The University of Texas MD Anderson Cancer Center

A Phase II Trial of Bevacizumab with Carboplatin and Weekly Paclitaxel as First-Line Treatment in Epithelial Ovarian, Primary Peritoneal, and Fallopian Tube Carcinoma

Study Drug

Bevacizumab (Avastin®)
Paclitaxel
Carboplatin

Support Provided By

Genentech, Inc.

Sponsor Investigator

Anil K. Sood

Sub-Investigators

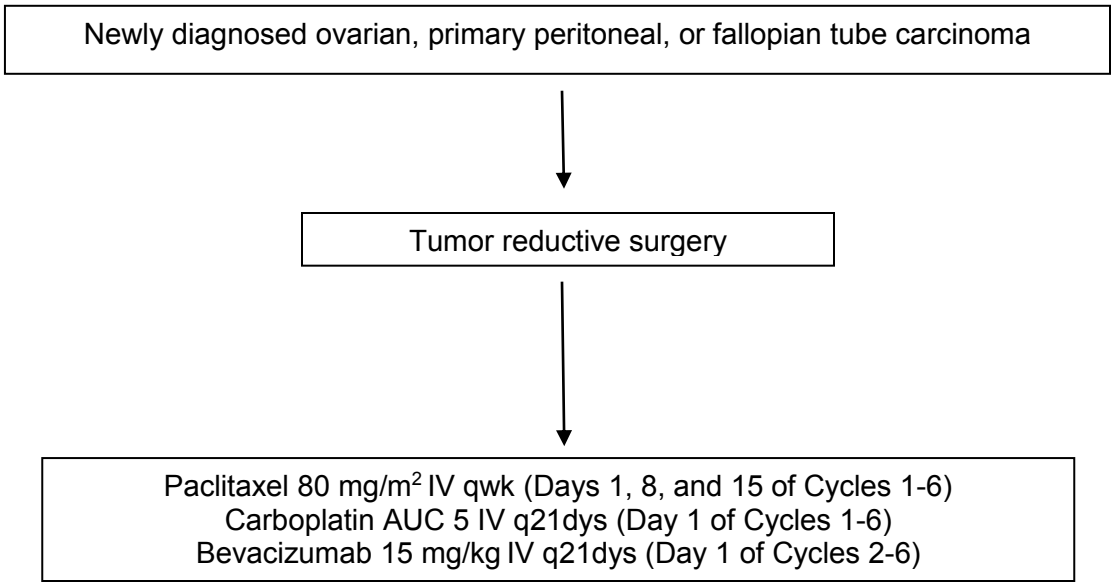
Robert Coleman

Study Number: Protocol 2009-0186

Protocol Version Date: Version 1.0, Revised January 14, 2013

TABLE OF CONTENTS

SCHEMA


Newly diagnosed ovarian, primary peritoneal, or fallopian tube carcinoma
Tumor reductive surgery
Paclitaxel 80 mg/m2 IV qwk (Days 1, 8, and 15 of Cycles 1-6)
Carboplatin AUC 5 IV q21dys (Day 1 of Cycles 1-6)
Bevacizumab 15 mg/kg IV q21dys (Day 1 of Cycles 2-6)

1.0 BACKGROUND

1.1 Ovarian Cancer, Primary Peritoneal Carcinoma, and Fallopian Tube Carcinoma

Over 21,000 new cases of ovarian, primary peritoneal, and fallopian tube cancers are expected to be diagnosed in 2008 with approximately 15,520 deaths caused by these diseases.[1] Due to a paucity of effective screening modalities, most patients are diagnosed in the advanced stages of the disease. The current standard of care consists of a total abdominal hysterectomy, bilateral oophorectomy, and extensive tumor debulking followed by tri-weekly administration of carboplatin and paclitaxel. With this treatment regimen, over 50% of patients achieve a complete initial clinical response, but the majority of patients recur within the first 2 years with only 10-30% achieving long-term survival.[2] Additionally, this treatment combination is associated with high rates of fatigue, as well as hematologic and neurologic toxicity.[3, 4] New first-line treatment regimens are being investigated in order to improve the initial response rate and prolong the time to recurrence in these patients while improving dose-delaying toxicity profiles.

1.2 New Strategies for Treatment

In order to improve cytotoxic activity through increased dose delivery, several phase I and II studies have evaluated the feasibility of weekly paclitaxel and carboplatin as first-line and salvage chemotherapy in patients with ovarian cancer.[5-8] Recent data demonstrated that patients treated with dose dense weekly administration of paclitaxel at 80 mg/m2 given with carboplatin (AU 6) every 3 weeks had longer PFS compared to those treated with standard tri-weekly carboplatin and paclitaxel (27.9 vs. 17.1 months, p=0.0014).[9] Overall survival at 2 years was also longer in the patients receiving dose dense treatment (83.6% vs. 77.7%, p=0.05). Toxicities were similar between both groups except grade 3 and 4 anemia was reported more frequently in the dose dense group. As front-line therapy, Sehouli et al. treated patients with FIGO stages IIB-IV disease after optimal tumor resection with weekly paclitaxel (100 mg/m2) followed carboplatin (AUC 2) and found the median progression free survival (PFS) and overall survival (OS) to be 21 and 43 months, respectively.[6] Additionally, patients with recurrent disease treated with weekly paclitaxel and carboplatin were found to have an overall response rate of 80% with 100% response rate in platinum-sensitive patients.[8, 10] Toxicity profile was also found to be improved with weekly chemotherapeutic dosing.[5-7] Reduced myelosuppression and fewer side effects allow patients to continue their scheduled chemotherapy with fewer dose delays. Additionally, the use of weekly paclitaxel and carboplatin in advanced breast cancer demonstrated comparable efficacy to the traditional tri-weekly regimen with decreased incidence of grade 3 and 4 toxicities.[11]

1.3 Angiogenesis-Targeted Therapeutics

Angiogenesis and neovascularization are required for tumor growth and invasion and play a significant role in disease metastasis.[12, 13] Several studies have demonstrated that analysis of angiogenic factors may be correlated with ovarian cancer progression and prognosis.[14-16] Vascular-endothelial growth factor (VEGF) is an angiogenic promoter and ligand that binds to the VEGF receptor 2 and triggers the angiogenic-signaling pathway.

