine if surgical secondary cytoreduction in addition to adjuvant chemotherapy increases the duration of overall survival in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer.

1.22 To determine if the addition of bevacizumab to the second-line and maintenance phases of treatment increases the duration of overall survival relative to second-line paclitaxel and carboplatin alone in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer.

1.3 Secondary objectives: **(08/04/08)**

1.31 To determine if the addition of bevacizumab to the second-line and maintenance phase of treatment increases the duration of progression-free survival relative to second-line paclitaxel and carboplatin alone in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer.

1.32 To prospectively determine the incidence of carboplatin and paclitaxel hypersensitivity in these patients undergoing retreatment with both agents as first recurrence therapy.

1.33 To determine if surgical secondary cytoreduction in addition to adjuvant chemotherapy increases quality of life (QOL) in patients with recurrent platinum sensitive epithelial ovarian cancer, peritoneal primary or Fallopian tube cancer, as measured by the FACT-O trial outcome index and Rand SF-36 physical functioning scale.

1.34 To determine if the addition of bevacizumab to the second-line and maintenance phases of treatment increases QOL relative to second-line paclitaxel and carboplatin alone in patients with recurrent platinum sensitive epithelial ovarian, peritoneal primary or Fallopian tube cancer.

1.4 Translational Research Hypotheses **(08/04/08)**

The following translational research hypotheses will be tested in the tissue and serum specimens submitted from GOG-0213 patients undergoing secondary surgical cytoreduction.

1.41 Molecular and biochemical profiles can be identified that are associated with time to first disease recurrence or death.

1.42 Molecular determinants can be identified within patients with platinum-sensitive recurrent ovarian, peritoneal primary or Fallopian tube carcinoma which predicts for sensitivity/resistance to combination chemotherapy with or without bevacizumab followed with or without maintenance bevacizumab therapy.

1.5 Translational Research Objectives **(08/04/08)**

The following translational research objectives will be evaluated in the tissue and serum specimens submitted from GOG-0213 patients undergoing secondary surgical cytoreduction.

Note: Testing of banked samples will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

1.51 To define molecular and biochemical profiles associated with the duration of progression-free survival in platinum-sensitive recurrent ovarian, peritoneal primary or Fallopian tube carcinoma treated with combination chemotherapy with or without bevacizumab followed with or without maintenance bevacizumab therapy in the presence or absence of secondary surgical cytoreduction.

1.52 To identify molecular determinants that predict sensitivity or resistance to carboplatin and paclitaxel with or without bevacizumab followed with or without maintenance bevacizumab therapy.

1.53 To bank DNA from whole blood for research and evaluate the association between single nucleotide polymorphisms (SNPs) and measures of clinical outcome including overall survival, progression-free survival and adverse events.**(06/22/09)**

2.0 BACKGROUND AND RATIONALE

2.1 Rationale for Selected Approach and Trial Design

Ovarian cancer remains the most lethal primary gynecologic malignancy in the United States. This year over 16,000 women will die from their disease. The principle reason for this outcome is disease recurrence and the emergence of drug resistance. Patients with recurrent disease frequently undergo multiple cycles of multiple drug regimens. Those fortunate to achieve a response to chemotherapy are however, rarely cured and find that their remission cycles are short-lived. Even if a complete response is re-achieved it is usually of a shorter duration than the first disease-free interval. Those not achieving a response to recurrence therapy live less than 2 years. While effective therapy following disease recurrence is a major unmet need, few interventions have successfully altered the natural history of recurrence. We propose to address two important interventions, surgery and combination chemotherapy with biologics, neither previously studied in a prospective randomized design, in order to determine their impact on survival.

2.2 Rationale for Surgery

The capacity of cytoreductive surgery to improve survival for patients with advanced, newly diagnosed epithelial ovarian cancer is generally accepted.[1] However, the role of tumor-reductive surgery for patients with recurrent disease continues to evolve.[2] Several series have demonstrated the importance of tumor reductive surgery prior to the initiation of second-line chemotherapy.[1, 3, 4] Preliminary results indicate a maximal survival benefit for patients rendered visibly disease-free prior to second-line therapy.[1, 4, 5] The frequency of reported optimal operative outcomes has ranged from 37% to 83% in small series, using various criteria for "optimal cytoreduction".[6] The relative importance that differences in study cohorts, attitude, technical capability and experience have in accounting for variation of operative outcomes is unknown. In a recent series, the largest yet published, approximately 80% of the patients had complete cytoreduction.[5] Clinical criteria such as the median age, median disease-free interval, amount of prior chemotherapy, performance status, size of intra-abdominal disease, and locations of disease suggests patients in that series to have disease at least as advanced as other reports.[1, 3, 4, 7] That investigation prospectively demonstrated that secondary cytoreductive surgery, followed by salvage chemotherapy, allows survival that is significantly improved. The 34.4 month overall median survival from the time of secondary operation and the 35.9 month overall median survival from the time of recurrence in the most recent series exceed what is typically reported in the salvage chemotherapy literature. Another noteworthy observation from this study was that the median survival after diagnosis of recurrence for patients who did not have salvage

chemotherapy before secondary operation (48.4 months) dramatically exceeded the overall median survival for those who were pretreated (24.9 months). Furthermore, an estimated 40% of the patients operated on before administration of salvage therapy survived more than five years after recurrence compared to only 15% in the pretreated group. Of note, patients whose disease responded to a recent repeat course of platinum containing agents, and patients treated with non-platinum containing agents before secondary operation, both had poor survival, that did not remotely approach the overall group who had secondary cytoreductive operations prior to salvage chemotherapy. Perhaps pretreatment with salvage chemotherapy induces drug resistance. Regardless, limiting the role of surgery to palliation of symptoms for patients who failed multiple salvage regimens and the strategy of treating with salvage chemotherapy before an attempt at secondary cytoreductive surgery may greatly diminish the chances for subsequent survival. Confirmation of this observation within the context of a multi-center randomized trial may dramatically improve the survival potential for women with recurrent epithelial ovarian cancer.

2.3 Rationale for Combination Chemotherapy (10/01/12)

Most patients medically suitable to undergo therapy at the time of recurrence will be offered chemotherapy. To date, a limited number of agents (i.e. etoposide, liposomal doxorubicin, topotecan, etc) have been formally approved for administration in this setting. In addition, several other agents have been studied and are documented to have clinical activity. Joining these novel agents are the taxanes and platinates commonly used as standard therapy in the front-line setting. In light of this expansion of potentially active chemotherapeutics, physicians are administering more agents, longer to more patients. Nonetheless, the degree to which this practice is benefiting patients in terms of survival is unclear.

An additional challenge lies in how to determine when to recommend which agents or combinations to patients with recurrent disease. A common determinant for many clinicians lies in reference to the patient's time in remission following front-line therapy. Those disease-free for more than six months are commonly considered to be potentially sensitive to retreatment with platinum. Response characteristics with single agent platinum in this setting produce results similar to patients treated with novel agents. Patients with longer disease-free interval are commonly treated with combination platinum and taxane therapy similar to the regimens received as primary therapy. The degree to which this philosophy of care has affected survival is unknown but data from the limited number of randomized trials would suggest the following:

- Non-platinum novel agents such as topotecan, gemcitabine, liposomal doxorubicin, and paclitaxel have similar response and survival characteristics as compared to platinum in randomized phase III trials.

- No difference in response has been observed in these novel agents among platinum sensitive or resistant patients. However, treatment with liposomal doxorubicin demonstrated a survival benefit in comparison to topotecan in the absence of a response benefit among patients with platinum-sensitive disease.[8] The reasons for this are not clear but may relate to either intrinsic drug activity or to trial design (limited availability to liposomal doxorubicin in topotecan failures).
- Platinum, and platinum combinations have favorable response characteristics in platinum-sensitive patients.[9, 10] Platinum and taxane combination therapy appears to be at least as effective as single agent platinum and data from one large phase III trial would suggest clinical superiority.[11] Although the randomized population in that trial was dissimilar to those commonly treated in the US, a second randomized phase II clinical trial in a more selective population essentially confirmed the observed benefit.[12] Further, a randomized clinical trial of gemcitabine and carboplatin demonstrated superiority in progression-free survival over carboplatin alone in platinum-sensitive patients.[13] Although a survival benefit was not demonstrated, the trial was underpowered to address this endpoint.
- Recently, gemcitabine, carboplatin and bevacizumab was compared to gemcitabine and carboplatin demonstrating further enhancement in progression-free survival (12.4 mos vs 8.4 mos, HR 0.48, 95% CI:0.39-0.61), response rate (79% vs 57%, $p<0.0001$) and duration of response (10.4 mos vs 7.4 mos, 95% CI: 0.41-0.70). Although immature at the time of reporting, there was no overall survival benefit with nearly 50% of events recorded.[73]

  From these observations, it would appear the greatest activity and potential for survival enhancement lies in combination, platinum-based chemotherapy among those deemed potentially platinum (and taxane) sensitive. As demonstrated above, a survival benefit is also suspected in this cohort for surgery. A randomized trial is needed to evaluate the addition of surgery to combination therapy to determine their impact on survival.

2.31 Docetaxel

Taxanes are a class of anticancer agents that exert cytotoxic effects by their unique inhibition of microtubular assembly by stabilizing tubulin polymerbundles.14, 15 Both paclitaxel and docetaxel belong to the taxane family and have demonstrated activity in tumors that are refractory to conventional chemotherapy regimens. Paclitaxel is a diterpene plant product derived from the bark of the Western yew (Taxus brevifolia), while docetaxel is a semisynthetic derivative of 10-deacetylbaccatin III, a compound extracted from the needles of the European yew (Taxus baccata). While the relative efficacy of paclitaxel and docetaxel has not been compared clinically, docetaxel has increased activity in vitro, as well as clinical activity in paclitaxel resistant tumors.

In Vitro Activity.
The cytotoxicity of docetaxel in comparison with paclitaxel was evaluated in several murine and human long-term cell culture lines. Docetaxel was found to be generally more cytotoxic (1.3-12-fold), a result that could be explained by its higher achievable intracellular concentration, its higher affinity for microtubules, and its slower cellular efflux.[14-21]Furthermore, docetaxel affects centromere organization resulting in abortive mitosis.[22] These cellular events may account for the greater cytotoxicity of docetaxel compared to that seen with paclitaxel. In terms of cross-resistance with other antitumor agents, there was cross-resistance to docetaxel in multidrug-resistant sublines such as P388/DOX3, CEM/VLB 1000 and Chinese hamster ovary AUXB1 line.[23] However, no cross-resistance to docetaxel was observed in CHO cells expressing a low level of vincristine-resistance but P-glycoprotein positive.[23] This means that cross-resistance to docetaxel was not definitively observed in sublines expressing the MDR phenotype.[24]These findings were in agreement with cell line studies showing that docetaxel was active in paclitaxel-resistant cells.[16]In addition, there was a lack of cross-resistance to cisplatin in certain cell lines.[17,22]

Efficacy in Murine Tumor Models
In a murine tumor model with B16 melanoma, docetaxel demonstrated clear superiority to paclitaxel, having a 2.7 times greater log cell kill than paclitaxel.[25] Docetaxel at a dose of 100 mg/m^2 has demonstrated significant activity with response rates of 23-40% as second-line therapy in platinum resistant ovarian carcinoma.[26-28] More recently, its activity in paclitaxel-resistant tumors has been studied. The use of docetaxel at a dose of 100 mg/m^2 every 21 days in paclitaxel-resistant breast cancer has demonstrated a 17.5% response rate in 41 evaluable patients.[29] Additionally, the use of docetaxel at this same dose in paclitaxel-resistant ovarian cancer has recently demonstrated a 37.5% response rate in 8 evaluable patients.[30] The in vitro, in vivo and clinical data make docetaxel an excellent agent to evaluate after primary platinum and paclitaxel therapy. Hematologic toxicity is the dose-limiting toxicity, with neutropenic fever occurring in 8- 48% of patients.[26-28]Hematologic toxicity is considerably more severe with poorer hepatic function.[31]A comparative study of patients with or without liver dysfunction treated with docetaxel at a dose of 100 mg/m^2 was recently reported. Patients with impaired liver function defined as an SGOT or SGPT > 1.5 x upper limit of normal or alkaline phosphatase > 2.5 x upper limit of normal, had a higher rate of neutropenic fever 23.8% vs 12.9% (p=0.06) and toxic death 11.9% vs 1.7%, (p=0.001). For that reason strict criteria for hepatic function are required for this study.

Efficacy in Humans

Several phase II and one randomized phase III trial have been conducted evaluating clinical efficacy of docetaxel in primary and recurrent ovarian cancer. Rose et al., reporting on behalf of the GOG, demonstrated a 22.4% overall response rate (5% CR and 17% PR) in 60 patients with platinum and taxane resistant recurrent disease (defined as progression on or within 6 months of completion of primary therapy). Docetaxel for this trial was administered at 100 mg/m^2. Grade IV hematologic toxicity was observed in 75% of patients at this dose.[32]Similarly, Verschraegen et al., reported a 23% response rate and a median PFS of 3.5 months among 30 assessable patients in a slightly less resistant population. Grade IV granulocytopenia occurred in 72% of protocol patients and like the Rose trial was a reflection of higher docetaxel dosing (100 mg/m^2).[30] Markman, evaluated docetaxel (75 mg/m^2) in 30 taxane-resistant ovarian cancer patients. In this study, taxane-resistance was defined as progression on or within3 months of paclitaxel therapy. Patients with longer intervals from paclitaxel were to be retreated with that agent – and progressed – prior to docetaxel. In this trial, 3 patients (10%) had an objective response. Hematologic toxicity was reduced (30%, Grade IV), likely a reflection of reduced dosing.[33]

Based on objective clinical activity in these resistant patient cohorts, a randomized clinical trial comparing taxane and platinum combination therapy in front line ovarian cancer treatment was conducted and recently reported. Vasey and colleagues reported similar PFS (15.0 vs 14.8 months, HR: 0.97 (0.83-1.13) and OS rate at 24 months (64.2% vs. 68.9%, HR: 1.13 (0.92-1.39) for the docetaxel/carboplatin combination compared with the industry standard paclitaxel/carboplatin. In this 1077 patient trial toxicity was significantly different with more hematological toxicity seen in the docetaxel combination (Grade III/IV granulocytopenia 94% vs. 84%, $P < 0.001$) but more severe and longer lasting sensory-motor neurotoxicity for paclitaxel/carboplatin (11% vs. 30, $P < 0.001$).[34]These trials establish clinical efficacy and safety for docetaxel and suggest possible non-cross resistance with paclitaxel. Given the lack of a clear dose response for this agent we propose to utilize 75 mg/m^2 to initiate the trial.

2.4 Rationale for Angiogenesis Targeted Therapy

Angiogenesis is one of the cardinal processes leading to invasion and metastasis of solid tumors. The angiogenic-signaling pathway may be triggered by the release of angiogenic promoters such as vascular endothelial growth factor (VEGF) from tumor cells and normal endothelial cells into the local microenvironment. There is accumulating evidence that angiogenesis plays a central role in ovarian cancer disease progression and prognosis.[35-38]A strong relationship exists between the expression of angiogenesis biomarkers and the behavior of epithelial ovarian cancer, suggesting pharmacological inhibitors of

angiogenesis could arrest tumor progression.[39,40] Neutralizing anti-VEGF monoclonal antibodies have demonstrated therapeutic activity in a variety of pre-clinical solid tumor models.[41] Bevacizumab is a recombinant humanized version of a murine anti-human VEGF monoclonal antibody, named rhuMAb VEGF. Bevacizumab has been advanced into clinical development for use as a single agent to induce tumor growth inhibition in patients with solid tumors and for use in combination with cytotoxic chemotherapy to delay the time to disease progression in patients with metastatic solid tumors.[42] A recent phase II trial of single agent bevacizumab for patients with recurrent, platinum/taxane refractory epithelial ovarian and peritoneal primary cancer has been reported in the GOG (GOG-0170D). Sixty-two women were enrolled in the phase II trial, and objective responses were observed in 17.7%.[43] Response duration was 10.3 months. This was an extremely unusual observation for a compound presumed to be at best cytostatic when administered as a single agent. Further exploration in combination with chemotherapy is warranted in ovarian cancer patients given the survival benefits observed for bevacizumab-combinations in other solid tumors such as breast, renal, lung and colon cancers.

2.5 Rationale for Combination Cytotoxic and Biologic Therapy

Evidence from pre-clinical studies and recent phase II and III clinical trials in other solid tumors has demonstrated enhanced anti-tumor activity of traditional cytotoxic regimens, when combined with bevacizumab. For example, Devore and colleagues reported on a three-arm phase II randomized trial of carboplatin/paclitaxel with or without bevacizumab (7.5 mg/kg or 15 mg/kg dose levels) every 21 days until disease progression, in 99 patients with stages IIIB and IV non-small cell lung cancer. Response rates were 21.9 percent (7/32 patients) in the low dose and 42.9 percent (14/35 patients) in the high dose bevacizumab combination arms, compared to a response rate of 31.3 percent (10/32 patients) in the chemotherapy alone arm. A phase II/III trial in this patient population has been conducted by ECOG; the final analysis of this study is pending.

