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 v3.0 (CTCAE) Grade1.

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, IND #113912)**(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.

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)**

The Comprehensive Adverse Event 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 via AdEERS (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.

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 2.2, October 21, 2011[1]

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 4.0 Term)			**Specific Protocol Exceptions to Expedited Reporting (SPEER)** (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr. 3)***

		Blood and lymphatic system disorders - Other (renal thrombotic microangiopathy)	
	Febrile neutropenia		***Febrile neutropenia (Gr. 3)***
CARDIAC DISORDERS			
		Acute coronary syndrome	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Supraventricular tachycardia		***Supraventricular tachycardia (Gr. 3)***
		Ventricular arrhythmia	
		Ventricular fibrillation	
EAR AND LABYRINTH DISORDERS			
	Vertigo		
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[2]	
	Gastrointestinal hemorrhage[3]		***Gastrointestinal hemorrhage[3] (Gr. 2)***
	Gastrointestinal obstruction[4]		
		Gastrointestinal perforation[5]	
		Gastrointestinal ulcer[6]	
	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)***
	Infusion related reaction		***Infusion related reaction (Gr. 2)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr. 3)***
	Pain		***Pain (Gr. 3)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr. 2)***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[7]		***Infection[7] (Gr. 3)***
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Gastrointestinal anastomotic leak	
	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)***