Specific targeting of VEGF with neutralizing anti-VEGF monoclonal antibodies has been identified as a potential mechanism through which tumor angiogenesis can be disrupted, and various studies have demonstrated potential therapeutic activity using these biological agents.[17, 18]

1.4 Bevacizumab Clinical Experience

Bevacizumab has been studied in a multitude of Phase I, II, and III clinical trials in more than 5000 patients and in multiple tumor types. In addition, data are available from 3,863 patients enrolled in two postmarketing studies in metastatic colorectal cancer (CRC). Approximately 130,000 patients have been exposed to bevacizumab as a marketed product or in clinical trials. The following discussion summarizes bevacizumab's safety profile and presents some of the efficacy results pertinent to this particular trial. Please refer to the bevacizumab Investigator Brochure for descriptions of all completed Phase I, II, and III trials reported to date.

In a large phase III study (AVF2107g) in patients with metastatic colorectal cancer, the addition of bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor (VEGF), to irinotecan/5-fluorouracil/leucovorin (IFL) chemotherapy resulted in a clinically and statistically significant increase in duration of survival, with a hazard ratio of death of 0.67 (median survival 15.6 vs. 20.3 months; $p < 0.001$).[19] Similar increases were seen in progression-free survival (6.2 vs. 10.6 months; $p < 0.001$), overall response rate (35% vs. 45%; $p < 0.01$) and duration of response (7.1 vs. 10.4 months; $p < 0.01$) for the combination arm versus the chemotherapy only arm (Bevacizumab Investigator Brochure, October 2005).

Based on the survival advantage demonstrated in Study AVF2107g, bevacizumab was designated for priority review and was approved on 26 February 2004 in the United States for first-line treatment in combination with IV 5-FU–based chemotherapy for subjects with metastatic colorectal cancer.

Additional data from Phase III trials in metastatic colorectal cancer (E3200), non–small cell lung cancer (NSCLC; E4599), and metastatic breast cancer (E2100) have also demonstrated clinical benefit from bevacizumab when added to chemotherapy.[20-22] In Study E3200, the addition of bevacizumab to FOLFOX chemotherapy resulted in improved overall survival compared with FOLFOX alone (13.0 vs. 10.8 months, respectively, $HR = 0.75$; $p < 0.01$) in a population of previously treated CRC patients.[22]

There was also improved overall survival in first-line NSCLC patients treated with carboplatin/paclitaxel + bevacizumab compared with chemotherapy alone (12.3 vs. 10.3 months, respectively; $HR = 0.80$; $p = 0.003$).[20] The results from this trial were the basis for FDA approval of bevacizumab for use in combination with carboplatin + paclitaxel as first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic, non-squamous NSCLC in October 2006. Finally, patients with untreated metastatic breast cancer (E2100) who received bevacizumab in combination with weekly paclitaxel had a marked improvement in PFS compared with chemotherapy alone (11.8 vs. 5.9 months, respectively; $HR = 0.60$; $p < 0.001$) [21] (see the Bevacizumab Investigator Brochure for additional details).

Bevacizumab Safety Profile

In the initial Phase I and II clinical trials, four potential bevacizumab-associated safety signals were identified: hypertension, proteinuria, thromboembolic events, and hemorrhage. Additional completed Phase II and Phase III studies of bevacizumab as well as spontaneous reports have further defined the safety profile of this agent. Bevacizumab-associated adverse events identified in phase III trials include congestive heart failure (CHF) primarily in metastatic breast cancer, gastrointestinal perforations, wound healing complications, and arterial thromboembolic events (ATE). These and other safety signals are described in further detail as follows and in the Bevacizumab Investigator Brochure.

Hypertension: An increased incidence of hypertension has been observed in patients treated with bevacizumab. Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS).[23, 24]

There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. Monitoring of blood pressure is recommended during bevacizumab therapy. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.

Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved. If hypertension cannot be controlled with medical therapy, bevacizumab therapy should be permanently discontinued. Bevacizumab should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria: An increased incidence of proteinuria has been observed in patients treated with bevacizumab compared with control arm patients. In the bevacizumab-containing treatment arms of clinical trials (across all indications), the incidence of proteinuria (reported as an adverse event) was up to 38% (metastatic CRC Study AVF2192g). The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been grade 1. NCI-CTC Grade 3 proteinuria was reported in up to 3% of bevacizumab-treated patients, and Grade 4 in up to 1.4% of bevacizumab-treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of bevacizumab therapy. Bevacizumab should be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome)

Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence from the dose-finding, Phase II trials (AVF0780g, AVF0809s, and AVF0757g) suggesting that Grade 1 proteinuria may be related to bevacizumab dose.

Proteinuria will be monitored by urine protein:creatinine (UPCR) ratio at least every 6 weeks.

Thromboembolic Events: Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal, have been reported in patients treated with bevacizumab in the colorectal cancer trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials.

Venous thromboembolism (including deep venous thrombosis, pulmonary embolism, and thrombophlebitis: In the phase III pivotal trial in metastatic CRC, there was a slightly higher rate of venous TE events in patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone (19% vs. 16%).

In Study AVF2107g, a Phase III, pivotal trial in metastatic CRC, VTE events, including deep venous thrombosis, pulmonary embolism, and thrombophlebitis, occurred in 15.2% of patients receiving chemotherapy alone and 16.6% of patients receiving chemotherapy + bevacizumab.