More importantly, a recently reported phase III trial, AVF2107, of over 800 previously untreated patients with metastatic colorectal cancer randomized to receive either bevacizumab for one year plus the Saltz chemotherapy regimen (5-FU/Leucovorin/CPT-11, IFL) or the Saltz regimen plus placebo for one year met its primary endpoint of improving overall survival. The magnitude of benefit observed far exceeded what the study was designed to demonstrate. The trial also met the secondary endpoints of progression-free survival, response rate, and duration of response (see following table).

	IFL/Bevacizumab (n = 403)	**IFL/Placebo (n = 412)**	**Hazard Ratio (p-value)**
Response Rate	44.9%	34.7%	(0.0029)
Median TTP	10.6 mos	6.2 mos	(0.00001)
Median Survival	20.3 mos	15.6 mos	0.65

(0.00003)

Bleeding, thrombosis, asymptomatic proteinuria and hypertension were identified in phase II studies as possible safety events, but only Grade 3 hypertension and arterial thrombosis events were clearly increased in this phase III study.

Preliminary results from a more recent, large, randomized phase III trial for patients with advanced colorectal cancer who had previously received treatment show that those who received bevacizumab in combination with an oxaliplatin regimen known as FOLFOX4 (oxaliplatin, 5-fluorouracil and leucovorin) had a significantly prolonged survival over patients who received FOLFOX4 alone. The Data Monitoring Committee overseeing the trial, known as E3200, recommended that the results of a recent interim analysis be made public because the study had met its primary endpoint of demonstrating improved overall survival, which was 17% longer in the bevacizumab arm. Specifically, the median overall survival in the bevacizumab plus FOLFOX4 arm was 12.5 months compared to 10.7 months for patients treated with FOLFOX4 alone. There was a 26 percent reduction in the risk of death (hazard ratio of 0.74) for patients in this study who received bevacizumab plus FOLFOX4 compared to those who received FOLFOX4 alone. Treatment toxicities observed in this study were consistent with those adverse effects observed in other clinical trials in which bevacizumab was combined with chemotherapy. These included hypertension and bleeding as more predominant in the bevacizumab arm.

Multiple phase I-III trials, such as those cited above, have demonstrated the safety and tolerability of bevacizumab with traditional schedules and dosing of carboplatin and paclitaxel.

2.6 Gastrointestinal Perforation/Fistula

GI perforations/fistulas were rare but occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal phase III trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving 5-FU/bevacizumab compared to 0.3% in patients receiving IFL alone. In various phase II series of bevacizumab in recurrent ovarian cancer the rate of GI perforation has ranged from 0-14%. No phase III randomized trials of bevacizumab alone or in combination with chemotherapy have been conduct heretofore. Review of cases reported to CTEP in an open-label phase II ovarian cancer trial of bevacizumab did not specifically isolate risk factors for this complication; however, most patients were heavily pretreated and had abdominal tumor burden (CTEP IND Action Letter, October 4, 2005). GI perforation has also been reported in patients with gastric/esophageal cancer, pancreatic cancer, or co-morbid GI conditions such as diverticulitis and gastric ulcer. **GI perforation should be included in the differential diagnosis of patients on**

bevacizumab therapy presenting with abdominal pain, fever of unclear source, or rectal/abdominal abscess.

2.7 Rationale for Clinical Trial Design **(10/01/12)**

Bevacizumab was selected for evaluation in combination with standard chemotherapy based on preliminary phase II single agent data obtained in patients with recurrent epithelial ovarian and peritoneal primary cancers and results from a phase III clinical trial in patients with metastatic colorectal cancer demonstrating a survival benefit to patients receiving bevacizumab with standard cytotoxic chemotherapy compared with patients receiving standard chemotherapy alone. Recently, evidence of enhanced progression-free survival was observed for combination bevacizumab with gemcitabine and carboplatin followed by bevacizumab maintenance to progression in women with platinum-sensitive recurrent ovarian cancer.[73]Based on the mechanism of action of bevacizumab, there may be benefit to extended therapy until disease progression, in extending PFS or OS in this patient population. Therefore, combination chemotherapy is compared against combination carboplatin/paclitaxel/bevacizumab or carboplatin/gemcitabine/bevacizumab with bevacizumab maintenance therapy.

2.8 Rationale for Evaluation of Hypersensitivity

Expansion of the use of platinum and taxane compounds for the treatment of recurrent disease has ushered in an increasing awareness of problematic drug-specific hypersensitivity reactions (HSRs).[44-48]The syndrome is manifested by flushing, dyspnea/bronchospasm, back pain, chest discomfort, pruritus, erythema, nausea, hypotension and occasionally bradycardia/tachycardia. They are profound experiences for patients. Although reported as early as the 1970's for platinum and the 1980's for paclitaxel, prophylaxis has been unable to completely eradicate these reactions often considered by investigators as severe enough to warrant agent discontinuation. Markman, reporting on 205 patients treated with carboplatin, documented 24 (12%) with HSR occurring after a median of 8 courses. He noted that without prophylaxis, only 1 of 3 patients retreated with the agent were able to undergo infusion.[49]Recently, however, several investigators have reported in small single institution studies the success of retreatment programs for those patients suffering hypersensitivity reactions to either or both carboplatin and paclitaxel. These regimens, which include slower infusion, prolonged and repeated premedication prophylaxis and accelerated dosing over time, have been largely successful. Brown and colleagues reported on 32 patients demonstrating hypersensitivity reactions while undergoing treatment for gynecological malignancies. Twenty-three patients had recurrent ovarian or peritoneal cancer. Reactions to platinum (cisplatin and carboplatin) and paclitaxel were observed. Seventeen patients underwent a desensitization protocol and had re-treatment attempted. Seven out of 8 platinum HSRs and 8 out of 10 paclitaxel HSRs were successfully re-treated following desensitization. Lee and colleagues also reported successful reinfusion of paclitaxel, carboplatin or both in 57 patients

(255 courses) using a desensitization protocol. Twelve percent of patients had breakthrough symptoms described as of lower severity than the index event – these were also successfully controlled and enabled subsequent retreatment.[48]

The incidence of hypersensitivity is largely unknown particularly in this era of nearly universal paclitaxel and platinum re-treatment. Estimates range from 2-16% for paclitaxel and 5-20% for cisplatin and carboplatin with the latter being reported with increasing frequency. No prospective trials to date have evaluated this incidence in the recurrent setting. Information will be useful in developing strategies to predict or modify re-treatment to avoid these dramatic complications of infusion.

2.9 Rationale for Quality of Life Assessment

The quality of life (QOL) component of this trial has two foci: evaluating the effects of the cytoreductive surgery and assessing the impact of adding bevacizumab to second-line paclitaxel and carboplatin for second-line and maintenance therapy.

The primary QOL question with regard to the surgery randomization is whether cytoreductive surgery is associated with improved quality of life due to its anti-tumor effect. The evaluation of this question is critical because, although cytoreductive surgery has the potential to increase survival and improve QOL through reducing tumor burden, potential surgical complications and recovery from surgery may adversely affect QOL. Thus, secondary cytoreductive surgery may initially produce a decline in quality of life, while patients recover from surgery and complications, followed by an improvement in quality of life due to reduced tumor burden.

With regard to the chemotherapy, the principle QOL question is whether the addition of bevacizumab to second-line carboplatin and paclitaxel, followed by maintenance therapy with bevacizumab is associated with better quality of life than carboplatin and paclitaxel combination therapy. The addition of maintenance treatment may present additional toxicities such as fatigue, rash, and diarrhea.[50-52]These toxicities could affect a range of quality of life areas.

Quality of life will be assessed using the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) a 37-item questionnaire that measures physical, functional, social, and emotional well-being, along with a subscale that measures concerns specific to women with ovarian cancer. The physical, functional, social, and emotional well-being subscales comprise the FACT-G (General), which is considered appropriate for use with patients with any form of cancer. Version 4 of the FACT-G is widely used and has undergone psychometric testing and demonstrates good reliability and validity consistent with previously published data on earlier versions. In a validation study of the FACT-O (FACT-G subscales plus ovarian-specific subscales), the total scale and subscales demonstrated very

good to excellent internal consistency reliability (0.74-0.92) and test-retest reliability (0.72-0.88).[53] Validity of the FACT-O was demonstrated by correlation with other quality of life measures, and by its relationship to performance status, treatment status, and disease stage. The FACT-O, particularly the physical well-being, functional well-being, and ovarian subscales were sensitive to changes in performance status over a two-three month period. To assess the effects of bevacizumab-related side effects on QOL, questions from the FACIT measurement system have been added related to rash, concerns about appearance, diarrhea, fatigue, and appetite (labeled "Additional Concerns (TSE)".

In order to evaluate the effect of surgery on quality of life, patients will complete the Physical Functioning Subscale of the Rand 36-Item Short Form Health Survey (Rand SF-36). The Physical Functioning (PF) Subscale is a 10-item subscale of the Rand SF-36a global quality of life questionnaire, designed to assess quality of life of patients across all medical conditions [54-56].

The PF Subscale consists of items concerning activities of daily living: walking, climbing stairs, bathing, dressing, and performance of physical activities, with each item rated on a three-point scale of limitation of activity due to the patients' health, from "not limited" to "limited a lot." Internal consistency of the PF subscale is excellent, with an alpha co-efficient ranging from 0.89 to 0.92.[56] The PF subscale has been found to significantly correlate with other physical functioning measures (Sickness Impact Profile [SIP], r=.67-.78; shortened Arthritis Impact Measurement Scale (sAIMS, r=.60). Further evidence of validity was provided by the PF subscale distinguishing between patients with serious and mild medical conditions.[57]Furthermore, the PF subscale has been found to be responsive to changes in functioning after surgical procedures (thoracic surgery for treatment of non-small-cell lung cancer, abdominal aortic aneurysm repair, and total hip arthroplasty [58]), and sensitive to differences in quality of life between laparoscopic and open surgical procedures [59,60] and between epidural and patient-controlled analgesia after colonic surgery.[57] Norms have been developed for all subscales of the SF-36, by gender and age groups, based upon 2,474 respondents, as well as for patients with physical limitations.[58,59]

Eight questions will be included to measure specific quality of life problems after surgery (labeled "Additional Concerns (S)" in). These questions will address issues such as pain, fatigue, problems with the surgical incision, and ostomy appliances. Similar questions have been used in GOG-0152 (A Phase III Randomized Study of Cisplatin And Taxol® with Interval Secondary Cytoreduction versus Cisplatin and Paclitaxel in Patients with Suboptimal Stage III Epithelial Ovarian Carcinoma). Several of the questions were taken from questionnaires in the FACIT quality of life measurement system.[61] others were drafted to be similar in format to FACIT questions.

2.10 Background and Rationale for Translational Research**(08/04/08)**

The translational research component of this protocol will focus on the molecular and biochemical phenotype of recurrent ovarian cancer. It is well known that the vast majority of patients with advanced ovarian cancer who respond to initial therapy will recur. However, these recurrent tumors remain essentially a molecular enigma because of their general unavailability for analysis. A brief review of the GOG Tissue Bank demonstrated that less than 5% of ovarian cancer specimens are from sources other than the primary tumor. Further, only 22 specimens of recurrent ovarian cancer with attached clinical data have been banked.

This protocol provides an extraordinary opportunity to study these tumors, characterize them on a molecular basis, compare them to the original primary tumor, and determine the basis for disease recurrence and altered drug sensitivities. In the past five years, over 600 manuscripts on expression profiling of cancers using microarray technology have been published, illustrating the recognized utility of this approach in exploring questions of tumor biology and clinical correlates. The principles of class prediction and class discovery as they apply to the molecular classification of human cancers were exemplified by Golub et al., who used oligonucleotide microarrays to monitor gene expression in acute leukemias as a test case.[62] Class prediction identified and validated a subset of informative genes whose expression was highly correlated with previously defined classes. Further, subsequent studies have utilized these approaches to provide proof of the "molecular profiling principle" as well as to gain novel insights into clinical cancer problems. Using a specialized, lymphoid cell-specific cDNA microarray, Alizadeh et al. performed expression profiling of diffuse large B-cell lymphomas and identified two molecularly distinct forms of this malignancy that correlated with overall survival.[63]

Further, recent work on the problem of drug resistance has detailed multiple potential biochemical mechanisms, which may be critical for the development of drug resistance in ovarian cancer. For instance the expression level of DNA repair enzymes and membrane transporters have been implicated in cisplatin resistance while microtubule mutations have been shown to affect paclitaxel sensitivity.[64, 65] These *in vitro* determined mechanisms require testing and validation on in vivo derived tumor specimens.

GOG-0213 patients with platinum-sensitive, recurrent epithelial ovarian, peritoneal primary or Fallopian tube carcinoma undergoing secondary cytoreduction will be able to provide archival formalin-fixed and paraffin-embedded primary or metastatic tumor, a pre-op serum specimen, a pre-op plasma specimen, formalin-fixed recurrent tumor, frozen recurrent tumor, formalin-fixed normal tissue and/or frozen normal tissue to establish an enduring resource for defining the molecular and biochemical phenotype of recurrent ovarian cancer. The pre-op serum and plasma will be prepared from blood drawn prior to secondary cytoreductive surgery. The exact choice of the biomarkers and profiles to be evaluated and the assays to be performed in the tissue, serum and plasma

specimens submitted for the GOG-0213 patients undergoing secondary cytoreduction will be reevaluated based on evolving data in the field.

2.11 Rationale for Banking DNA from Whole Blood for Research **(06/22/09)**

The National Cancer Institute is encouraging Cooperative Clinical Trial Groups including the Gynecologic Oncology Group to bank whole blood from women participating in clinical trials such that the blood specimens will be linked to clinical outcome data (progression-free survival, overall survival, response and adverse effects) and information regarding treatment. The purpose of this effort is to support research including pharmacogenomic and pharmacogenetic research.

Women who are candidates for this clinical trial or who have already been enrolled on GOG-0213 will be asked to give permission for 10 ml of their blood to be collected for this research study and for future research. No matter what the women decide to do, it will not affect their care. The women can still participate in this GOG study even if they do not allow their blood to be collected and used for this research study and/or for future research. Women already enrolled on GOG-0213 will need to be re-consented for this collection.

2.12 Single Nucleotide Polymorphisms (SNPs) and SNP Profiling**(06/22/09)**

It is well known that individual single nucleotide polymorphisms (SNPs) and SNP profiles are associated with many clinical aspects of cancer. This includes risk of developing invasive cancer, risk of recurrence of cancer, patient survival and chemotherapy toxicity. We propose to use genome wide SNP-association studies and individual SNP analyses to identify SNPs which correlate with a variety of clinical measures including but not limited to patient survival, recurrence of disease, response, and toxicity

2.13 Rationale for the inclusion of fallopian tube carcinoma (FTCA)

Primary carcinoma of the fallopian tube is among the rarest malignancies of the female genital tract accounting for approximately 3.3/1,000,000 women annually. Despite its rarity, the disease shares many features of ovarian and primary peritoneal cancer including, risk factors (age and nulliparity), genomic alterations (LOH 3q and 8q, 1q, 5p, 7q, 12p and 20q), genetic abnormalities (Her 2-neu, P53, and k-ras mutations), natural history (local followed peritoneal metastases), response to chemotherapy, and anticipated survival by stage.[66-68] The latter feature is modeled after primary ovarian cancer as well. Most strikingly though is the relationship between BRCA mutation and the attendant increased risk of fallopian tube cancer over baseline. A life-time risk increase of 120 fold over background has been reported for women who harbor BRCA mutation. In fact, women diagnosed with FTCA may be at greater risk for harboring a BRCA mutation than women diagnosed with ovarian cancer. As such, women undergoing risk-reducing bilateral salpingo-oophorectomy (RRBSO) are

recommended to have as much of the fallopian tube resected as possible and undergo step-sectioning as is performed for the ovary.

Since there appears to be a common set of environmental and genetic risk factors for FTCA and ovarian cancer, it is not surprising that the clinical approach for these two neoplasms is similar including primary surgical resection and debulking or staging, adjuvant platinum- and taxane-based chemotherapy and surveillance protocols (including CA-125). Based on these features and the lack of consensus as to the precise diagnostic criteria separating primary entities of the ovary, fallopian tube and peritoneum it is appropriate to consider FTCA within this spectrum of disease.

2.14 Inclusion of Women and Minorities

The Gynecologic Oncology Group and GOG participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire ovarian, fallopian tube and peritoneal primary cancer population treated by participating institutions.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

3.10 Patients enrolled after August 28, 2011 must be candidates for cytoreductive surgery and consent to have their surgical treatment determined by randomization.**(08/29/11)(12/19/11)**

3.11 Patients must have histologic diagnosis of epithelial ovarian carcinoma, peritoneal primary or Fallopian tube carcinoma, which is now recurrent.

3.12 Patients with the following histologic epithelial cell types are eligible: Serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's Tumor, or adenocarcinoma not otherwise specified (N.O.S.).

3.13 Patients must have had a complete response to front-line platinum-taxane therapy (at least three cycles).**(08/04/08)**

3.131 A complete response to front-line chemotherapy must include: negative physical exam, negative pelvic exam and normalization of CA125, if elevated at baseline. Although not required, any radiographic assessment of disease status (e.g. CT, MRI, PET/CT, etc) obtained following the completion of primary therapy (defined in 3.133) should be considered negative for disease.

3.132 All patients must have also had a treatment-free interval without clinical evidence of progressive disease of at least 6 months from completion of front-line chemotherapy (both platinum and taxane). Front-line therapy may have included a biologic agent (i.e. bevacizumab).

3.133 Front-line treatment may include maintenance therapy following complete clinical or pathological response. However, maintenance cytotoxic chemotherapy must be discontinued for a minimum of 6 months prior to documentation of recurrent disease. Patients receiving maintenance biological therapy **or hormonal therapy** are ELIGIBLE provided their recurrence is documented more than 6 months from primary cytotoxic chemotherapy completion (includes maintenance chemotherapy) AND a minimum 4 weeks has elapsed since their last infusion of biological therapy.**(06/22/09)**

3.14 Patients must have clinically evident recurrent disease for the purpose of this study,**(08/29/11)**

3.142 *Measurable disease*(RECIST) 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 more than or equal to 20 mm when measured by conventional techniques, MRI or CT, or more than or equal to 10 mm when measured by spiral CT.

3.15 Patients must have adequate:

3.151 Bone marrow function: Absolute neutrophil count (ANC) greater than or equal to 1,500/mm^3, equivalent to Common Toxicity Criteria for Adverse Events v4.0 (CTCAE) Grade 1.

3.152 Platelets greater than or equal to 100,000/mm^3. (CTCAE Grade 0-1).

3.153 Renal function: Creatinine (non-IDMS) ≤ 1.5 x institutional upper limit normal (ULN), CTCAE Grade 1 **(03/15/10) (08/23/10)**

3.154 Hepatic function:

3.1541 Total bilirubin ≤ 1.5 ULN (CTCAE Grade 1).

3.1542 SGOT/AST and Alkaline Phosphatase ≤ 2.5 times the upper limit of normal in the absence of liver metastasis. SGOT/AST and Alkaline Phosphatase <5.0 times ULN in the presence of liver metastasis.

3.155 **This criterion applies only to the patients enrolled before August 29, 2011 and those enrolled after this date electing to receive Bevacizumab.**

Patients must have a urine protein-to-creatinine ratio (UPCR) < 1.0 mg/dL. The UPCR has been found to correlate directly with the amount of protein excreted in a 24 hr urine collection. Specifically, a UPCR of 1.0 is equivalent to 1.0 gram of protein in a 24-hour urine collection. Obtain at least 4 ml of a random urine sample in a sterile container (does not have to be a 24 hour urine). Send the sample to the lab with a request for urine protein and creatinine levels [separate requests]. The lab will measure protein concentration (mg/dL) and creatinine concentration (mg/dL). The UPCR is derived as: protein concentration (mg/dL) / creatinine concentration (mg/dL).

3.16 (This eligibility criterion does not apply to patients enrolled after August 28, 2011).**(08/29/11)(12/19/11)**Patients who are not candidates for surgical cytoreduction are eligible for the chemotherapy randomization. Patients are not considered candidates for surgical cytoreduction if complete cytoreduction in the estimation of the investigator is impossible or a medical infirmity precludes exploration and debulking.

3.17 Patients must have met the pre-entry requirements specified in Section 7.0.

3.18 Patients must have signed an approved informed consent and authorization permitting release of personal health information.

3.19 Patients must have a GOG Performance Status of 0, 1, or 2.

3.110 Patients must be at least 18 years old.

3.2 Ineligible Patients

3.21 Patients who have received more than one previous regimen of chemotherapy (maintenance is not considered a second regimen).

3.22 Patients receiving concurrent immunotherapy, or radiotherapy.

3.23 Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis are excluded.

3.24 Patients whom have already undergone secondary cytoreduction for recurrent disease are excluded.**(08/29/11)**

3.25 Patients with a prior histologic diagnosis of borderline, low malignant potential (grade 0) epithelial carcinoma that was surgically resected and who subsequently developed an unrelated, new invasive epithelial ovarian or peritoneal primary cancer are eligible provided that they meet the criteria listed in Section 3.12.

3.26 Patients who require parenteral hydration or nutrition and have evidence of partial bowel obstruction or perforation.

3.27 Patients who have received prior chemotherapy for any abdominal or pelvic tumor (other than ovarian, fallopian tube, and primary peritoneal) are excluded. **(06/22/09) (03/15/10)**

3.28 Patients with synchronous primary endometrial cancer, or a past history of primary endometrial cancer, are excluded, unless all of the following conditions are met: Stage not greater than I-B; no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly

differentiated subtypes, including papillary serous, clear cell or other FIGO Grade 3 lesions.

3.29 Patients with uncontrolled infection.

3.30 Patients with concurrent severe medical problems unrelated to the malignancy that would significantly limit full compliance with the study or expose the patient to extreme risk or decreased life expectancy.

3.31 Patients with ≥ grade 2 peripheral neuropathy

3.32 Patients with a history of allergic reactions to carboplatin and/or paclitaxel or chemically similar compounds. Patients with allergic (hypersensitivity) reactions to these chemotherapeutic agents are **NOT** excluded **IF** they were successfully retreated following a desensitization program or protocol.

3.33 **This criterion applies only to the patients enrolled before August 29, 2011 and those enrolled after this date electing to receive Bevacizumab.(10/01/12)**

Patients with known hypersensitivity to Chinese hamster ovary cell products or other recombinant human or humanized antibodies.

3.34 Patients of childbearing potential, not practicing adequate contraception, patients who are pregnant or patients who are nursing are not eligible for this trial. To date, no fetal studies in animal or humans have been performed. The possibility of harm to a fetus is likely. Bevacizumab specifically inhibits VEGF, which is responsible for the formation of new blood vessels during development, and antibodies can cross the placenta. Therefore, bevacizumab should not be administered to pregnant women. In addition, there are unknown immediate and long-term consequences of chemotherapy administration to these women. In addition, surgical exploration as mandated by randomization during pregnancy may cause imminent mortal consequences. Further, it is not known whether bevacizumab is excreted in human milk. Because many drugs are excreted in human milk, bevacizumab should not be administered to nursing women. Subjects will be apprised of the large potential risk to a developing fetus.

3.35 Patients with other invasive malignancies, with the exception of non-melanoma skin cancer, who had (or have) any evidence of the other cancer present within the last 5 years or whose previous cancer treatment contraindicates this protocol therapy.

3.36 **This criterion applies only to the patients enrolled before August 29, 2011 and those enrolled after this date electing to receive Bevacizumab.(10/01/12)**

Patients with active bleeding or pathologic conditions that carry high risk of bleeding such as a known bleeding disorder, coagulopathy, or tumor involving major vessels.

3.37 **This criterion applies only to the patients enrolled before August 29, 2011 and those enrolled after this date electing to receive Bevacizumab.(10/01/12)**

Patients with a history or evidence upon physical examination of CNS disease, including primary brain tumor, seizures not controlled with standard medical therapy, any brain metastases or a history of stroke within 5 years of the first date of treatment on this study.

3.38 **This criterion applies only to the patients enrolled before August 29, 2011 and those enrolled after this date electing to receive Bevacizumab. (10/01/12)**

Patients with clinically significant cardiovascular disease. This includes:

3.381 Patients with significant cardiac conduction abnormalities, i.e. PR interval > 0.24 sec or 2nd or 3rd degree AV block.

3.382 Uncontrolled hypertension, defined as systolic > 150 mm Hg or diastolic > 90 mm Hg.

3.383 Myocardial infarction, cardiac arrhythmia or unstable angina < 6 months prior to registration.

3.384 New York Heart Association (NYHA) Grade II or greater congestive heart failure.

3.385 Serious cardiac arrhythmia requiring medication.

3.386 Grade II or greater peripheral vascular disease (exception: episodes of ischemia < 24 hrs in duration, that are managed non-surgically and without permanent deficit).**(03/15/10)**

3.387 History of CVA within six months.

3.39 **This criterion applies only to the patients enrolled before August 29, 2011 and those enrolled after this date electing to receive Bevacizumab.(10/01/12)**

Patients who have had a major surgical procedure, open biopsy, dental extractions or other dental surgery/procedure that results in an open wound, or significant traumatic injury within 28 days prior to the first date of treatment on this study, or anticipation of need for major surgical procedure during the course of the study; patients with placement of vascular access device or core biopsy within 7 days prior to the first date of treatment on this study.

3.391 Patients undergoing pre-treatment secondary cytoreduction will undergo therapy with bevacizumab on cycle #2 (See Section 5.234).

3.392 Patients undergoing pre-treatment surgery for purposes other than cytoreduction may also participate provided they meet eligibility in Section 3.1. Patients randomized to arms containing bevacizumab must wait a minimum of 28 days since that procedure to begin protocol treatment. Patients who undergo an uncomplicated port placement must wait a minimum of 7 days to begin protocol treatment. **(03/15/10)**

4.0 STUDY MODALITIES

4.1 Carboplatin (Paraplatin®, NSC # 241240)

4.11 Formulation: Carboplatin is supplied as a sterile lyophilized powder available in single-dose vials containing 50 mg, 150 mg and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

4.12 Solution Preparation: Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 ml
150 mg	15 ml
450 mg	45 ml

These dilutions all produce a carboplatin concentration of 10 mg/ml.

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

4.13 Storage: Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

4.14 Stability: When prepared as directed, carboplatin solutions are stable for eight hours at room temperature. Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded eight hours after dilution.

4.15 Supplier: Commercially available from Bristol-Myers Squibb Company.

4.16 Administration: See Section 5.2.

4.17 Adverse effects:
Hematologic: Myelosuppression
Gastrointestinal: Nausea, vomiting, diarrhea, abdominal pain, constipation
Neurologic: Peripheral neuropathy, ototoxicity, visual disturbances, change in taste, central nervous system symptoms
Renal: Abnormal renal function test results including serum creatinine, blood urea nitrogen, and creatinine clearance

Hepatic: Abnormal liver function tests including bilirubin, SGOT, and alkaline phosphatase
Electrolyte Changes: Abnormally decreased serum electrolyte values reported for sodium, potassium, calcium, and magnesium.
Allergic Reactions: Rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension.

Injection Site Reactions: Redness, swelling, pain; necrosis associated with extravasation has been reported.
Other: Pain, asthenia, alopecia. Cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in 6% or less of the patients. Cardiovascular events (cardiac failure, embolism, cerebrovascular accidents) were fatal in less than 1% of patients and did not appear to be related to chemotherapy. Cancer-associated hemolytic-uremic syndrome has been reported rarely. Malaise, anorexia, and hypertension have been reported as part of post-marketing surveillance.

*See FDA-approved package insert for a comprehensive list of adverse events associated with carboplatin.

4.2 Paclitaxel (Taxol®, NSC #673089)

4.21 Formulation: Paclitaxel is a poorly soluble plant product from the western yew, Taxus brevifolia. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water.

Paclitaxel is supplied as a sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. It is also available in 100 and 300 mg vials.

4.22 Solution Preparation: Paclitaxel, at the appropriate dose, will be diluted in 500-1000 ml of 0.9% Sodium Chloride injection, USP or 5% Dextrose injection, USP (D5W) (500 ml is adequate if paclitaxel is a single agent). Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexlphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized.

NOTE: Formation of a small number of fibers in solution (within acceptable limits established by the USP Particulate Matter Test for LVPs) has been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: IVEX-

II, IVEX-HP or equivalent) into the IV fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

4.23 Storage: The intact vials can be stored in a temperature range between 2-25° C (36-77°F).

4.24 Stability: Commercially available paclitaxel will be labeled with an expiration date. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

4.25 Supplier: Commercially available from Bristol-Myers Squibb Company.

4.26 Administration: Paclitaxel, at the appropriate dose and dilution, will be given as a 3-hour continuous IV infusion. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the IV administration sets (polyethylene or polyolefin) that are used to infuse parenteral Nitroglycerin. Nothing else is to be infused through the line where paclitaxel is being administered. See section 5.2.

4.27 Adverse Effects: Hematologic: Myelosuppression
Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis
Heart: Arrhythmia, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia
Pulmonary: Pneumonitis
Blood Pressure: Hypotension, hypertension (possibly related to concomitant medication--Dexamethasone)
Neurologic: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy
Skin: Infiltration: erythema, induration, tenderness, rarely ulceration, injection-recall reactions, erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)
Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus
Liver: Increased SGOT, SGPT, bilirubin, alkaline phosphatase and triglycerides, hepatic failure, hepatic necrosis
Other: Alopecia, fatigue, arthralgia, myalgia, light-headedness, myopathy, headaches

Other, Vision: Sensation of flashing lights, blurred vision, scintillating scotomata

*See FDA- approved package insert for a comprehensive list of adverse events associated with paclitaxel.

4.3 Bevacizumab (NSC #704865) **(08/04/08) (12/19/11)**

All investigators who receive a copy of the protocol should also obtain a copy of the Investigator's Brochure (IB). IB's are available from the Pharmaceutical Management Branch, CTEP, DCTD, NCI and may be obtained by emailing the IB Coordinator (ibcoordinator@mail.nih.gov) or by calling the IB Coordinator at 301-496-5725.

4.31 Description: Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody, consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions. Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.

4.32 How Supplied: Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration in a 400 mg (25mg/ml – 16 mL) fill glass vial containing bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. Japanese institutions may use 400 mg or 100 mg vials of commercially available Avastin.

4.33 Storage and Stability: Bevacizumab is shipped on blue ice for next day delivery. On receipt, bevacizumab should be stored in the refrigerator (2° to 8°C) and should remain refrigerated until just prior to use. Do not freeze. Do not shake. Shelf-life studies of bevacizumab are continuing. Investigators will be notified when lots have expired. The sterile single use vials contain no antibacterial preservatives; therefore, vials should be discarded eight hours after initial entry.

4.34 Preparation: Vials contain no preservative and are intended for single use only. Place the calculated dose in 100 mL of 0.9% Sodium Chloride for injection. Once diluted in 0.9% Sodium Chloride for injection, the bevacizumab solution must be administered within 8 hours.

4.35 Administration: Bevacizumab is administered intravenously as a continuous infusion. The initial dose should be administered over a minimum of 90 minutes. If no adverse reactions occur after the initial dose, the second dose should be administered over a minimum of 60 minutes. If no adverse reactions occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes.

If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

To insure complete delivery of bevacizumab, flush the IV infusion line with 0.9% sodium chloride. The following are two recommended methods for flushing the bevacizumab IV infusion line:
1. When the bevacizumab infusion is complete, add an additional 50mL of 0.9% sodium chloride for injection to the bevacizumab infusion bag. Continue the infusion until a volume equal to that of the volume contained in the tubing has been administered.
2. Replace the empty bevacizumab infusion bag with a 50mL bag of 0.9% sodium chloride for injection and infuse a volume equal to the volume contained in the tubing.
Please note: the flush is not included in the total recommended infusion times.