The incidence of NCI-CTC Grade ≥ 3 venous VTE events in one NSCLC trial (E4599) was higher in the bevacizumab-containing arm compared to the chemotherapy control arm (5.6% vs. 3.2%). One event (0.2%) was fatal in the bevacizumab-containing arm; not fatal events were reported in the carboplatin/paclitaxel arm (see Bevacizumab Investigator Brochure).
In metastatic CRC clinical trials, the incidence of VTE events was similar in patients receiving chemotherapy + bevacizumab and those receiving the control chemotherapy alone.

In clinical trials across all indications the overall incidence of VTE events was 2.8%–17.3% in the bevacizumab-containing arms compared with 3.2%–15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the risk of VTE event compared with chemotherapy alone. However, patients with metastatic CRC who receive bevacizumab and experienced a VTE event may be at higher risk for recurrence of VTE event.

Arterial Thromboembotic Events: An increased incidence of ATE events was observed in patients treated with bevacizumab compared with those receiving control treatments. ATE events include cerebrovascular accidents, myocardial infarction, transient ischemic attacks (TIAs), and other ATE events. In a pooled analysis of data from five randomized Phase II and III trials (mCRC [AVF2107g, AVF2192g, AVF0780g]; locally advanced or metastatic NSCLC [AVF0757g]; metastatic breast cancer [AVF2119g]), the incidence rate of ATE events was 3.8% (37 of 963) in patients who received chemotherapy + bevacizumab compared with 1.7% (13 of 782) in patients treated with chemotherapy alone. ATE events led to a fatal outcome in 0.8% (8 of 963) of patients treated with chemotherapy + bevacizumab and 0.5% (4 of 782) of patients treated with chemotherapy alone. Cerebrovascular accidents (including TIAs) occurred in 2.3% of patients treated with chemotherapy + bevacizumab and 0.5% of patients treated with chemotherapy alone. Myocardial infarction occurred in 1.4% of patients treated with chemotherapy + bevacizumab compared with 0.7% of patients

treated with chemotherapy alone (see the Bevacizumab Investigator Brochure for additional details).

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO 2005.[25] Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

Gastrointestinal perforation: Patients with metastatic carcinoma may be at increased risk for the development of gastrointestinal perforation and fistula when treated with bevacizumab and chemotherapy. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory processes and gastrointestinal perforation to bevacizumab treatment has not been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab. Gastrointestinal perforation has been reported in other trials in non-colorectal cancer populations (e.g., ovarian, renal cell, pancreas, breast, and NSCLC) and may be higher in incidence in some tumor types.

Fistula: Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae in the GI tract are common (1%–10% incidence) in patients with metastatic CRC, but uncommon (0.1%−1%) or rare (0.01%–0.1%) in other indications. In addition, fistulae that involve areas of the body other than the GI tract (e.g., tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly (0.1%–1%) in patients receiving bevacizumab in clinical studies and postmarketing reports. Events were reported at various timepoints during treatment, ranging from 1 week to > 1 year following initiation of bevacizumab, with most events occurring within the first 6 months of therapy.

Permanently discontinue bevacizumab in patients with tracheoesophageal fistulae or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

Wound healing complications: Wound healing complications such as wound dehiscence have been reported in patients receiving bevacizumab. In an analysis of pooled data from two trials in metastatic colorectal cancer, patients undergoing surgery 28-60 days before study treatment with 5-FU/LV plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone.[26]

Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half life of bevacizumab is 21 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

Hemorrhage: Overall, grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight phase I, II, and III clinical trials in multiple tumor types (Bevacizumab Investigator Brochure, October 2005). The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage.

Tumor-Associated Hemorrhage: Major or massive pulmonary hemorrhage or hemoptysis has been observed primarily in patients with NSCLC. Life-threatening and fatal hemoptysis was identified as a bevacizumab-related adverse event in NSCLC trials. These events occurred suddenly and presented as major or massive hemoptysis. Among the possible risk factors evaluated (including squamous cell histology, treatment with anti-rheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumor location, and cavitation of tumors during therapy), the only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology.

GI hemorrhages, including rectal bleeding and melena have been reported in patients with CRC, and have been assessed as tumor-associated hemorrhages.

Tumor-associated hemorrhages were also seen rarely in other tumor types and locations, including a case of CNS bleeding in a patient with hepatoma with occult CNS metastases and a patient who developed continuous oozing of blood from a thigh sarcoma with necrosis.

Mucocutaneous Hemorrhage: Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen.

There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

Reversible Posterior Leukoencephalopathy Syndrome: There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with RPLS, a rare neurologic disorder that can present with the following signs and symptoms (among others): seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is mandatory to confirm the diagnosis of RPLS. In patients who develop RPLS, treatment of specific symptoms, including control of hypertension, is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known.[23, 24]

Congestive heart failure: In clinical trials CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In the Phase III clinical trial of metastatic breast cancer (AVF2119g), 7 (3%) bevacizumab-treated patients experienced CHF, compared with two (1%) control arm patients. These events varied in severity from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF requiring hospitalization and treatment. All the patients treated with bevacizumab were previously treated with anthracyclines (doxorubicin cumulative dose of 240–360 mg/m^2). Many of these patients also had prior radiotherapy to the left chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy.[27]

In a randomized, Phase III trial of patients with previously untreated metastatic breast cancer (E2100), the incidence of LVEF decrease (defined as NCI-CTC Grade 3 or 4) in the paclitaxel + bevacizumab arm was 0.3% versus 0% for the paclitaxel alone arm

No information is available on patients with preexisting CHF of New York Heart Association (NYHA) Class II–IV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials.

Prior anthracyclines exposure and/or prior radiotherapy to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors.