4.36 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Bevacizumab (NSC #704865) **(08/23/10) (12/19/11) (09/29/14) (10/03/16)**

Revised Bevacizumab CAEPR – Version 2.5, May 2, 2018

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Bevacizumab (rhuMAb VEGF, NSC 704865)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3540 patients.* Below is the CAEPR for Bevacizumab (rhuMAb VEGF).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, May 2, 2018[1]

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
		Hemolytic uremic syndrome	
CARDIAC DISORDERS			
	Cardiac disorders - Other (supraventricular arrhythmias)[2]		***Cardiac disorders - Other (supraventricular arrhythmias)[2] (Gr 3)***

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Chest pain - cardiac[3]	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction[3]	
		Ventricular arrhythmia	
		Ventricular fibrillation	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Colitis		***Colitis (Gr 3)***
	Constipation		***Constipation (Gr 3)***
	Diarrhea		***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[4]	
	Gastrointestinal hemorrhage[5]		***Gastrointestinal hemorrhage[5] (Gr 2)***
	Gastrointestinal obstruction[6]		
		Gastrointestinal perforation[7]	
		Gastrointestinal ulcer[8]	
	Ileus		
	Mucositis oral		***Mucositis oral (Gr 3)***
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 3)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 3)***
	Pain		***Pain (Gr 3)***
HEPATOBILIARY DISORDERS			
		Gallbladder perforation	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 2)***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[9]		***Infection[9] (Gr 3)***
		Infections and infestations - Other (necrotizing fascitis)	
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		***Infusion related reaction (Gr 2)***
		Injury, poisoning and procedural complications - Other (anastomotic leak)[10]	
	Wound complication		***Wound complication (Gr 2)***
	Wound dehiscence		***Wound dehiscence (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 3)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hyperglycemia		
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 3)***
		Avascular necrosis[11]	
	Generalized muscle weakness		
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[12]		
	Myalgia		***Myalgia (Gr 3)***
	Osteonecrosis of jaw[13]		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
	Peripheral sensory neuropathy[14]		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Hematuria		***Hematuria (Gr 3)***
		Nephrotic syndrome	
	Proteinuria		***Proteinuria (Gr 2)***
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Reproductive system and breast disorders - Other (ovarian failure)[15]			
		Vaginal fistula	
	Vaginal hemorrhage		***Vaginal hemorrhage (Gr 3)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr 2)***
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Cough		***Cough (Gr 3)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		***Epistaxis (Gr 3)***
	Hoarseness		***Hoarseness (Gr 3)***
		Pulmonary hypertension	
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***
VASCULAR DISORDERS			
		Arterial thromboembolism[3,16]	
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 3)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation, and atrial flutter.

[3]The risks of arterial thrombosis such as cardiac or CNS ischemia are increased in elderly patients and in patients with a history of diabetes.

[4]Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[6]Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[7]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation.

[8]Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[9]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[10]Anastomotic leak may include Gastric anastomotic leak; Gastrointestinal anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak.

[11]There have been reports of non-mandibular osteonecrosis (avascular necrosis) in patients under the age of 18 treated with bevacizumab.

[12]Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

[13]Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

[14]Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

[15]Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

[16]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

Adverse events reported on bevacizumab (rhuMAb VEGF) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that bevacizumab (rhuMAb VEGF) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Disseminated intravascular coagulation; Hemolysis; Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Atrioventricular block complete; Atrioventricular block first degree; Cardiac arrest; Myocarditis; Pericardial effusion; Restrictive cardiomyopathy; Right ventricular dysfunction
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (tympanic membrane perforation); Hearing impaired; Tinnitus; Vertigo
ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blindness); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (corneal epithelial defect); Eye disorders - Other (ischemic CRVO); Eye disorders - Other (macular pucker); Eye disorders - Other (transient increased IOP > or =30 mm Hg); Eye pain; Floaters; Keratitis; Optic nerve disorder; Photophobia; Retinal detachment; Retinal tear; Retinopathy; Vitreous hemorrhage; Watering eyes
GASTROINTESTINAL DISORDERS - Ascites; Cheilitis; Colonic stenosis; Dry mouth; Dysphagia; Enterocolitis; Esophageal pain; Esophageal stenosis; Flatulence; Gastrointestinal disorders - Other (peritonitis); Oral pain; Pancreatitis; Proctitis; Rectal mucositis; Rectal stenosis; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema face; Edema limbs; Edema trunk; Facial pain; Fever; Flu like symptoms; Gait disturbance; Injection site reaction; Localized edema; Multi-organ failure; Sudden death NOS
HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder necrosis; Gallbladder obstruction; Hepatic failure; Hepatic necrosis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Arterial injury; Bruising; Burn; Dermatitis radiation; Fracture

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood antidiuretic hormone abnormal; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Electrocardiogram QT corrected interval prolonged; Forced expiratory volume decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Chest wall pain; Fibrosis deep connective tissue; Head soft tissue necrosis; Joint effusion; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neck pain; Osteonecrosis; Pain in extremity; Pelvic soft tissue necrosis; Soft tissue necrosis lower limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Arachnoiditis; Ataxia; Central nervous system necrosis; Cerebrospinal fluid leakage; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Facial nerve disorder; Hydrocephalus; Leukoencephalopathy; Memory impairment; Myasthenia gravis; Nervous system disorders - Other (increased intracranial pressure); Paresthesia; Peripheral motor neuropathy; Pyramidal tract syndrome; Seizure; Somnolence; Tremor; Vasovagal reaction
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Libido decreased; Psychosis
RENAL AND URINARY DISORDERS - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Dysuria; Renal and urinary disorders - Other (ureterolithiasis); Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain; Erectile dysfunction; Irregular menstruation; Pelvic pain; Vaginal discharge
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Atelectasis; Hypoxia; Nasal congestion; Pulmonary fibrosis; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (dry nares); Respiratory, thoracic and mediastinal disorders - Other (pulmonary infarction)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Hyperhidrosis; Nail loss; Pain of skin; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders - Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Skin ulceration; Stevens-Johnson syndrome
VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Lymphocele; Phlebitis; Vasculitis

Note: Bevacizumab (rhuMAb VEGF) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

4.37 General Information on Adverse Effects of Bevacizumab **(06/22/09)**

Based on clinical trials with bevacizumab as monotherapy or in combination with chemotherapy, the most common adverse events of any severity include asthenia, pain, headache, hypertension, diarrhea, stomatitis, constipation, epistaxis, dyspnea, dermatitis and proteinuria. The most common grade 3-4 adverse events were asthenia, pain, hypertension, diarrhea and leukopenia. The most serious AEs include life-threatening or fatal hemorrhage, arterial thromboembolic events, gastrointestinal perforation and wound dehiscence; these events were uncommon but occurred at an increased frequency compared to placebo or chemotherapy controls in randomized studies.

The following is a description of major adverse events associated with bevacizumab therapy. A list of Comprehensive Adverse Events and Potential Risks (CAEPR)in NCI-CTCAE v5.0 terms is included above. Reference may also be made to the Investigators' Brochure and the FDA package insert (www.fda.gov/cder/foi/label/2004/125085lbl.pdf).

Infusion-Related Reactions: Infusion reactions with bevacizumab were uncommon (<3%) and rarely severe (0.2%). Infusion reactions may include rash, urticaria, fever, rigors, hypertension, hypotension, wheezing, or hypoxia. Currently, there is no adequate information on the safety of retreatment with bevacizumab in patients who have experienced severe infusion-related reactions.

Hypertension: Hypertension is common in patients treated with bevacizumab, with an incidence of 20-30% across trials. Initiation or increase of anti-hypertensive medications may be required, but in most cases, blood pressure (BP) can be controlled with routine oral drugs. However, incidents of hypertensive crisis with encephalopathy or cardiovascular sequelae have been rarely reported. BP should be closely monitored during bevacizumab therapy and the goal of BP control should be consistent with general medical practice. Bevacizumab therapy should be suspended in the event of uncontrolled hypertension.

Proteinuria: Proteinuria has been seen in all bevacizumab studies to date, ranging in severity from an asymptomatic increase in urine protein (incidence of about 20%) to rare instances of nephrotic syndrome (0.5% incidence). Pathologic findings on renal biopsies in two patients showed proliferative glomerulonephritis. NCI-CTCAE grade 3 proteinuria (> 3.5gm/24 hour urine) is uncommon, but the risk may be higher in patients with advanced RCC. In the phase 2 randomized study in RCC, 24-hour urine was collected in a subset of patients enrolled, and grade 3 proteinuria was found in 4 patients in the 10 mg/kg-arm (n=37), 2 patients in the 3mg/kg arm (n=35) and none in the placebo arm (n=38). The safety of continuing bevacizumab in patients with moderate or severe proteinuria has not been adequately tested.

Hemorrhage: The incidence of hemorrhage is increased with bevacizumab therapy. Epistaxis is common, occurring in 20-40% of patients, but it is generally mild and rarely requires medical intervention. Life-threatening and fatal hemorrhagic events have been observed in bevacizumab studies and included pulmonary hemorrhage, CNS bleeding and gastrointestinal (GI) bleeding. In a phase 2 study in non-small cell lung cancer, 6 cases of life-threatening hemoptysis or hematemesis were reported among 66 patients treated with bevacizumab and chemotherapy; 4 of these events were fatal.[97] In the pivotal phase 3 trial in advanced colorectal cancer, the rate of GI hemorrhage (all grades) was 24% in the IFL/bevacizumab arm

compared to 6% in the IFL arm; grade 3-4 hemorrhage was 3.1% for IFL/bevacizumab and 2.5% for IFL. Serious GI hemorrhage has also been observed in clinical trials with bevacizumab in patients with pancreatic cancer or varices treated with bevacizumab.

Arterial Thromboembolic Events: The risk of arterial thromboembolic events is increased with bevacizumab therapy, and such events included cerebral infarction, transient ischemic attack (TIA), myocardial infarction and other peripheral or visceral arterial thrombosis. In the pivotal trial in CRC

(AVF2107), the incidence of arterial thromboembolic events was 1% in the IFL/placebo arm compared to 3% in the IFL/ bevacizumab arm. A pooled analysis of five randomized studies showed a two-fold increase in these events (4.4% vs 1.9%). Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk.[98] In patients $\geq$ 65 years treated with bevacizumab and chemotherapy, the rate of arterial thromboembolic events was approximately 8.5%.

Gastrointestinal Perforation/Fistula: GI perforations/fistulas were rare but occurred at an increased rate in bevacizumab-containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal phase 3 trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/bevacizumab and 4% in patients receiving 5-FU/bevacizumab compared to 0.3% in patients receiving IFL alone. GI perforation has also been reported in patients with gastric/esophageal cancer, pancreatic cancer, ovarian cancer or co-morbid GI conditions such as diverticulitis and gastric ulcer. **GI perforation should be included in the differential diagnosis of patients on bevacizumab therapy presenting with abdominal pain, fever of unclear source, or rectal/abdominal abscess.**

Wound Healing Complications: Bevacizumab delays wound healing in rabbits, and it may also compromise or delay wound healing in patients. Bowel anastomotic dehiscence and skin wound dehiscence have been reported in clinical trials with bevacizumab. The appropriate interval between surgery and initiation of bevacizumab required to avoid the risk of impaired wound healing has not been determined. However, all clinical trials with bevacizumab have required a minimum of 28 days from prior major surgery; experience in the pivotal trial in advanced CRC suggests that initiation of bevacizumab 29-50 days following surgery should be associated with a very low incidence of wound dehiscence. The optimal interval between termination of bevacizumab and subsequent elective

surgery has not been determined either. In the pivotal study in CRC, 40 patients on the IFL/bevacizumab arm and 25 patients on the ILF/placebo arm underwent major surgery while on study; among them, significant post-operative bleeding or wound healing complications occurred in 4 of the 40 patients from the IFL/bevacizumab arm and none of the 25 patients from the IFL alone arm. Decisions on the timing of elective surgery should take into consideration the half-life of bevacizumab (average 21 days, with a range of 11-50 days).

Congestive Heart Failure: The risk of left ventricular dysfunction may be increased in patients with prior or concurrent anthracycline treatment. In phase 3 controlled clinical trials in metastatic breast cancer (AVF 2119g) in which all patients had received prior anthracyclines, congestive heart failure (CHF) or cardiomyopathy were reported in 7 patients (3%) in the bevacizumab/capecitabine arm compared to 2 (1%) in the capecitabine-only arm. No increase in CHF was observed in CRC trials with bevacizumab in combination with IFL or 5-FU.

Venous Thrombosis: Venous thromboembolic events reported in bevacizumab trials included lower extremity deep vein thrombosis (DVT), pulmonary embolism and rarely, mesenteric or portal vein thrombosis. In the pivotal phase 3 trial of IFL ± bevacizumab (given at 5 mg/kg q2w), the overall incidences of G3-4 venous thromboembolic events were comparable in the two arms (15.1 vs 13.6%).

Fertility and Pregnancy: Clinical data are lacking regarding the immediate or long-term effect of bevacizumab on fertility and pregnancy. However, bevacizumab is known to be teratogenic and detrimental to fetal development in animal models. In addition, bevacizumab may alter corpus luteum development and endometrial proliferation, thereby having a negative effect on fertility. As an IgG1, it may also be secreted in human milk. Therefore, fertile men and women on bevacizumab studies must use adequate contraceptive measures and women should avoid breast feeding. The duration of such precautions after discontinuation of bevacizumab should take into consideration the half-life of the agent (average 21 days, with a range of 11 to 50 days).

Immunogenicity**:** As a therapeutic protein, there is a potential for immunogenicity with bevacizumab. With the currently available assay with limited sensitivity, high titer human anti-bevacizumab antibodies have not been detected in approximately 500 patients treated with bevacizumab.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), or similar leukoencephalopathy syndrome: RPLS/PRES are clinical syndromes related to vasogenic edema of the white matter and have rarely been

reported in association with bevacizumab therapy (<1%). Clinical presentations may include altered mental status, seizure, and cortical blindness. MRI scans are required for diagnosis: typical finding are vasogenic edema in the white matter of the posterior parietal and occipital lobes, and less frequently in the anterior distributions and the gray matter. In RPLS associated with bevacizumab mild or significant BP elevations were seen in some but not all cases. RPLS/ PRES should be in the differential diagnosis in patients presented with unexplained mental status change, visual disturbance, seizure or other CNS finding. MRI is the key to diagnosis. This syndrome is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent irreversible tissue damage. **(06/22/09)**

Neutropenia: when combined with chemotherapy, bevacizumab increased the risk of neutropenia compared to chemotherapy alone. In a phase 3 trial with IFL +/- bevacizumab in colorectal cancer, grade 3-4 neutropenia was 21% in the bevacizumab arm + IFL vs 14% in the IFL arm (grade 4 neutropenia was 3% vs 2%). In a phase 3 trial with carboplatin and paclitaxel +/- bevacizumab in NSCLC, the bevacizumab-containing arm was associated with an increased rate of grade 4 neutropenia (27% vs 17%), febrile neutropenia (5.4% vs 1.8%), and an increased risk of infection with neutropenia (4.4% vs 2.0%) with three fatal cases in the bevacizumab + chemotherapy arm vs none in the chemotherapy control arm .**(06/22/09)**

4.38 Agent Ordering and Agent Accountability **(08/04/08)**

NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

4.39 Agent may be requested by completing a Clinical Drug Request (NIH-986) and mailing it to the Drug Management and Authorization Section, PMB, DCTD, NCI, 9000 Rockville Pike, EPN Room 7149, Bethesda, MD

20892-7422 or faxing it to (301) 480-4612. For questions call (301) 496-5725.

4.40 Agent Inventory Records - The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record (DAR) Form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)**(6/22/09)**

4.41 Under Japanese regulation, because bevacizumab is commercially available and approved by the PMDA for this indication, it can no longer be supplied free of charge. As of (03/09/15), Japanese sites enrolling and/or treating patients on this study must use commercially available bevacizumab. Japanse institutional pharmacies will handle drug accountability **(03/09/15)**

4.4 Docetaxel (Taxotere® RP-56976, NSC #628503)

4.41 Formulation: Docetaxel is supplied as a sterile, non-pyrogenic, non-aqueous viscous solution in single dose vials containing 20mg/0.5mL or 80mg/2mL of docetaxel. Each mL contains 40mg docetaxel (anhydrous) and 1040mg polysorbate 80.

4.42 Docetaxel requires dilution prior to use. A sterile, non-pyrogenic, single dose diluent is supplied for this purpose. The diluent for docetaxel contains 13% (w/w) ethanol in water for injection and is supplied in vials.

4.43 Storage: Unopened vials of docetaxel are stable to the date indicated on the package when stored between 2 and 25°C (36 and 77°F). Protect from light.

4.44 Preparation: Docetaxel must be combined with its supplied diluent (final concentration = 10mg/mL) and then further diluted prior to infusion. Docetaxel should be diluted in 0.9% Sodium Chloride for Injection, USP or 5% Dextrose Injection, USP to produce a final concentration of 0.3 to 0.74mg/mL. The fully prepared docetaxel infusion solution should be used within 4 hours (including the infusion duration).

NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.

All patients should be premedicated with oral corticosteroids for 3 days starting 1 day prior to docetaxel administration in order to reduce the

incidence and severity of fluid retention as well as the severity of hypersensitivity reactions.

4.45 Adverse Effects: Consult the package insert for the most current and complete information.

4.46 Supplier: Commercially available from Aventis. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

4.5 Gemcitabine**(10/01/12)**

4.51 Formulation: Gemcitabine is supplied as a lyophilized powder in sterile vials containing 200 mg or 1 gram of gemcitabine as the hydrochloride salt (expressed as the free base), mannitol and sodium acetate.

4.52 Gemcitabine requires dilution prior to use. The lyophilized product will be reconstituted with normal saline added to the vial in order to make a solution ideally containing 10 mg/ml or </= 40 mg/ml for 200 mg and 1 gram vials.

4.53 Storage: Unopened vials of gemcitabine are stable to the date indicated on the package when stored between 2 and 25°C (36 and 77°F). Once the drug has been reconstituted, it should be stored at controlled room temperature (range, 20 to 25°C) and used within 24 hours.

4.54 Preparation: An appropriate amount of drug will be administered as prepared or diluted with an additional 100 ml of normal saline. Once the drug has been reconstituted, it should be stored at controlled room temperature (range, 20 to 25°C) and used within 24 hours.

4.55 Administration: Gemcitabine will be infused over 1 hour

4.56 Adverse Effects: Consult the package insert for the most current and complete information.

4.57 Supplier: Commercially available from Eli Lilly Pharmaceuticals. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

4.6 Pathology Requirements **(6/22/09)**

4.61 Eligible Patients: Patients must have histologic diagnosis of epithelial ovarian carcinoma, peritoneal primary or Fallopian tube carcinoma, which is now recurrent. Patients with the following histologic epithelial cell

types are eligible: Serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's Tumor, or adenocarcinoma not otherwise specified (N.O.S.).

4.62 Ineligible Patients: Patients with a gynecologic malignancy other then epithelial ovarian carcinoma, peritoneal primary or Fallopian tube carcinoma.

4.63 Requirements and Instructions: Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility for the protocol. See section 7.2 and 10.2 for specific requirements and instructions for the stained pathology slides, pathology reports and forms.

5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

Before patient entries will be accepted, an official signed CTSU IRB Certification Form and a CTSU IRB/Regulatory Approval Transmittal Sheet (forms can be downloaded at **www.ctsu.org**) must be received by the CTSU Regulatory Office. These forms can be faxed or mailed to:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
1-888-823-5923
FAX 215-569-0206

5.1 Patient Entry and Registration **(09/29/14)**

All site staff will use OPEN to enroll patients to this study. OPEN can be accessed at on the GOG web menu page and clicking on the OPEN link.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user id and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the GOG or CTSU roster.
- To perform registrations you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

5.2 Treatment Plan **(06/22/09)**

5.21 Patients meeting eligibility requirements will be considered first for the surgical randomization aspect of the trial. Suitability for secondary cytoreduction will be made by the individual patient's Attending Physician. Guidelines for consideration in assessing candidacy for secondary cytoreduction are listed in Section 5.211. If the patient is considered to be a suitable surgical candidate she will undergo randomization as outlined in Section 5.22.

(The following two sentences do not apply to patients enrolled onto the study after August 28, 2011): If the patient is considered not to be a suitable surgical candidate she will be allowed to participate in the chemotherapy randomization aspect of the trial as outlined in Section 5.23. Patients undergoing surgical randomization will also be randomized to a chemotherapy regimen at the same time. **(08/29/11)(12/19/11)**

5.211 Guidelines for Secondary Cytoreduction: The goal of secondary cytoreduction is **COMPLETE REMOVAL OF ALL VISIBLE DISEASE**. While no specific eligibility can be globally provided, patients with recurrent disease which will not be addressed at surgery should not undergo surgical randomization. In general, women with carcinomatosis and/or ascites make poor surgical candidates as the diffusion of disease usually precludes complete cytoreduction. Similarly, women with parenchymal organ disease (e.g. lung, liver, pancreas, kidney, bone, etc) are poor candidates, if the disease is felt unresectable by preoperative evaluation. Assessment of candidacy will be made by physical exam, laboratory and imaging (MRI, PET/CT and/or CT). Although it is

recognized that patients with longer treatment-free intervals may be considered better surgical candidates (providing some expansion of the preoperative tumor volume characteristics) than those with shorter treatment-free intervals, the primary tenet of surgery for this study in all women enrolled in this arm is complete surgical resection (no visible residual).

5.22 Randomization I: ***Surgery***: Patients entered onto the surgical arm of the trial will undergo abdominal exploration with cytoreduction as outlined in (Appendix II) within 4 weeks of registration. Chemotherapy will be administered following recovery up to 6 weeks after surgery. A discussion with the study chair is required if study treatment is not initiated within 6 weeks of surgery.**(6/22/09) (03/15/10)**

5.23 Randomization II: ***Chemotherapy*. (Between Dec 6, 2007 and August 28, 2011 the following 4 treatment arms were randomly assigned to patients enrolled into this study. Beginning August 29, 2011 all patients are required to be surgical candidates, and only the surgical component of treatment is randomized. For these later patients the systemic treatment, which consists of either paclitaxel+carboplatin (as described for arms I and III) or gemcitabine+carboplatin (as described for arms V and VII) or paclitaxel+carboplatin+bevacizumab (as described for arms II and IV) or gemcitabine+carboplatin+bevacizumab (as described for arms VI and VIII) is selected and declared prior to enrolling onto the study. (08/29/11)(12/19/11) (10/01/12)**

Patient chooses systemic treatment with either:
a) carboplatin + paclitaxel or gemcitabine or
b) carboplatin + paclitaxel or gemcitabine + bevacizumab

5.231 Regimens: **(06/22/09) (03/15/10) (10/01/12)**

Arm	Surgery	Chemotherapy*	Schedule	Maintenance Regimen
I	No	Paclitaxel 175 mg/m^2 ** Carboplatin AUC 5	Every 21 days (Section 5.24)	None
II	No	Paclitaxel 175 mg/m^2 ** Bevacizumab 15 mg/kg Carboplatin AUC 5	Every 21 days (Section 5.25)	Bevacizumab 15 mg/kg every 21 days until progression or toxicity precludes further treatment.

V	No	Gemcitabine 1000 mg/m^2 d1 & d8 Carboplatin AUC 4 day 1	Every 21 days (Section 5.24)	None
VI	No	Gemcitabine 1000 mg/m^2 d1 & d8 Bevacizumab 15 mg/kg Carboplatin AUC 4 day 1	Every 21 days (Section 5.25)	Bevacizumab 15 mg/kg every 21 days until progression or toxicity precludes further treatment.
III	Yes	Paclitaxel 175 mg/m^2 ** Carboplatin AUC 5	Every 21 days (Section 5.24)	None
IV	Yes	Paclitaxel 175 mg/m^2 ** Bevacizumab 15 mg/kg Carboplatin AUC 5	Every 21 days (Section 5.25)	Bevacizumab 15 mg/kg every 21 days until progression or toxicity precludes further treatment.
VII	Yes	Gemcitabine 1000 mg/m^2 d1 & d8 Carboplatin AUC 4 day 1	Every 21 days (Section 5.24)	None
VIII	Yes	Gemcitabine 1000 mg/m^2 d1 & d8 Bevacizumab 15 mg/kg Carboplatin AUC 4 day 1	Every 21 days (Section 5.25)	Bevacizumab 15 mg/kg every 21 days until progression or toxicity precludes further treatment.

*All chemotherapy doses on day one unless otherwise indicated. For those patients randomized to cytoreductive surgery, bevacizumab is to be started at the 2nd cycle of therapy.
** Note: docetaxel 75mg/m^2 IV over 1 hour may be substituted for paclitaxel (see Sections 5.233and 6.161).

5.232 Patients continue to receive maintenance treatment until disease progression or until adverse events prohibit further therapy.

5.233 Sequence and timing of drug administration: **(08/04/08) (03/15/10)(08/29/11)(12/19/11)(10/01/12)**

- **Paclitaxel** will be infused over 3 hours. (Note, for circumstances in which docetaxel should be substituted for paclitaxel: Docetaxel will be administered as a 1 hour IV infusion at a starting dose of 75 mg/m^2 see Sections 6.161 and 6.167).
- **Bevacizumab** administration will be as a short intravenous infusion following paclitaxel infusion. Anaphylaxis precautions should be observed during bevacizumab

administration. The initial dose would be administered over 90 ± 15 minutes. If no adverse reactions (including fever and or chill) occur, the second dose should be administered over a minimum of 60 ± 10 minutes. If no adverse reactions occur after the second dose, all subsequent doses should be administered over a minimum of 30 minutes.

- **Bevacizumab has been associated with an increase in wound complications and bowel perforations in post-operative patients. Thus, patients in Randomization I who undergo surgery and are to receive bevacizumab after Randomization II will have the first cycle of therapy without bevacizumab. They will receive it in cycle #2.**
- **Gemcitabine will be administered over 60 minutes on days 1 and 8 of each 21-day cycle. Patients will be monitored prior to each dose with a complete blood count, including differential counts.**
- **Carboplatin** will be administered as a 60-minute infusion. When administered in conjunction with other medications, carboplatin will be infused after the other agents. Carboplatin, either alone or in combination should be premedicated with dexamethasone (either IV or PO), anti-histamine H1 (such as diphenhydramine) and anti-histamine H2 (such as cimetidine, ranitidine, or famotidine).

5.234 Pre-Medication:**(10/01/12)**

For all courses where paclitaxel is to be administered, it is recommended that a preparative regimen be employed one hour prior to the treatment regimen on that day to reduce the risk associated with hypersensitivity reactions. This regimen should include dexamethasone (either IV or PO), anti-histamine H1 (such as diphenhydramine) and anti-histamine H2 (such as cimetidine, ranitidine, or famotidine).

When carboplatin and paclitaxel are administered with bevacizumab, it is recommended that the preparatory regimen as outlined above should be given 30 minutes if IV or 60 minutes if PO before infusion to reduce the risk of hypersensitivity associated with these agents.

In the event of a prior bevacizumab hypersensitivity reaction the prophylactic regimen should be repeated prior to subsequent doses of bevacizumab (Section 5.2551). Thus, the patient will be premedicated prior to paclitaxel AND prior to bevacizumab.

For all courses where docetaxel is to be administered, (see Sections 6.161 and 6.167) it is recommended that patients be premedicated with dexamethasone 8 mg orally taken the night before, morning of, and evening after each treatment (total dose, 24 mg/wk), and an anti-histamine H1 (diphenhydramine 25-50 mg IVP or orally, or an equivalent dose of an alternate H_1 blocker such as loratadine or fexofenadine) one hour prior to docetaxel.

5.235 Antiemetic Regimens**(10/01/12)**

It is anticipated that nausea and vomiting may be a significant side effect of each regimen. The following representative antiemetic regimens are suggested:

- Ondansetron 8-32 mg IV 30 minutes prior to administration of chemotherapy and dexamethasone 10-20 mg IV 30 minutes prior to drug administration or,
- 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 $\geq$ 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 V4.0 Grade 3 hemorrhage and receiving full-dose anticoagulation will be taken off study treatment. For all other patients with CTCAE V4.0

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 V4.0 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 V4.0 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, v4.0 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 ≤ 150 mm Hg and diastolic ≤ 90 mmHg, continue therapy;
- For uncontrolled hypertension (systolic > 150 mm Hg or diastolic > 90) or symptomatic hypertension less than CTCAE V4.0 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 V4.0 Grade 4, persists after three weeks after holding treatment, the patient is removed from study.
- Any patient developing CTCAE V4.0 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 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 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

Note: Testing of banked samples will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

7.31 Specimen Requirements **(08/04/08) (06/22/09) (03/09/15)**

If the patient gives permission for her specimens to be collected and used for this optional translational research component, then participating institutions within the United States are required to submit the patient's specimens as outlined below (unless otherwise specified).

Required Specimen (Specimen Code)	Collection Time Point	Sites Ship Specimens to
ALL PATIENTS		
Whole Blood (WB01) 7-10mL drawn into purple top (EDTA) tube(s)	Prior to or after starting study treatment	GOG Tissue Bank within 26 weeks of registration[2]
SURGICAL ARM PATIENTS ONLY		
FFPE Primary or Metastatic Tumor (FT01)* 1st Choice: Block 2nd Choice: 16 unstained slides (charged, 5µm)	Prior to all treatment	GOG Tissue Bank within 8 weeks of registration[2]
Pre-Op Serum (SB01) Prepared from 7-10mL of blood drawn into plain red top tube(s)	*Optional* - Prior to secondary cytoreductive surgery	GOG Tissue Bank within 1 week of surgery[2]
Pre-Op Plasma (PB01) Prepared from 7-10mL of blood drawn into purple top (EDTA) tube(s)		
FFPE Recurrent Tumor (FR01)* 1st Choice: Block 2nd Choice: 16 unstained slides (charged, 5µm)	At time of secondary cytoreductive surgery	
Snap Frozen Recurrent Tumor (RR01)* At least 0.2g in foil		
FFPE Normal Tissue (FN01)* 1st Choice: Block 2nd Choice: 16 unstained slides 5um thick	*Optional* - At time of secondary cytoreductive surgery	
Snap Frozen Normal Tissue (RN01)* At least 0.2g in foil		

* A copy of the corresponding pathology report must be shipped with all tissue specimens (tumor and normal) sent to the GOG Tissue Bank.

2 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, Email: GOGBank@nationwidechildrens.org

7.3.2 Laboratory Testing **(03/09/15)**

7.3.2.1 Creation of Tissue Microarrays (TMAs)

A series of TMAs to study biomarkers of recurrence, survival, and/or treatment response/resistance will be created. The specific types of TMAs that will be created will depend on FFPE block submissions and the clinical outcomes observed for these cases.

Unstained sections from TMAs (or conventional blocks for cases not represented on the TMAs) will be distributed to Dr. Michael Birrer and/or other investigators approved by the GOG Committee on Experimental Medicine (CEM) for biomarker, genomic, proteomic, and/or SNP analyses.

7.3.2.2 Light Microscopy

Light microscopy will be done to characterize the histopathologic features of tissue specimens undergoing molecular and biochemical profiling and to satisfy some of the specimen selection

criteria for gene expression profiling. Stained sections will be reviewed by Dr. William Rodgers, chair of the GOG Pathology Committee, and other members of the committee.

7.3.2.3 Biomarker Analysis

Multiple types of biomarker analyses (e.g., immunohistochemistry (IHC), reverse phase array, conventional immunoblot assays, quantitative RT-PCR) will be done to expand the current understanding of the biology, progression, metastasis, and responsiveness of recurrent ovarian and peritoneal primary cancer.

IHC will be done using sections from conventional blocks and/or TMAs by Dr. Michael Birrer, the GOG Receptors and Targets Core Laboratory, and/or other CEM-approved investigators.

Reverse phase array and conventional immunoblot analyses will be done using lysates from frozen recurrent tumor, microdissected recurrent tumor cells, and normal tissue.

Quantitative RT-PCR will be done to identify and/or validate prognostic or predictive markers of recurrence, survival, and treatment response/resistance. In addition, these assays will be used to validate individual markers identified in gene expression microarray studies.

7.3.2.4 Genomic Profiling

Gene expression microarray analysis will be done using RNA isolated from frozen recurrent tumor and normal tissue and an appropriate platform to define gene expression patterns associated with disease progression, spread of disease, response to treatment, and/or patient outcome. These studies will be done by Dr. Michael Birrer and/or other CEM-approved investigators.

7.3.2.5 Proteomic Profiling

Proteomic profiling will be done using pre-op serum to define protein/peptide fragment patterns that are associated with disease progression, spread of disease, and response to treatment or patient outcome. Proteomic studies will be done by CEM-approved investigators.

7.3.2.6 SNP Analysis

Whole blood will be shipped to the GOG Tissue Bank for immediate processing, extraction of DNA, and Q/C. DNA will be shipped to Dr. Michael Birrer and/or other CEM-approved investigators for whole genome SNP association studies and/or evaluation of individual SNPs.

7.3.3 Future Research **(03/09/15)**

Details regarding the banking and use of translational research specimens for future research can be found in Appendix III.

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

7.41 Patients in the secondary cytoreduction arm will complete the quality of life questionnaire packet (which includes the FACT-O and the RAND SF-36 physical functioning questionnaire) before surgery and before the first cycle of chemotherapy. The FACT-O is available in Spanish and French. Requests should be submitted to the GOG Statistical and Data Center. Patients in the no surgery arm will complete the quality of life questionnaire packet before the first cycle of chemotherapy. Follow-up questionnaires will be completed prior to beginning of the third cycle (approximately six weeks from the start of treatment) and prior to beginning of the sixth cycle (or approximately 15 weeks from the start of treatment). Additional quality of life assessments will be done at six and twelve months after initiating chemotherapy. If a patient progresses or is removed from the study treatment, continue to follow the schedule of QOL assessments when possible regardless of subsequent treatments. Whenever possible, QOL questionnaires should be administered at the clinic visit before the patient is seen by the physician and before evaluations (e.g., results of CA-125 or scans) are shared with her. In the event that the questionnaires are not administered at the clinic visit, the QOL data can be collected by telephone or mail as back-up methods, with telephone data collection being the preferred back-up method.

7.42 The Quality of Life Liaison (Nurse\Data Manager) at each institution has overall responsibility for the administration of the study questionnaire.