A Phase II trial in patients with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or LVEF decrease to < 40%) among 48 patients treated with sequential cytarabine, mitoxantrone, and bevacizumab. All but 1 of these patients had significant prior exposure to anthracyclines as well.[28]

Two additional studies investigated concurrent administration of anthracyclines and bevacizumab. In 21 patients with inflammatory breast cancer treated with neoadjuvant docetaxel, doxorubicin, and bevacizumab, no patients developed clinically apparent CHF; however, patients had asymptomatic decreases in LVEF to < 40%.[29] In a small Phase II study in patients with soft tissue sarcoma, 2 of the 17 patients treated with bevacizumab and high-dose doxorubicin (75 mg/m^2) developed CHF (one Grade 3 event after a cumulative doxorubicin dose of 591 mg/m^2, one Grade 4 event after a cumulative doxorubicin dose of 420 mg/m^2); an additional 4 patients had asymptomatic decreases in LVEF.[30]

Other studies in patients with various tumor types and either a history of anthracycline exposure or concomitant use with bevacizumab are ongoing.

Patients receiving concomitant anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA scans or echocardiograms (ECHOs) with a normal LVEF.

Neutropenia: Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone.[20]

Additional Adverse Events: See the Bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

1.5 Other Study Drug(s) Background

1.5.1 Paclitaxel (Taxol®)

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. It is commercially available from Bristol-Myers Oncology and is supplied as a sterile solution concentrate, 6 mg/ml available in 5 ml (30 mg/vial), 16.7 ml (100 mg/vial) and 50 ml (300 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.

Paclitaxel Safety Profile

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, radiation recall reactions

Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus

Liver: Increased SGOT, SGPT, bilirubin and alkaline phosphatase, hepatic failure, hepatic necrosis

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

Other: Alopecia, fatigue, arthralgia, myalgia, light-headedness, myopathy

1.5.2 Carboplatin (Paraplatin®)

Carboplatin is a DNA alkylating agent which produces predominantly cell-cycle nonspecific interstrand DNA cross-links. It is commercially available from Bristol-Myers Squibb and is supplied as a sterile, pyrogen-free, 10mg/mL aqueous solution in multi-dose vials containing 50mg/5mL, 150mg/15mL, 450mg/45mL, or 600g/60mL of carboplatin.

Carboplatin Safety Profile

Hematologic: Myelosuppression, bleeding

Gastrointestinal: Nausea and vomiting, diarrhea, constipation, stomatitis, mucositis, abdominal pain

Heart: Heart failure, stroke, thrombosis

Pulmonary: Bronchospasm

Blood Pressure: Hypotension, hypertension (possibly related to concomitant medication--Dexamethasone)

Neurologic: Muscle weakness, peripheral neuropathy, dizziness, confusion, visual changes, tinnitus, ototoxicity, sensory changes (taste)

Skin: Discomfort at injection site, erythema, swelling, pain, necrosis associated with extravasation

Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus

Liver: Increased SGOT, SGPT, bilirubin and alkaline phosphatase, hepatic failure, hepatic necrosis

Renal: Increased BUN and creatinine, renal failure, abnormal blood electrolytes (hyponatremia, hypokalemia, hypocalcemia, hypomagnesemia)

Vision: Vision loss

Other: Alopecia, infection, asthenia

1.6 TRANSLATIONAL RESEARCH RELATED TO ANTI-VEGF THERAPY

1.6.1 Genomic Analysis

The genomic research component of this protocol will focus on the discovery and validation of genes who expression may predict progression-free survival in patients with advanced stage ovarian cancer. Despite treatment with surgery and chemotherapy at the time of initial diagnosis, the disease usually recurs, and most patients die within two years of diagnosis. However, a small subset of patients experience a more indolent disease course and may be disease free for a substantial period of time. These patients may survive five years or more and should perhaps be monitored and treated differently than those with more rapid, progressive disease. At this time, no tool exists to predict the clinical course of disease from the time of initial diagnosis.

Transcription profiling utilizes large-scale gene-expression analysis technology to identify differentially expressed genes and molecular signatures.[31, 32] Data obtained from expression analyses has been used to examine tumor biology and to identify potential biomarkers as clinical correlates.[32] We hypothesize that transcription profiling will provide differential gene signatures in patients with advanced staged ovarian cancer who experience different progression-free survival times and may require individualized treatment regimens. Thus, these discoveries will help determine the molecular and biochemical basis of disease in patients with advanced staged ovarian, fallopian tube, and primary peritoneal carcinoma.

1.6.2 Cytokine Analysis

Cytokine levels have been evaluated as potential diagnostic and prognostic markers in ovarian cancer. They function primarily to regulate immunity, hematopoeisis, and inflammation. Systemic cytokine levels differ in cancer patients, possibly due to an interaction between the disease and the immune system resulting in cytokine production.[33] Various cytokines, including IL-6, IL-7, and IL-8, have been associated with ovarian cancer and identified as potential therapeutic and diagnostic tools for the disease.[34-36] Additionally, levels of vascular endothelial growth factor (VEGF) have been found to correlate significantly with patient survival and to be an independent prognostic indicator in overall survival in patients with ovarian cancer.[37]

Plasma studies are included as an optional procedure to evaluate the correlation between cytokine levels with progression-free and overall survivals in patients treated with the bevacizumab, carboplatin, and weekly paclitaxel. Previous studies indicate that the pre-treatment levels of VEGF in plasma, not serum, are associated with progression-free and overall survival in patients with persistent or recurrent endometrial cancer or uterine leiomyosarcoma.[38, 39] The exact choice of biomarkers to be evaluated and assays to be performed on plasma specimens will be reevaluated based on evolving data in the field. At the appropriate time, the current translational research objectives will be amended to incorporate a definitive translational research objective regarding angiogenic markers and cytokines that can be tested and validated utilizing specimens submitted for this protocol. A summary of relevant laboratory data will also be provided at that time to establish the background and rationale for that amendment.