7.43 The Nurse\Data Manager should read the instructions printed on the questionnaire to the patient and ensure the patient understands the instructions. It is important to assure the patient that all material on the questionnaire is confidential and will not be shared with the health care team and that it will not become part of the medical record.

7.44 Assistance in reading the questionnaire is permitted if the patient is unable to complete the questionnaire on her own (e.g., difficulty in reading,

elderly). It is important not to influence the response of the patient. Note why the patient required assistance and what assistance was given.

7.45 Patients should be instructed to answer all the questions regardless of whether the symptoms or conditions asked about are related to cancer or cancer treatment. Discourage family members from being present during questionnaire completion or from influencing patient's response.

7.46 Review the questionnaire for completeness before the patient leaves.

7.47 If the patient has marked more than one answer per question, ask the patient which answer best reflects how she is feeling.

7.48 If the patient has skipped a question or questions, assure that she noted in the space provided that she has chosen not to answer those questions.

7.49 It is essential that questionnaires be completed according to the schedule described in Section 7.1.

7.410 If the patient refuses or cannot complete the questionnaire at any time point, she should be asked to do so at the next scheduled administration time.

7.411 The patient may withdraw from the quality of life section of the protocol for any reason. The reason must be documented on the form.

7.412 The Quality of Life Liaison may attend a training session held at a biannual GOG meeting.

8.0 EVALUATION CRITERIA

8.1 Parameters of Response – GOG RECIST Criteria

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

8.12 Baseline documentation of "Target" and "Non-Target" lesions

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

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

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

8.13 Best Response

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

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

8.132 Partial Response (PR) is at least a 30% decrease in the sum of longest dimensions (LD) of all *target* measurable lesions taking as reference the baseline sum of LD. There can be no unequivocal progression of *non-target* lesions and no new lesions. Documentation by two disease assessments at least 4 weeks apart is required. In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam, which is not radiographically measurable, a 50% decrease in the LD is required.

8.133 Increasing Disease is at least a 20% increase in the sum of LD of *target* lesions taking as references the smallest sum LD or the appearance of new lesions **within 8 weeks of study entry**. Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician within 8 weeks of study entry is also considered increasing disease (in this circumstance an explanation must be provided). In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam, which is not radiographically measurable, a 50% increase in the LD is required.

8.134 Symptomatic deterioration is defined as a global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression.

8.135 Stable Disease is any condition not meeting the above criteria.

8.136 Inevaluable for response is defined as having **no** repeat tumor assessments following initiation of study therapy *for reasons unrelated to symptoms or signs of disease*.

8.14 Progression (measurable disease studies) is defined as ANY of the following:

- At least a 20% increase in the sum of LD target lesions taking as reference the smallest sum LD recorded since study entry
- In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam which is not radiographically measurable, a 50% increase in the LD is required taking as reference the smallest LD recorded since study entry
- The appearance of one or more new lesions
- Death due to disease without prior objective documentation of progression
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression

- Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician (in this circumstance an explanation must be provided) **(06/22/09)**
- Progression based on serum CA-125:
    - Patients with elevated CA-125 pretreatment with normalization of CA-125 must show evidence of CA-125 during study treatment greater than or equal to two times the upper normal limit on two occasions at least one week apart

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

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

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

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

- Appearance of any new clinical, radiological or histological evidence of disease since study entry
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of recurrence
- Death due to disease without prior objective documentation of recurrence
- Progression based on serum CA-125:
    - Patients with elevated CA-125 pretreatment with normalization of CA-125 must show evidence of CA-125 during study treatment greater than or equal to two times the upper normal limit on two occasions at least one week apart

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

- or -

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

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

8.15 Recurrence (following CR) is defined as **ANY** of the following:

- Appearance of any new clinical, radiological or histological evidence of disease since study entry
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of recurrence
- Death due to disease without prior objective documentation of recurrence
- Increase in serum CA-125 levels as follows:
  - Patients with CA-125 in the normal range must show evidence of CA-125 greater than or equal to two times the upper normal limit on two occasions at least one week apart. When disease progression is defined by CA-125 criteria alone, imaging using the same modality and encompassing the same field as in the initial pretreatment evaluation should be obtained within 2 weeks that such progression is documented (see Section 7.1). If the disease progression is noted on imaging, then the date of progression will be the date of the imaging studies. Otherwise, the date of progression will be the date of the first CA-125 level that indicates progression. **(08/23/10)**

8.16 Survival is the observed length of life from entry into the study to death or the date of last contact.

8.17 Progression-Free Survival (measurable disease studies) is the period from study entry until disease progression, death or date of last contact.

8.18 Recurrence-Free Survival (non-measurable disease studies) is the period from study entry until disease recurrence, death or date of last contact.

8.19 Subjective Parameters including performance status, specific symptoms, and side effects are graded according to the CTCAE v4.0.

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 v5.0 expedited AEs must be reported to the GOG. All expedited AE reports should be submitted by using the CTEP Adverse Event Reporting System (CTEP-AERS). Submitting a report through CTEP-AERS serves as notification to GOG, and satisfies the GOG requirements for expedited AE reporting.

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

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

Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Study Procedure:

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

Beginning October 1, 2011, the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will be utilized for AE reporting through

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	With Hospitali-zation	Without Hospitali-zation	With Hospitali-zation	Without Hospitali-zation	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	7 Days	Not Required	7 Days	Not Required	7 Days	7 Days
Possible Probable Definite	Not Required	Not Required	Not Required	7 Days	Not Required	7 Days	Not Required	7 Days	7 Days

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after surgery require reporting as follows:

CTEP-AERS 7 calendar day report:
- At least Grade 3 with hospitalization or prolongation of hospitalization, or
- Persistent causes, significant disabilities/incapacities

[2] **Grade 5:** All deaths within 30 days of the surgical procedure must be reported within 7 calendar days using expedited reporting regardless of causality.

Please see exceptions below under the section entitled, "Additional Instructions or Exceptions to Expedited Reporting Requirements for Surgical Trials."

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the CTEP-AERS system. CTCAE v 4.0 is located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of this Version of CTCAE. CTCAE v 4.0 definition is also available on the GOG member web site (https://gogmember.gog.org under MANUALS). **(09/26/11)**

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning **April 1, 2018**. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

- Expedited AE reporting timelines defined:
  "7 calendar days" – A complete CTEP-AERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grades 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported

regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities and/or incapacities must be reported via CTEP-AERS if the event occurs following a protocol procedure.

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

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Surgical Trials:

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

10.14 Procedures for Expedited Adverse Event Reporting

10.141 CTEP-AERS Expedited Reports: Expedited reports are to be submitted using CTEP-AERS available at http://ctep.cancer.gov. The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.

Up until September 30, 2011, AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v3.0, the event can be reported as: "Secondary malignancy-Other (specify)". **(09/26/11)**

Starting October 1, 2011 when use of CTCAE v4.0 begins: AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment related secondary malignancy. **(09/26/11)**

Starting April 1, 2018 when use of CTCAE v5.0 begins: AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v5.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment related secondary malignancy.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to GOG by telephone at: 215-854-0770. An electronic report MUST be submitted immediately upon re-establishment

of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

10.2 ADVERSE EVENT REPORTING FOR AN INVESTIGATIONAL AGENT (TO USE FOR PATIENTS WHO SELECT BEVACIZUMAB AFTER AUGUST 28, 2011) **(12/19/11)**

10.21 Definition of Adverse Events (AE)

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

10.22 Reporting Expedited Adverse Events

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

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

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

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

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

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

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning **April 1, 2018**. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

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

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

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 7 calendar day report:

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

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

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

March 2005

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

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

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) with the exception as listed below (grade 2-4 myelosuppression) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

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

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

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

- Reference the SPEER (Specific Protocol Exceptions to Expedited Report) for the subset of AEs that are protocol specific exceptions to expedited reporting via CTEP-AERS. Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If the CAEPR for a protocol agent is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required. For questions or comments regarding the SPEER or CAEPR, please contact the CTEP-AERS MD Help Desk at CTEP-AERSmd@tech-res.com**(12/19/11)**

- *"All Grades 2, 3 and 4 myelosuppression (including neutropenia, anemia, and thrombocytopenia) regardless of the need for hospitalization is exempt from expedited reporting*."

10.24 Procedures for Expedited Adverse Event Reporting:**(12/19/11)**

10.241 CTEP-AERS Expedited Reports: Expedited reports are to be submitted using CTEP-AERS available at http://ctep.cancer.gov. The NCI guidelines for expedited adverse event reporting requirements are also available at this site.

Up until September 30, 2011, AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v3.0, the event can be reported as: "Secondary malignancy-Other (specify)". **(09/26/11)**

Starting October 1, 2011 when use of CTCAE v4.0 begins: AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment related secondary malignancy.**(09/26/11)**

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning **April 1, 2018.** All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

10.25 Automated CDUS reporting

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

10.3 ADVERSE EVENT REPORTING FOR A COMMERICIAL AGENT (TO BE USED FOR PATIENTS NOT TAKING BEVACIZUMAB AFTER AUGUST 28, 2011) **(08/29/11) (12/19/11)**

10.31 Phase 2 and 3 Trials Utilizing a Commercial Agent: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of Any Commercial Study Agent

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

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

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

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning **April 1, 2018.** All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

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

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

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

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 7 calendar day report:

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

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

Please see exceptions below under the section entitled, "Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent." March 2005

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

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

  "7 calendar days" – A complete CTEP-AERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported to GOG via CTEP-AERS if the event occurs following treatment with a commercial agent.

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

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

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

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

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

10.32 Procedures for Expedited Adverse Event Reporting:

10.321 CTEP-AERS Expedited Reports: Expedited reports are to be submitted using CTEP-AERS available at http://ctep.cancer.gov. The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.

Starting **April 1, 2018** when use of CTCAE v5.0 begins: AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v5.0, the event(s) may be reported as

either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment related secondary malignancy.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to GOG by telephone at: 215-854-0770. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

10.33 Automated CDUS reporting

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

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

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

Form±	**Due within**		**Copies** *	**Comments**
	Weeks	**Event**		
Form R (Registration Form)	2	Registration	1	Mandatory Submission via SEDES
Form OSR (Recurrent Gynecologic Cancer - On Study Form)	2	Registration	1	Mandatory Submission via SEDES
Specimen Consent Application	1	Registration °	N/A	Complete Online
Form DR (Pretreatment Summary Form	2	Registration		Mandatory Submission via SEDES
Form D2M (Solid Tumor Evaluation Form) #	2	Registration	1	Mandatory Submission via SEDES

Primary Disease Form F (Pathology Form) Pathology Report Pathology Slides Secondary Cytoreductive Surgery Form F (Pathology Form Pathology Report	 6 6 6 6 6	 Registration Registration Registration Surgery*** Surgery***	 3 3 ** 3 3	 Submit together to the SDC via postal mail Submit together to the SDC via postal mail
Cytoreductive Surgery: Form C (Surgical Reporting Form) Operative Report Discharge Summary	 6 6 6	Surgery***	 1 2 2	Mandatory Submission via SEDES Submit via postal mail Submit via postal mail
Form SP-FT01-0213[1] FFPE primary or metastatic tumor tissue	8	Registration		Mandatory submission via SEDES[2]
Form SP-SB01-0213 pre-op serum (optional)	1	Surgery		Mandatory submission via SEDES[2]
Form SP-PB01-0213 pre-op plasma (optional)	1	Surgery		Mandatory submission via SEDES[2]
Form SP-FR01-0213[1] FFPE recurrent tumor tissue	1	Surgery		Mandatory submission via SEDES[2]
Form SP-RR01-0213[1] frozen recurrent tumor tissue	1	Surgery		Mandatory submission via SEDES[2]
Form SP-FN01-0213[1] FFPE normal tissue (optional)	1	Surgery		Mandatory submission via SEDES[2]
Form SP-RN01-0213[1] frozen normal tissue (optional)	1	Surgery		Mandatory submission via SEDES[2]
Form SP-WB01-0213 whole blood	26	Registration		Mandatory submission via SEDES[2]
Form T (Common Toxicity Reporting Form) -post op**** #	2	Surgery***	1	Mandatory Submission via SEDES
Form D2R-Cycle Dose Drug Form # 	2 2	Completion of each cycle of therapy	1	Mandatory Submission via SEDES
Form T (Common Toxicity Reporting Form) #	2	Beginning of each subsequent cycle	1	Mandatory Submission via SEDES
Form D2M (Solid Tumor Evaluation Form) #	2	Clinical response assessment	1	Mandatory Submission via SEDES
Form BMR (Biomarker Reporting Form) ±	2	Prior to surgery, prior to each cycle of therapy and during follow-up	1	Mandatory Submission via SEDES
FACT-O**** (Scantron Form)	2	Prior to surgery	1	If randomized to surgery submit the original Scantron form to the GOG SDC via postal mail
FACT-O**** (Scantron Form)	2	Prior to cycle 1, 3 and 6 and at 6 and 12 months	1	Submit the original Scantron form to the GOG SDC via postal mail

		after starting chemotherapy.		
Form SRGSTAT (Surgical Status Form)	52	Registration	1	Mandatory Submission via SEDES
Form Q0 (Treatment Completion Form	2	Completion of study treatment	1	Mandatory Submission via SEDES
Form Q (Follow-up Form)	2	Disease progression, death, and post-treatment follow-up	1	Mandatory submission via SEDES quarterly for 2 years, semi-annually for 3 more years, yearly thereafter

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

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

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

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

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

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

1 A copy of the corresponding pathology report must be shipped with all tissue specimens (tumor and normal) sent to the GOG Tissue Bank.

2 Form SP must be submitted regardless of whether the specimen is submitted for research.

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

This study utilizes the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) for defining and grading adverse events to be reported on GOG case report forms. A GOG CTCAE v4.0 Manual is available on the GOG member web site (http://www.gog.org under MANUALS) and can be mailed to the institution registering a patient to this study if requested.**(09/26/11)**

11.0 STATISTICAL CONSIDERATIONS

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

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

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

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

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

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

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

11.15 No cytoreductive surgery

11.16 Cytoreductive surgery performed prior to initiating systemic therapy.

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

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

11.2 Measures of Efficacy and safety

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

11.21 Primary efficacy endpoint: Overall survival

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

11.23 Safety endpoints: frequency and severity of adverse events (Common Terminology Criteria for Adverse Events (CTCAE) – version 4.0).

11.3 Treatment efficacy

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

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

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

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

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

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

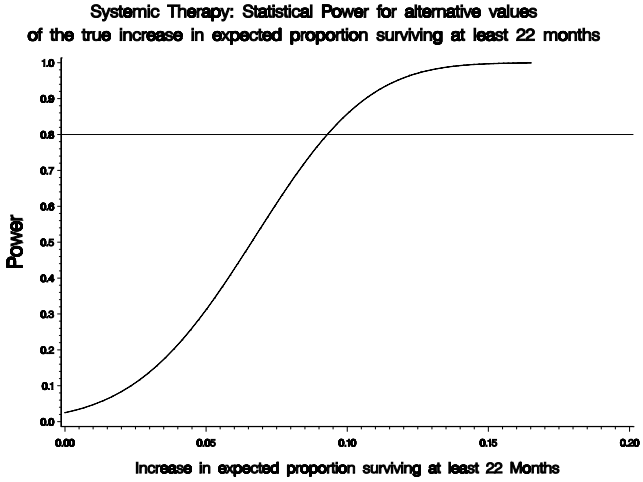

Figure 1.

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

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

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

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

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

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

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

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

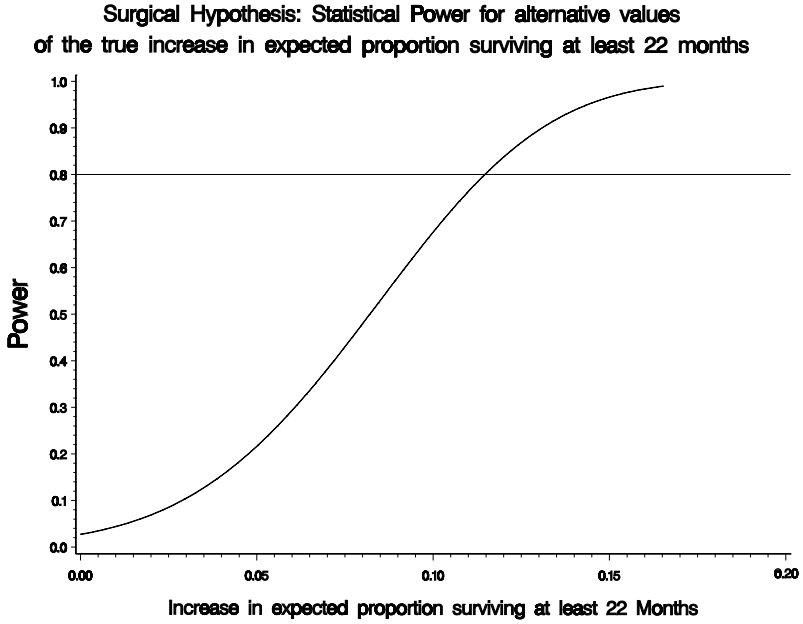

Figure 2.

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

An addendum to the statistical considerations to increase the target accrual to the surgical component of the study. ***(10/13/15)***
The number of individuals originally planned to be enrolled onto the surgical component of this study was 360. As of Aug 1, 2015 there have been 354 patients enrolled. Accrual rate has increased over the past 18 months and the study is currently enrolling 6 patients per month. Women who are deemed to be surgical candidates tend to have a better than expected prognosis and the overall death rate among those enrolled onto this component of this study is lower than originally

anticipated. At this time the surgical component of the study is at 30% information time. The target accrual will be increased (125 individuals) from 360 individuals to 485. At the current accrual rate this target accrual is expected to be completed in Spring-2017. If the target accrual was unchanged, then the date of study maturity is mid-2021 to early 2022. Increasing the target accrual by 125 individuals is expected to reduce the time until full maturity by approximately 2.5 years. The number of events required for full maturity and the schedule for the planned interim analysis are not being changed by this amendment.

Interim Analyses: Interim analyses are planned when there are at least 110 deaths reported among all those patients randomly allocated (prior to August 29, 2011) to the CT regimen (approximately 50% of the full information of the systemic therapy component of this study), The actual time for the interim analyses will coincide with the nearest scheduled Data Monitoring Committee (DMC) meeting for which the required number of events has occurred. The semi-annual DMC meetings coincide with the GOG business meetings which are held in January and July each year and the precise date of these meetings is set without confidential knowledge of the study results. **(10/01/12)**

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

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

The interim analysis that will occur at approximately the 50% of the total information time for H_{01} (or H_{02}) will also include futility analyses. Since the purpose of the study is to identify interventions that increase overall survival duration, consideration will be given to stopping randomization to the experimental interventions (CTB or cytoreductive surgery) if it exhibits poorer survival relative to its control treatment (CT or no surgical intervention,

respectively) indicated by an adjusted hazard ratio, $\Delta_{01} > 1.0$ (or $\Delta_{02} > 1.0$) at the time of the interim analyses. This interim decision rule decreases the statistical power for each pair-wise comparison by less than 1%. The results of the interim analyses are reviewed by the GOG Data Monitoring Committee (DMC). The decision to terminate randomization to any particular regimen includes consideration of toxicities, treatment compliance, progression-free survival, and results from external studies.

Final analysis: The study will be considered sufficiently mature to permit a final assessment of H_{01} when there are at least 214 deaths reported among those patients assigned to the standard regimen (CT). The study will be considered sufficiently mature to permit an assessment of H_{02} when there at least 250 deaths reported among those enrolled (and randomized) onto the surgical component of this study. The previously described logrank test will be performed and the corresponding treatment hazard ratio will be estimated. The critical values for rejecting the null hypotheses will be adjusted for interim analyses, using the O'Brien and Fleming-like type I error spending function proposed by Lan and DeMets (1986).

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

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

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

Grading and classification of adverse events will follow the CTCAE v. 4.0 toxicity criteria. The primary analysis will consist of comparing the relative odds of grade 3 or worse toxicities occurring during and following study treatment that are reported to be at least possibly related to study treatment. Specific attention

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

11.4 Quality of Life

There are primarily three quality of life issues of interest:

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

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

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

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

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

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

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

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

Differences in FACT-TOI scores between patients receiving CT and CTB: Data available from GOG-172 provides some estimates that can be used for planning the current study. In that study women with advanced ovarian cancer received 6 cycles of a platinum-taxane based treatment. The mean and variance of the baseline FACT-TOI scores were 67.2 and 15.9, respectively. The correlation between the baseline FACT-TOI score and the same score reported 3 to 6 weeks after the sixth cycle of treatment was 0.36. The target sample size for this study is based on study objective 1 and is 660 patients (330 patients in each arm). It is anticipated that 90% of the patients will report FACT-TOI scores prior to initiating treatment and prior to treatment cycle 6. If bevacizumab truly changes patients' FACT-TOI scores 4.0 units after 6 cycles of treatment, the targeted sample size has about 91% power for an analysis of covariance, when the type I error is limited to 5% for a two tail test. However, a linear mixed model will be used for the final analysis of this data since this approach is more efficient, accommodates missing data, and accounts for correlations due to repeated measurements from the same individual. The actual power for this analysis, however, depends on the unknown pattern of missing values.

Difference in Rand SF-36 Physical Functioning (PF) subscale after surgery:
This analysis will include those patients who were candidates for surgery and consented to have their surgical intervention determined through randomization. A paired t-test will be used to test the null hypothesis that there is no difference between baseline PF scores and the PF scores prior to cycle 1 for those patients randomized to cytoreductive surgery. The paired t-test is generally robust for moderate sample sizes when the distribution of PF scores is not normal. Data from GOG-2222 can be used for planning purposes. In that study, patients with newly diagnosed endometrial cancer completed the SF-36 PF subscale prior to initiating study treatment. When the scores are rescaled (0-100), the mean and standard deviation were 75.9 and 27.8, respectively. Assuming that at least 485 patients will be eligible and consent to participate in this component of the study, this sample size has 84% power for detecting a true difference of 7.5 units, when type I error is limited to 5% for a two-tail test. **(10/13/15)**

Differences in FACT-TOI scores between patients undergoing cytoreductive surgery and patients not undergoing cytoreductive surgery. This analysis will

include those patients who were candidates for surgery and consented to have their surgical intervention determined through randomization. There will be up to 5 or 6 time points for patients to report their FACT-TOI scores, depending on whether the patient was randomized to the secondary cytoreductive surgery arm of the study. There are no specific hypotheses being posited for how the treatment groups will differ in their mean QOL scores over time. Therefore, a linear mixed model will be used to model the difference in mean QOL scores over time. That is, the mean QOL scores will be modeled in order to compare those patients randomized to secondary cytoreductive surgery vs no surgery, as well as, the differences in mean QOL scores among the three types of systemic therapy. The model will assess whether there is evidence of a treatment-time interaction as well as whether differences in mean QOL scores between treatment groups varies as a linear or possibly a quadratic function of time.

11.5 Translational Research Statistical Considerations

Overview

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

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

Anticipated sample size for translational objectives

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

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

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

Identifying biologic/molecular profiles
Investigators will not be restricted to utilizing a particular technique for building the classifier. In fact, several classifiers may be identified. However, prior to the validation phase a single classifier corresponding to the primary study objective will be selected and deemed the 'final' classifier. Data from the validation dataset will not be used to select the 'final' classifier.

Reliability
The classifier should provide similar results for the same experimental unit. That is, a biologic specimen with a high prognostic index score should exhibit a high prognostic index score when it is re-evaluated. An index score which cannot be replicated lacks test-retest reliability. This occurs when there are other sources of between-specimen variation that are uncontrolled in the experiment.

In order to assess reliability some specimens will be selected from the training set for repeat assessment. While randomly selecting specimens from the training set for replication is preferable, it may be necessary to randomly select from a subset of the training set due to the availability of adequate biologic material. When possible, the samples will be identified in such a way that the laboratory investigator will be unable to identify which specimens are replicates. These samples will have their biomarkers (i.e. gene expression, serum marker) assessed twice. Since replication can be expensive, depending of the laboratory procedure, the number of samples selected for replication will vary from a dozen to a few dozen, depending on practical considerations like cost and feasibility. The data from the replicated samples will be used to assess reliability of the putative index before proceeding to the validation phase. Reproducibility is a prerequisite for a clinically useful classifier.

Validation

Prior to initiating the validation phase, the 'final' classifier will be completely documented (i.e. computer program or pseudo-code). This documentation will be reviewed by individuals in the GOG Statistical and Data Center (SDC) who are not participating in the analyses. The purpose of this review will be to determine whether the final classifier has been unambiguously defined.

The c-index will be used to measure the classifier's predictive ability. This index assesses the strength of the rank correlation between the predicted outcome and the actual outcome. If the classifier produces a continuous prognostic score and response is dichotomous, then the c-index is comparable to the Wilcoxon two-sample rank score. It can be calculated by taking all possible pairs of individuals in which one individual responded and the other did not respond. In this case, the c-index is the proportion of these pairs in which the responder has a higher predicted probability of responding. A c-index value of 0.5 indicates a useless classifier, and a value of 1.0 indicates perfect prediction. The c-index is Somer's rank correlation index when it is rescaled to vary linearly from 0 to 1. The c-index can be used when the outcome is partially censored survival time. In this case it measures the proportion of all pairs of individuals in the data set in which the individual with the expected lower risk of failure is known to survive longer.

Other descriptive summaries of predictive ability will also be considered including: Kaplan-Meier curves when the outcome is a time-to-failure or a ROC curve when the outcome is dichotomous.

The publication which describes the results for the primary objective of this study will include a description of the accuracy of the final classifier. While other classifiers may also be described, the final classifier will be clearly distinguished from the other classifiers. The documentation describing the final classifier will be available to other investigators from the SDC upon request.

After the study objectives have been completed, the GOG may elect to make some or all of the validation data set available to other investigators, since the specimens in the training set may become exhausted. Any classifiers developed subsequently will not be permitted to claim that they were independently validated without additional supporting external evidence.

11.6 The anticipated distribution of patients' race and ethnicity for the systemic therapy portion of this trial is (all are female):

White (not Hispanic)	584
Black (not Hispanic)	39
Hispanic	14
Asian	17
American Indian or Alaskan Native	3
Native Hawaiian or other Pacific Islander	3

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APPENDIX I

FIGO STAGE GROUPING FOR PRIMARY CARCINOMA OF THE OVARY

(1985)

These categories are based on findings at clinical examination and/or surgical exploration. The histologic characteristics are to be considered in the staging, as are results of cytologic testing as far as effusions are concerned. It is desirable that a biopsy be performed on suspicious areas outside the pelvis.

Stage I	Growth limited to the ovaries.
Stage IA	Growth limited to one ovary; no ascites. No tumor on the external surface; capsule intact.
Stage IB	Growth limited to both ovaries; no ascites. No tumor on the external surfaces; capsules intact.
Stage IC*	Tumor either Stage IA or IB but with tumor on the surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage II	Growth involving one or both ovaries with pelvic extension.
Stage IIA	Extension and/or metastases to the uterus and/or tubes.
Stage IIB	Extension to other pelvic tissues.
Stage IIC*	Tumor either Stage IIA or IIB but with tumor on the surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage III	Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals Stage III. Tumor is limited to the true pelvis but with histologically verified malignant extensions to small bowel or omentum.
Stage IIIA	Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces.
Stage IIIB	Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Nodes negative.
Stage IIIC	Abdominal implants >2 cm in diameter and/or positive retroperitoneal or inguinal nodes.
Stage IV	Growth involving one or both ovaries with distant metastasis. If pleural effusion is present there must be positive cytologic test results to allot a case to Stage IV. Parenchymal liver metastasis equals Stage IV.

* In order to evaluate the impact on prognosis of the different criteria for allotting cases to Stage IC or IIC, it would be of value to know if rupture of the capsule was (1) spontaneous or (2) caused by the surgeon and if the source of malignant cells detected was (1) peritoneal washings or (2) ascites.

APPENDIX II

SECONDARY CYTOREDUCTIVE SURGICAL PROCEDURE

Purpose : Maximum resection of recurrent ovarian cancer.

Timing: Surgical exploration should be undertaken within 4 weeks of study entry.

Content of Procedure:

1.0 The abdominal incision must be adequate to explore the entire abdominal cavity and allow safe cytoreductive surgery. A vertical incision is recommended but not required.
2.0 All peritoneal surfaces including the undersurface of both diaphragms and the serosa and mesentery of the entire gastrointestinal tract will be visualized and palpated for evidence of metastatic disease.
3.0 Visible metastatic abdominal and pelvic disease should be resected or ablated completely, if possible.
4.0 Diaphragmatic recurrent disease should be resected. Ablation of disease with electrocautery (e.g. Argon Beam Coagulator) is acceptable.
5.0 Surgical evaluation of the pelvic and paraortic node bearing areas requires resection if not performed on initial staging/debulking procedure. If incomplete nodal resection was previously documented, unresected areas should be excised.
6.0 Solid organ metastases (spleen and liver) should be considered for resection. Treatment by Radio Frequency Ablation (RFA) is acceptable.

Goal: Surgical goal of cytoreduction is to reduce volume of residual disease to smallest quantity possible (no visible residual).

Reporting: The size (two dimensions) and location of residual disease will be recorded.

APPENDIX III **(03/09/15)**
– TRANSLATIONAL RESEARCH SPECIMEN PROCEDURES

I. Summary of the Specimen Requirements

If the patient gives permission for her specimens to be collected and used for this optional translational research component, then participating institutions within the United States are required to submit the patient's specimens as outlined below (unless otherwise specified).

Specimen (Specimen Code)	Collection Time Point	Sites Ship Specimens to
ALL PATIENTS		
Whole Blood (WB01) 7-10mL drawn into purple top (EDTA) tube(s)	Prior to or after starting study treatment	GOG Tissue Bank within 26 weeks of registration[2]
SURGICAL ARM PATIENTS ONLY		
FFPE Primary or Metastatic Tumor (FT01)* 1st Choice: Block 2nd Choice: 16 unstained slides (charged, 5µm)	Prior to all treatment	GOG Tissue Bank within 8 weeks of registration[2]
Pre-Op Serum (SB01) Prepared from 7-10mL of blood drawn into plain red top tube(s)	*Optional* - Prior to secondary cytoreductive surgery	GOG Tissue Bank within 1 week of surgery[2]
Pre-Op Plasma (PB01) Prepared from 7-10mL of blood drawn into purple top (EDTA) tube(s)		
FFPE Recurrent Tumor (FR01)* 1st Choice: Block 2nd Choice: 16 unstained slides (charged, 5µm)	At time of secondary cytoreductive surgery	
Snap Frozen Recurrent Tumor (RR01)* At least 0.2g in foil		
FFPE Normal Tissue (FN01)* 1st Choice: Block 2nd Choice: 16 unstained slides (charged, 5µm)	*Optional* - At time of secondary cytoreductive surgery	
Snap Frozen Normal Tissue (RN01)* At least 0.2g in foil		

1 A copy of the corresponding pathology report must be shipped with all tissue specimens (tumor and normal) sent to the GOG Tissue Bank.

2 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, Email: GOGBank@nationwidechildrens.org

II. Obtaining a GOG Bank ID for Translational Research Specimens

Only one GOG Bank ID (# # # # - # # - G # # #) is assigned per patient. All translational research specimens and accompanying paperwork must be labeled with this coded patient number. A GOG Bank ID can be obtained online via the Tissue Bank Portal on the GOG website (under Tools on the Web Menu page).

Obtain the patient's study ID (GOG #) for all protocols with translational research specimen requirements before requesting a Bank ID from the Tissue Bank Portal. **Be sure to indicate if the patient has a previous GOG # when registering.** This will ensure the patient is only assigned one Bank ID. The GOG ID - Bank ID Lookup on the Tissue Bank Portal can be used to search for an existing Bank ID.

Contact Support if you need assistance or have assigned more than one Bank ID to a patient (Email: support@gogstats.org; Phone: 716-845-7767).

III. Requesting Translational Research Specimen Kits
One single chamber specimen kit will be provided per patient for the collection and shipment of frozen serum, plasma, and tissue.

Translational research specimen kits can be ordered online via the Kit Management link on the GOG website (under Data Entry on the Web Menu page). Each site may order two kits per protocol per day (daily max = 6 kits).

Please contact the GOG Tissue Bank if you need assistance (Email: GOGBank@nationwidechildrens.org; Phone: 866-GOG-BANC/866-464-2262).

Be sure to plan ahead and allow time for kits to be shipped by ground transportation.

Note: Unused materials and kits should be returned to the GOG Tissue Bank.

IV. Labeling Translational Research Specimens
A waterproof permanent marker or printed label should be used to label each translational research specimen with:

GOG Bank ID (# # # # - # # - G # # #)
GOG protocol number (GOG- # # # #)
specimen code (see section I)
collection date (mm/dd/yyyy)
surgical pathology accession number (tissue specimens only)
block number (tissue specimens only)

Note: If labeling slides, only label on the top, front portion of the slide. Do not place a label on the back of the slide or over the tissue. The label must fit on the slide and should not be wrapped around the slide or hang over the edge.

V. Submitting Formalin-Fixed, Paraffin-Embedded Tissue
Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the specimen type (primary, metastatic, recurrent, normal). Primary and metastatic tumor should be collected prior to all treatment. Recurrent tumor and normal tissue should be collected prior to the study treatment. Only one block may be submitted per tissue type.