1.7 Study Rationale

The use of bevacizumab in gynecologic oncology has been studied in the setting of recurrent epithelial ovarian cancer. GOG-0170-D utilized single agent bevacizumab in persistent or recurrent ovarian or primary peritoneal cancer and examined clinical response by NCI/RECIST criteria and proportion surviving progression-free for at least 6 months.[40] Sixty-two patients were treated with bevacizumab 15 mg/kg intravenously every 21 days. Thirteen patients had clinical responses with approximately 40% surviving progression free for at least six months. Median PFS and overall survival were 4.7 and 17 months, respectively. Additionally, Genentech AVF 2949 found a median PFS and overall survival of 4.4 and 10.7 months, respectively when 44 patients with platinum-resistant ovarian or primary peritoneal cancers were treated in a phase II study with single agent bevacizumab 15 mg/kg every 3 weeks.[41]

The combination of bevacizumab with other cytotoxic therapies stems from preclinical models suggesting possible synergistic interactions.[42] It is hypothesized that increased sensitization to apoptosis or reversal of chemotherapeutic drug resistance occurs when the VEGF pathway is interrupted.[43] In a study published by Chura et al., 15 patients were treated with biweekly intravenous bevacizumab 10 mg/kg plus oral cyclophosphamide 50 mg daily.[44] Two patients (13.3%) had a complete response to treatment with 6 patients (40%) experiencing a partial response and 3 with stable disease. Median PFS was 4.4 months for these patients. Another study

evaluated 10 patients with advanced, recurrent, refractory ovarian cancer who were treated with biweekly bevacizumab (10 mg/kg) and weekly paclitaxel.[45] During the study, all evaluable patients experienced a decrease in CA125 within the first treatment cycle, and all experienced improved levels of pain, nausea, and ascites. No grade 3 or 4 toxicities were found.

Improved PFS or overall survival has been demonstrated in several phase III trials in metastatic colorectal, breast, and non-small cell lung cancer.[19-22] A phase III trial randomized 722 breast cancer patients to receive either weekly paclitaxel alone or with bevacizumab (10 mg/kg) on days 1 and 15.[21] Prolonged PFS (median 11.8 vs. 5.9 months, $p<0.001$) and objective response rate (36.9% vs. 21.2%, $p<0.001$) was noted in patients receiving the combination of paclitaxel and bevacizumab.

The observed spectrum and degree of toxicity, such as arterial thrombotic and renovascular events, is similar in these trials. However, GOG 170-D observed no gastrointestinal perforations or fistulae, unlike Genentech AVF 2949. During this trial, 5 such events occurred in 44 patients. This led to early termination of AVF 2949 and an IND Action Letter in 2005. Some of the events occurred after discontinuing bevacizumab for disease progression. The potential for gastrointestinal perforations or fistulae is unknown at this time in patients with advanced recurrent ovarian cancer, and statistical variation cannot be excluded without a controlled trial. Han et al. reviewed published data of open-labeled trials using bevacizumab in ovarian cancer and revealed an overall 5.2% incidence rate of gastrointestinal perforation. [46] The management of the perforations and fistulas has involved either surgery or abscess drainage with bowl rest. Specific risk factors for these events have not been identified and are currently under investigation in GOG 0218.

Limited data exists for the utilization of bevacizumab as first-line therapy in newly diagnosed ovarian cancer patients. Currently GOG 0218 and ICON7 are in the process of examining the use of bevacizumab in front-line ovarian cancer therapy. GOG 0218 is a three-arm placebo-controlled trial to compare the overall survival in patients with stage III or IV disease who receive carboplatin/paclitaxel alone, carboplatin/paclitaxel administered concurrently with bevacizumab, or carboplatin/paclitaxel administered concurrently with bevacizumab for an additional 16 cycles. ICON7 includes all patients with at least high-risk, early-stage disease and evaluates the PFS in a two-arm trial, carboplatin/paclitaxel alone compared to carboplatin/paclitaxel given concomitantly with bevacizumab for an extended 12 cycles.

A phase II study evaluated the response rate and toxicity of intravenous paclitaxel (175 mg/m2), carboplatin (AUC 5), and bevacizumab (15 mg/kg) administered every 21 days as primary induction therapy for patients with stage III or IV ovarian, primary peritoneal, or fallopian tube `adenocarcinoma.[47] Eighteen patients were evaluated with a total response rate of 80% (6 CR, 10 PR). A total of 116 cycles were administered with grade 3 and 4 neutropenia in 23.3% and 25% of cycles and no incidence of grades 3 or 4 thrombocytopenia or anemia. No incidence of bowel perforations occurred, and 2 patients developed grade 3 hypertension.

Dose dense administration of paclitaxel with weekly carboplatin prolongs PFS and overall survival.[9] Additionally, bevacizumab appears to be active as a

single agent in patients with recurrent ovarian and primary peritoneal cancer. Past studies have demonstrated improved response rate and prolonged PFS in breast and ovarian cancer patients when bevacizumab was given in combination with paclitaxel. Overall side effects to the combination of bevacizumab with carboplatin and paclitaxel appear to be tolerable. Based on this data, the combination of bevacizumab with carboplatin and weekly paclitaxel may be a potential therapeutic treatment option as front-line therapy for patients with newly diagnosed ovarian, fallopian tube, and primary peritoneal cancer.

2.0 OBJECTIVES

2.1 Primary

To determine whether patients with newly diagnosed ovarian, primary peritoneal, and fallopian tube cancers when treated with bevacizumab, carboplatin, and weekly paclitaxel can tolerate at least 4 cycles of therapy regardless of delay or dose modification.

2.2 Secondary

2.2.1 To estimate the efficacy of bevacizumab combined with carboplatin and weekly paclitaxel in patients with newly diagnosed ovarian, primary peritoneal, and fallopian tube cancers, as measured by progression-free survival.

2.2.2 To evaluate the response rate in patients with newly diagnosed ovarian, primary peritoneal, and fallopian tube cancers when treated with bevacizumab, carboplatin, and weekly paclitaxel.

2.3 Translational Research Objectives

2.3.1 To assess the predictive value of a set of angiogenic genes whose expression correlates with progression-free survival of patients with epithelial ovarian, peritoneal primary or fallopian tube cancer treated with bevacizumab, carboplatin, and weekly paclitaxel.

2.3.2 To assess the relationship among cytokines/chemokines, angiogenic factors, novel targets of interest, and clinical outcome including tumor response and progression-free survival in patients treated with bevacizumab, carboplatin, and weekly paclitaxel.

3.0 STUDY DESIGN

3.1 Description of the Study

Patients with newly diagnosed ovarian, primary peritoneal, or fallopian tube cancer will receive as induction therapy carboplatin (AUC 5) and paclitaxel (80 mg/m2) on Day 1 of Cycle 1. They will also receive paclitaxel (80 mg/m2) on Days 8 and 15 of Cycle 1. On Day 1 of Cycles 2 through 6, patients will receive carboplatin (AUC 5), paclitaxel (80 mg/m2) and bevacizumab (15 mg/kg). They will continue to receive paclitaxel (80 mg/m2) on Days 8 and 15.

Patients will be treated for a total of 6 cycles. One cycle of therapy consists of 21 days.

3.2 Rationale for Study Design

A recent study performed by the Japanese Gynecologic Oncology Group (JGOG) found the median progression-free survival and overall survival to be longer in ovarian cancer patients receiving weekly paclitaxel with carboplatin compared to tri-weekly carboplatin and paclitaxel.[9] Grade 3 and 4 anemia occurred more frequently, however, in the group receiving weekly treatment. Overall 60% of patients received at least 6 cycles of chemotherapy treatment on the study. A prospective trial utilizing tri-weekly carboplatin (AUC 6), bi-weekly bevacizumab (10 mg/kg), and weekly paclitaxel (80 mg/m^2) in melanoma patients found the regimen to be moderately well-tolerated with 62.2% of patients requiring dose reduction for toxicity.[48] This study is designed to evaluate the tolerability of combination bevacizumab and carboplatin with weekly paclitaxel as first-line treatment in patients with epithelial ovarian, primary peritoneal, and fallopian tube cancers in a single-arm, non-randomized, open label phase II study.

3.3 Outcome Measures

3.3.1 Primary Outcome Measures

The primary study outcome will be treatment success, defined as a patient completing at least 4 cycles of combination therapy (bevacizumab with carboplatin and weekly paclitaxel) regardless of delay or dose modification.

3.3.2 Secondary Outcome Measures

3.3.2.1 A secondary endpoint will be the evaluation of progression-free survival in patients treated with bevacizumab and carboplatin with weekly paclitaxel.

3.3.2.2 The evaluation of response proportion based on RECIST v1.1 criteria will be examined in patients treated with bevacizumab and carboplatin with weekly paclitaxel.

4.0 Safety Plan

See Section 4.1 for complete details of the safety evaluation for this study.

4.1 General Plan to Manage Safety

a. Bevacizumab-Specific

A number of measures will be taken to ensure the safety of patients participating in this trial. These measures will be addressed through exclusion criteria (see Section 5.3) and routine monitoring as follows.

Patients enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations will consist of medical interviews, recording of adverse events, physical examinations, blood pressure, and laboratory measurements. Patients will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption

or discontinuation at each study visit for the duration of their participation in the study. Patients discontinued from the treatment phase of the study for any reason will be evaluated ~30 days (28–42 days) after the decision to discontinue treatment (see Section 7.4.2) unless patients are discontinued from the study due to an ongoing bevacizumab-related Grade 4 or serious adverse event. These patients will continue to be followed until resolution of the event or until the event is considered irreversible.

Specific monitoring procedures are as follows:

- Hypertension will be monitored through routine evaluation of blood pressure prior to each bevacizumab treatment. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab.
- Proteinuria will be monitored by urine protein-creatinine ratio (UPCR) at least every 6 weeks.

Other Study Drug(s)-Specific

Please see Section 7.4.2 for detailed instructions for the management of study drug–related toxicities.

5.0 Study Subjects

5.1 Subject Selection

5.2 Inclusion Criteria

5.2.1 Patients with a histologic diagnosis of epithelial ovarian cancer, peritoneal primary carcinoma or fallopian tube cancer; FIGO stage III and IV defined surgically at the completion of initial abdominal surgery and with appropriate tissue available for histologic evaluation. The minimum surgery required is an abdominal surgery providing tissue for histologic evaluation and establishing and documenting the primary site and stage, as well as a maximal effort at tumor debulking. Those patients with stage III cancer in which the largest maximal diameter of any residual tumor implant at the completion of this initial surgery is no greater than 1 cm will be defined as “optimal;” all others will be defined as “suboptimal.”

5.2.2 The histologic features of the tumor must be compatible with a primary Müllerian epithelial adenocarcinoma. 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	Malignant Brenner's Tumor
Adenocarcinoma N.O.S.	

Patients may have co-existing fallopian tube carcinoma in-situ so long as the primary origin of invasive tumor is ovarian, peritoneal or fallopian tube.

5.2.3 Patients must be entered no later than 12 weeks after initial surgery performed for the combined purpose of diagnosis, staging and cytoreduction.

5.2.4 Patients with measurable and non-measurable disease are eligible. Patients may or may not have cancer-related symptoms.

5.2.5 Patients in this trial may receive ovarian estrogen +/- progestin replacement therapy as indicated at the lowest effective dose(s) for control of menopausal symptoms at any time, but not progestins for management of anorexia while on protocol directed therapy.