Every attempt should be made to provide a FFPE block; however, if a block cannot be provided on a permanent basis, then 16 unstained slides (charged, 5µm) should be submitted. All tissue sections should be cut sequentially from the same block.

Note: Stained slides to confirm patient eligibility by central pathology review are required for this protocol, but are NOT sent to the GOG Tissue Bank (see protocol for details). If these slides will be cut from the same block that will be submitted for translational research, your pathology department should cut these slides prior to submitting the block for translational research.

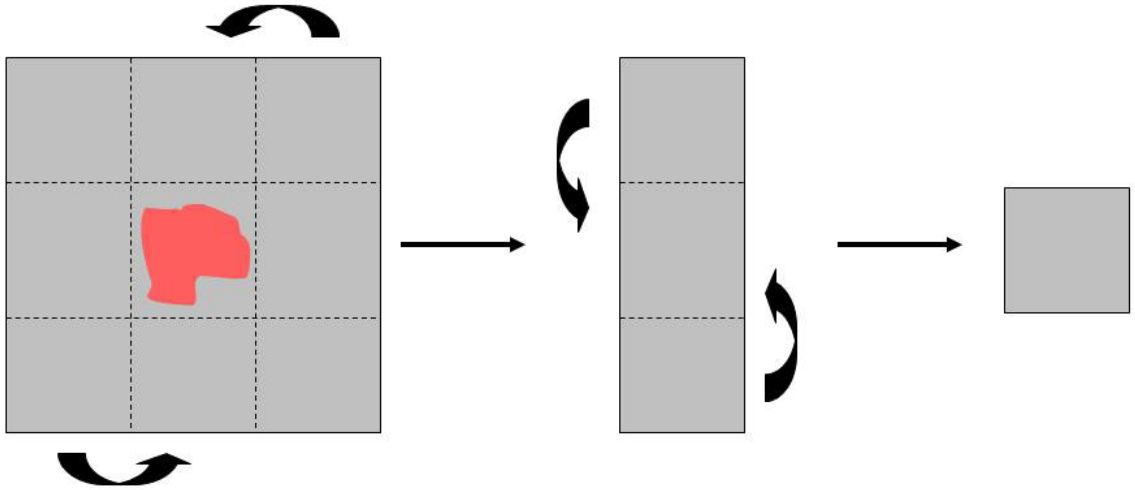
The type of specimen (block or slides) should be specified on Form SP.

If submitting recurrent tumor, include a comment on Form SP noting whether the tumor is from the primary site or the metastatic site.

All FFPE tissue should be submitted with the corresponding pathology report.

VI. Submitting Frozen Tissue

1. Label the zip-lock bag as described above. If using an adhesive label, place it inside the bag.
2. Snap freeze tissue within 15 minutes after surgery for optimal preservation. Place tissue on a piece of foil and fold foil around tissue as shown in diagram below. Snap freeze tissue on dry ice or in the vapor phase liquid nitrogen (do not submerge the tissue in liquid nitrogen). If neither dry ice nor liquid nitrogen is available, slow freeze tissue in a -70°C to -80°C freezer.



3. Once the tissue is frozen, place in pre-labeled zip-lock bag.
4. Immediately store snap frozen tissue in a liquid nitrogen freezer (at vapor phase), a -70°C to -80°C freezer, or by direct exposure with dry ice until ready to ship.

VII. Submitting Plasma

1. Label cryovials and a 15mL conical tube as described above. Use 2mL cryovials if plasma will be shipped to the GOG Tissue Bank.
2. Draw 7-10mL of blood into lavender/purple top (EDTA) tube(s).
3. Immediately after collection, gently invert the blood collection tube 5-10 times to mix the blood and EDTA.
4. Centrifuge the blood at 1000g for 15 minutes at 4ºC (preferred) or room temperature to separate the plasma (top, straw-colored layer) from the red blood cells (bottom, red layer).
5. Transfer the plasma into a pre-labeled 15mL conical tube and gently mix.
6. Quickly, evenly dispense (aliquot) the plasma into the pre-labeled cryovials and cap the tubes securely. Place a minimum of 0.25mL into each cryovial.
7. Immediately **freeze the plasma in an upright position** in a -70ºC to -80ºC freezer or by direct exposure with dry ice until ready to ship. If a -70ºC to -80ºC freezer is not available for storage, store, and ship, on dry ice within 24 hours of collection.

VIII. Submitting Serum

1. Label cryovials and a 15mL conical tube as described above. Use 2mL cryovials if serum will be shipped to the GOG Tissue Bank.
2. Draw 7-10mL of blood into red top tube(s).
3. Allow the blood to clot at 4°C (or in a bucket with ice) for at least 30 minutes but no longer than 3 hours.
4. Centrifuge the blood at 1000g for 15 minutes at 4ºC (preferred) or room temperature to separate the serum (top, straw-colored layer) from the red blood cells (bottom, red layer).
5. Transfer the serum into a 15mL conical tube and gently mix.
6. Quickly, evenly dispense (aliquot) the serum into the pre-labeled cryovials and cap the tubes securely. Place a minimum of 0.25mL into each cryovial.
7. Immediately **freeze the serum in an upright position** in a -70ºC to -80ºC freezer or by direct exposure with dry ice until ready to ship. If a -70ºC to -80ºC freezer is not available for storage, store and ship on dry ice within 24 hours of collection.

IX. Submitting Whole Blood

1. Label the lavender/purple top (EDTA) collection tube(s) as described above. Multiple tubes may be used to collect the required amount.
2. Draw 7-10mL of blood into the labeled lavender/purple top tube(s). A minimum of 3mL is needed for processing.
3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA.
4. Whole blood specimens should be refrigerated (4°C) until the specimens can be shipped. Ship whole blood to the GOG Tissue Bank the day the specimen is collected. If the whole blood absolutely cannot be shipped the day it is collected, the tube(s) should be refrigerated (4°C) until the specimen can be shipped.

X. Submitting Form SP

Form SP must be submitted via SEDES for each required specimen regardless of whether the specimen is submitted for research.

A copy of the SEDES-completed Form SP must accompany each specimen shipped to the GOG Tissue Bank (or alternate laboratory). Handwritten forms will not be accepted.

Note: A copy does not need to be sent if the specimen is not collected.

Retain a printout of the completed form for your records.

Please contact Support if you need assistance (Email: support@gogstats.org; Phone: 716-845-7767).

XI. Shipping Translational Research Specimens

A SEDES-completed copy of Form SP must be included for each translational research specimen.

A. FFPE Tissue

FFPE tissue and a copy of the corresponding pathology report should be shipped using your own container at your own expense to:

GOG Tissue Bank / Protocol GOG-0213
Nationwide Children's Hospital
700 Children's Dr., WA1340
Columbus, OH 43205
Phone: (614) 722-2865
FAX: (614) 722-2897
Email: GOGBank@nationwidechildrens.org

Do not ship FFPE tissue for Saturday delivery.

B. Frozen Specimen
Frozen serum, plasma, and tissue, including a copy of the corresponding pathology report for frozen tissue, should be shipped using the specimen kit provided to the GOG Tissue Bank (address above).

Frozen specimens should be shipped **Monday through Thursday for Tuesday through Friday delivery**. Do not ship frozen specimens on Friday or the day before a holiday. Note: Saturday delivery is not available for frozen specimens.

Frozen specimens should be stored in an ultra-cold freezing/storage space (i.e., ultra-cold ≤-70ºC freezer, liquid nitrogen, or direct exposure with dry ice) until the specimens can be shipped.

Shipping Frozen Translational Research Specimens in a Single Chamber Kit
1. Pre-fill the kit chamber about 1/3 full with dry ice.
2. Place the frozen specimens from each time point in a separate zip-lock bag.
3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Do not put more than 20 vials in the biohazard envelope. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible before sealing both envelopes.
4. Place the Tyvek envelope containing the frozen specimens into the kit and fill the chamber to the top with dry ice.
5. Insert a copy of Form SP for each specimen.
6. Place the cover on top of the kit. Tape the outer box of the kit closed with filament or other durable sealing tape. Please do not tape the inner chamber.
7. Print a pre-paid FedEx air bill using the Kit Management application (found under Data Entry on the Web Menu page). Attach the air bill.
8. Attach the dry ice label (UN1845) and the Exempt Human Specimen sticker.
9. Arrange for FedEx pick-up through your usual institutional procedure or by calling 800-238-5355.

C. Whole Blood
Whole blood specimens should be shipped to the GOG Tissue Bank (address above).

Whole blood specimens can be shipped to the GOG Tissue Bank **Monday through Friday for Tuesday through Saturday delivery**. Do not ship whole blood the day before a holiday. Use your own shipping container to ship specimens via **FedEx priority overnight**.

When shipping whole blood specimens, **your institution must comply with IATA standards** (www.iata.org). If you have questions regarding your shipment, contact the GOG Tissue Bank at GOGBank@nationwidechildrens.org or by phoning 866-GOG-BANC (866-464-2262).

To ship whole blood specimens you will need (1) a sturdy shipping container (e.g., a cardboard or styrofoam box), (2) a leak proof biohazard envelope with absorbent material*, (3) a puncture and pressure resistant envelope (e.g. Tyvek envelope), (4) an Exempt Human Specimen sticker, and (5) a pre-paid FedEx air bill.

**If you will be shipping whole blood specimens from more than one patient, please put each specimen in a separate plastic zip-lock bag before placing the specimens in the shipping bag. You may include up to four different blood specimens in one biohazard envelope.*

If you do not have these materials available at your institution, you may order them from any supplier (e.g., Saf-T-Pak; Phone: 800-814-7484; Website: www.saftpak.com).

Shipping Whole Blood Using Your Own Shipping Container

1. Place the whole blood specimen in a biohazard envelope containing absorbent material. Expel as much air as possible before sealing the bag.
2. Wrap the biohazard envelope in bubble wrap or another padded material.
3. Place the padded tube(s) into a Tyvek envelope. Expel as much air as possible before sealing the envelope.
4. Place the Tyvek envelope in a sturdy shipping container (e.g., cardboard FedEx box).
5. Insert a copy of Form SP for each specimen.
6. Attach an Exempt Human Specimen sticker to the outside of the shipping container.
7. Print a pre-paid FedEx air bill using the Kit Management application (found under Data Entry on the Web Menu page). Attach the air bill.
8. Make arrangements for FedEx pick-up through your usual institutional procedure or by calling 800-238-5355.

XII. Distributing Translational Research Specimens

Note: Testing of banked samples will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

The GOG Statistical and Data Center and Tissue Bank will coordinate the distribution of specimens to approved investigators.

Investigators will not be given access to any personal identifiers.

Investigators will be responsible for the direct supervision and oversight of translational research and for keeping accurate records.

Investigators will ensure the results are linked to the appropriate specimen-specific identifiers and are responsible for transferring relevant laboratory data to the Statistical and Data Center.

At the discretion of the Chair of the Committee on Experimental Medicine and the Director of the GOG Tissue Bank, investigators may be required to ship any specimens (or by-products) remaining after the completion of the translational research to the GOG Tissue Bank.

A. FFPE Tissue
Unstained sections of conventional blocks and/or TMAs will be batched shipped upon trial completion to:

Dr. Michael Birrer
Massachusetts General Hospital Cancer Center
Phone: (617) 726-8624
Fax: (617) 724-6898
Email: mbirrer@partners.org

B. Frozen Tissue
Unstained sections of frozen tissue will be batched shipped upon trial completion to Dr. Michael Birrer (address above).

C. Serum and Plasma
Aliquots of frozen serum and plasma will be batched shipped upon trial completion to Dr. Michael Birrer (address above).

D. Whole Blood
The GOG Tissue Bank will isolate DNA from whole blood. Aliquots of DNA will be batch shipped upon trial completion to Dr. Michael Birrer (address above).

XIII. Banking Translational Research Specimens for Future Research
Specimens will remain in the GOG Tissue Bank and made available for approved research projects if the patient has provided permission for the use of her specimens for future health research. The patient's choices will be recorded on the signed informed consent document and electronically via the online Specimen Consent Application. At the time of specimen selection for project distribution, the most recent consent information will be used.

GOG institutions can amend a patient's choices regarding the future use of her specimens at any time if the patient changes her mind.

If the patient revokes permission to use her specimens, the GOG Tissue Bank will destroy or return any remaining specimens. The patient's specimens will not be used for any further research; however, any specimens distributed for research prior to revoking consent cannot be returned or destroyed. In addition, the patient cannot be removed from any research that has been done with her specimens distributed prior to revoking consent.

Note: If return of specimens is requested shipping will be at the institution's expense.

APPENDIX IV

NCI Standard Protocol Language (as of March 26, 1998) Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement (CRADA):

The agents (hereinafter referred to as "Agent"), **Bevacizumab and Erlotinib**, used in this protocol are provided to the NCI under a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement (CRADA) between **Genentech, Inc.** (hereinafter referred to as "Collaborator") and the NCI Division of Cancer Treatment, Diagnosis. Therefore, the following obligations/guidelines apply to the use of the Agent in this study:

1. Agent may not be used outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Collaborator data for Agent are confidential and proprietary to Collaborator and should be maintained as such by the investigators.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different CTAs or CRADAs, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):

a. NCI must provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. The NCI encourages investigators to make data from clinical trials fully available to Collaborator for review at the appropriate time (see #5). Clinical trial data developed under a CTA or CRADA will be made available exclusively to Collaborator, the NCI, and the FDA, as appropriate.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for cooperative group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to the Collaborator must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator for advisory review and comment prior to submission for publication. Collaborator will have 30 days from the date of receipt for review. An additional 30 days may be requested in order to ensure that confidential and proprietary data, in addition to Collaborator's intellectual property rights, are protected. Copies of abstracts should be provided to Collaborator for courtesy review following submission, but prior to presentation at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Room 7111
Bethesda, Maryland 20892
FAX: (301) 402-1584

The Regulatory Affairs Branch will then distribute them to the Collaborator.

APPENDIX V

CARBOPLATIN DOSE CALCULATION INSTRUCTIONS

1) The Cockcroft-Gault formula will be used in GOG trials (not the Jelliffe formula).

2) Conversion of IDMS creatinine levels to "non-IDMS" values will not be permitted.

3) The carboplatin calculation tool on the GOG website has been updated. A legacy carboplatin calculator (using the Jelliffe formula and IDMS to "non-IDMS" conversion) is also available, if needed for dose modifications (see below).

Dosing of Carboplatin:

1) The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.

2) The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin **will not** need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

3) Carboplatin doses will be based on the subject's weight at baseline and will remain the same throughout the study. However, the doses will be recalculated if the patient has a weight change of greater than or equal to 10% from baseline.

4) In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using a **minimum value of 0.7 mg/dl**. If a patient is currently being dosed using a creatinine value less than 0.7 mg/dl, adjust dose with next planned treatment.

5) For trials where patients enter and are treated within less than or equal to 12 weeks of surgery: If a more appropriate (higher) baseline creatinine value is available from the pre-operative period (within 4 weeks of surgery date), that value may also be used for the initial estimation of GFR.

CALVERT FORMULA:

Carboplatin dose (mg) = target AUC x (GFR + 25)

NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.

Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.

The maximum allowed doses of carboplatin are:

AUC 6 = 900 mg

AUC 5 = 750 mg

AUC 4 = 600 mg

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (ml/min) is calculated by the method of Cockcroft-Gault using the following formula:

$$\textbf{Creatinine Clearance (mL/min)} = \frac{\textbf{[140-Age (years)] x Weight (kg) x 0.85}}{\textbf{72 x serum creatinine (mg/dl)}}$$

Notes:

1) Weight in kilograms (kg):

    a. Body Mass Index (BMI) should be calculated for each patient. A BMI calculator is available at the following link: http://www.nhlbisupport.com/bmi/
    b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25.
    c. **Adjusted** weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**.
    d. Adjusted weight calculation:
    Ideal weight (kg) = (((Height (cm)/2.54) – 60) x 2.3) + 45.5

    Adjusted weight (kg) = ((Actual weight – Ideal weight) x 0.40) + Ideal weight

    e. If a patient with BMI of greater than or equal to 25 is currently being dosed using actual weight, adjust dose with next planned treatment.

2) The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor).

At the time of a dose modification for toxicity:

1) If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

2) If the dose of carboplatin (mg) at the time of dose modification, is higher than the previous dose due to the use of the Cockcroft-Gault formula [when the previous dose was calculated using the Jelliffe formula and IDMS to "non-IDMS" conversion (if applicable)], use the same method that was used to calculate the previous dose [Jelliffe formula and IDMS to "non-IDMS" conversion (if applicable)], to calculate the dose of carboplatin (mg) at the time of dose reduction. A legacy carboplatin calculator is available on the GOG website for this purpose. This will ensure that the patient is actually receiving a dose reduction.