5.2.6 Patients with an ECOG Performance Status of 0, 1, or 2 (Appendix D).

5.2.7 Patients must have normal organ and marrow function as defined below:

- leukocytes >3,000/mcL
- absolute neutrophil count >1,500/mcL
- platelets >100,000/mcL
- total bilirubin <1.5 X institutional upper limits of normal
- AST(SGOT)/ALT(SGPT) <2.5 X institutional upper limit of normal
- Alkaline phosphatase (AP) <2.5 X institutional upper limit of normal
- creatinine <1.5X institutional upper limit of normal

OR

- creatinine clearance >50 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal

5.2.8 Ability to understand and the willingness to sign a written informed consent document.

5.3 Exclusion Criteria

5.3.1 Patients with a current diagnosis of borderline epithelial ovarian tumor (formerly “tumors of low malignant potential”) or recurrent invasive epithelial ovarian, primary peritoneal or fallopian tube cancer treated with surgery only (such as patients with stage Ia or Ib low grade epithelial ovarian or fallopian tube cancers) are not eligible. Patients with a prior diagnosis of a borderline tumor that was surgically resected and who subsequently develop an unrelated, new invasive epithelial ovarian, peritoneal primary or fallopian tube cancer are eligible, provided that they have not received prior chemotherapy for any ovarian tumor.

5.3.2 Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis are excluded. Prior radiation for localized cancer of the breast, head and neck, or skin is permitted, provided that it was completed more than three years prior to registration, and the patient remains free of recurrent or metastatic disease.

5.3.3 Patients who have received prior chemotherapy for any abdominal or pelvic tumor including neo-adjuvant chemotherapy for their ovarian, primary peritoneal or fallopian tube cancer are excluded. Patients may

have received prior adjuvant chemotherapy for localized breast cancer, provided that it was completed more than three years prior to registration, and that the patient remains free of recurrent or metastatic disease.

5.3.4 Patients who have received any targeted therapy (including but not limited to vaccines, antibodies, tyrosine kinase inhibitors) or hormonal therapy for management of their epithelial ovarian or peritoneal primary cancer.

5.3.5 Patients who are currently participating or planning to participate in an experimental drug study other than a Genentech-sponsored bevacizumab cancer study or who are receiving other investigational agents.

5.3.6 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 IB; 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.

5.3.7 With the exception of superficial basal cell and superficial squamous (skin) cell, carcinoma in situ of the cervix and other specific malignancies as noted above, patients with other invasive malignancies who had (or have) any evidence of the other cancer present within the last five years or whose previous cancer treatment contraindicates this protocol therapy are excluded.

5.3.8 Patients with acute hepatitis or active infection that requires parenteral antibiotics.

5.3.9 Patients with serious non-healing wound, ulcer, or untreated bone fracture. This includes a history of abdominal fistula or gastrointestinal perforation within 6 months prior to Day 1. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection are eligible but require weekly wound examinations until closure.

5.3.10 Patients with active bleeding or pathologic conditions that carry high risk of bleeding, such as known bleeding disorder, coagulopathy (in the absence of therapeutic anticoagulation), or tumor involving major vessels.

5.3.11 History of hemoptysis ($\geq$ 1/2 teaspoon of bright red blood per episode) within 1 month prior to Day 1.

5.3.12 Patients with history or evidence upon physical examination of CNS disease, including primary brain tumor, seizures not controlled with standard medical therapy, any brain metastases, or history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) or subarachnoid hemorrhage within six months of the first date of treatment on this study.

5.3.13 Patients with clinically significant cardiovascular disease. This includes:

5.3.13.1 Uncontrolled hypertension, defined as systolic > 140 mm Hg or diastolic > 90 mm Hg.

5.3.13.2 Myocardial infarction or unstable angina < 6 months prior to registration.

5.3.13.3 New York Heart Association (NYHA) Grade II or greater congestive heart failure (Appendix E).

5.3.13.4 Serious cardiac arrhythmia requiring medication. This does not include asymptomatic, atrial fibrillation with controlled ventricular rate.

5.3.13.5 CTCAE Grade 2 or greater peripheral vascular disease (at least brief (<24 hrs) episodes of ischemia managed non-surgically and without permanent deficit).

5.3.13.6 Prior history of hypertensive crisis or hypertensive encephalopathy

5.3.13.7 Significant vascular disease (e.g., aortic aneurysm, requiring surgical repair or recent peripheral arterial thrombosis) within 6 months prior to Day 1

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

5.3.15 Patients with known hypersensitivity to any component of bevacizumab

5.3.16 Patients with clinically significant proteinuria at screening as demonstrated by urine protein:creatinine (UPCR) ratio $\geq$ 1.0 at screening. The UPCR has been found to correlate directly with the amount of protein excreted in a 24 hour urine collection.[49, 50] 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 sample to lab with 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 follows: protein concentration (mg/dL)/creatinine (mg/dL).

5.3.17 Patients with or with anticipation of invasive procedures as defined below:

5.3.17.1 Major surgical procedure within 28 days from initiating bevacizumab or major procedures anticipated during the course of the study. This includes, but is not limited to abdominal surgery (laparotomy or laparoscopy) prior to disease progression, such as colostomy or enterostomy reversal, interval or secondary cytoreductive surgery, or second look surgery.

5.3.17.2 Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to the first date of bevacizumab therapy

5.3.18 Patients with ECOG Performance Grade of 3 or 4 (Appendix D).

5.3.19 Patients who are pregnant (positive pregnancy test) or nursing. Use of effective means of contraception (men and women) in subjects of child-bearing potential. To date, no fetal studies in animals or humans have been performed. The possibility of harm to a fetus is likely. Bevacizumab specifically inhibits VEGF, which is responsible for formation of new blood vessels during development, and antibodies can cross the placenta.

Therefore, bevacizumab should not be administered to pregnant women. Subjects will be apprised of the large potential risk to a developing fetus. 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. Patients of childbearing potential must agree to use contraceptive measures during study therapy and for at least six months after completion of bevacizumab therapy.

5.3.20 Patients under the age of 18.

5.3.21 Patients who have received prior therapy with any anti-VEGF drug, including bevacizumab.

5.3.22 Patients with clinical symptoms or signs of gastrointestinal obstruction and who require parenteral hydration and/or nutrition.

5.3.23 Patients with medical history or conditions not otherwise previously specified which in the opinion of the investigator should exclude participation in this study.

5.3.24 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

5.3.25 Known HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with bevacizumab. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

5.3.26 Inability to comply with study and/or follow-up procedures

6.0 STUDY DESIGN

6.1 Treatment Plan

6.1.1 This is an outpatient regimen. Patients will receive a total of 6 cycles of study medications. On days 1, 8, and 15, patients will receive 80 mg/m2 paclitaxel intravenously infused over 3 hours. On day 1 of Cycle 1, following paclitaxel administration, patients will receive carboplatin AUC 5. For Cycles 2-6, on Day 1, patients will receive carboplatin AUC 5 and bevacizumab 15 mg/kg infused intravenously following paclitaxel 80 mg/m2 administration.

6.1.2 Paclitaxel will be infused first followed by carboplatin and bevacizumab. Cycles will be repeated every 21 days.

6.1.3 Maximum body surface area used for dose calculations of paclitaxel will be 2.0 m^2. There will be no maximum milligram dosage of bevacizumab.

6.1.4 Patient weight at baseline will be used to determine the bevacizumab dose to be used for the duration of the study.

6.1.5 Doses of paclitaxel, carboplatin and bevacizumab may be rounded to the nearest 5 mg. After initial treatment, doses of paclitaxel and bevacizumab should be re-calculated based on any body weight change ≥ 10%.

6.1.6 Protocol therapy can be administered 1 day prior to or up to 1 week after scheduled administration date to allow for calendar events in patient's life (e.g. holidays, weddings, vacations, etc.) Any other deviations require Study Chair approval.

6.1.7 The minimum treatment period will be three cycles of protocol-directed therapy or a minimum of two cycles of bevacizumab.

6.1.8 Changes to chemotherapy regimen in patients found to have persistent disease after 6 cycles of protocol-directed therapy will be made at the discretion of the patient's treating physician.

6.2 Translational Research

6.2.1 Gene Expression Microarrays

The tumor repository will supply frozen tissue samples from 10 patients with PFS <= 6 mos and 10 patients with PFS >= 21 months. These subgroups will be chosen so that effects due to optimal/suboptimal debulking are separately estimable – we will avoid complete confounding. Once acquired, these samples will be profiled using gene expression microarrays (Affymetrix HGU133+v2) run contemporaneously as part of one operating batch, or in balanced blocks if multiple batches are needed. Genomic analysis will identify distinct molecular signatures and provide a foundation for the discovery of tumor response biomarkers in future larger, collaborative studies. The exact choice of biomarkers to be evaluated and validated will be reevaluated based on evolving data in the field.

6.2.2 Plasma Specimens

A pre-treatment plasma specimen collected prior to initiating front-line chemotherapy will be an optional procedure for all patients who have given informed consent for their blood to be drawn to prepare plasma for use in this research study Additional plasma specimens will be drawn prior to cycle 3 and after completion of the study. The exact choice of biomarkers to be evaluated and assays to be performed on plasma specimens will be reevaluated based on evolving data in the field. We will also examine CD5L/CD5, MSMP/MSMP interacting genes, inflammatory cytokines/chemokines and angiogenic factors in plasma and exosomes from these patients.

6.2.3 Immunohistochemistry

Immunohistochemistry will be performed for testing the predictive markers and novel genes involved in adaptive resistance to anti-VEGF therapy in the paraffin sections from this patients.

7.0 STUDY MEDICATION

7.1 Bevacizumab dosage and formulation

Bevacizumab will be given at 15 mg/kg IV on Day 1 of each 21 day cycle, beginning with Cycle 2. Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile liquid concentrate for solution for intravenous (IV) infusion. Bevacizumab will be supplied in 20-cc (400-mg) glass vials containing 16 mL bevacizumab (25 mg/mL). Vials contain bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection (SWFI), USP. Vials contain no preservative and are suitable for single use only.

For further details and molecule characterization, see the Bevacizumab Investigator Brochure.

7.1.1 Bevacizumab Administration

Bevacizumab will be diluted in a total volume of 100mL of 0.9% Sodium Chloride Injection, USP. Administration will be as a continuous IV infusion. Anaphylaxis precautions should be observed during study drug administration. It is not necessary to correct dosing based on ideal weight.

The initial dose will be delivered over 90±15 minutes. If the first infusion is tolerated without infusion-associated adverse events (fever and/or chills), the second infusion may be delivered over 60±10 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30±10 minutes.

If a subject experiences an infusion–associated adverse event, he or she may be premedicated for the next study drug infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30±10 minutes as long as the subject continues to be premedicated. If a subject experiences an infusion-associated adverse event with the 60-minute infusion, all subsequent doses should be given over 90±15 minutes. Similarly, if a subject experiences an infusion-associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60±10 minutes.

7.1.2 Bevacizumab Storage

Upon receipt of the study drug, vials are to be refrigerated at 2°C–8°C (36°F–46°F) and should remain refrigerated until just prior to use. DO NOT FREEZE. DO NOT SHAKE. Vials should be protected from light.

Opened vials must be used within 8 hours. VIALS ARE FOR SINGLE USE ONLY. Vials used for 1 subject may not be used for any other subject. Once study drug has been added to a bag of sterile saline, the solution must be administered within 8 hours.

7.2 PROTOCOL SPECIFIED CHEMOTHERAPY

7.2.1 Paclitaxel

7.2.1.1 Paclitaxel Administration

Paclitaxel (Taxol) 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 commercially available from Bristol-Myers Oncology. A sterile solution concentrate, 6 mg/ml available in 5 ml (30 mg/vial), 16.7 ml (100 mg/vial) and 50 ml (300 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.

Paclitaxel, at the appropriate dose, will be diluted in 250- 1000 cc of 0.9% Sodium Chloride injection, USP or 5% Dextrose injection, USP [D5W (500 cc's 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 polyvinylchloride (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 LVP's) 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.

Thirty minutes before the paclitaxel infusion is to begin the patient is further premedicated with dexamethasone 20 mg IV, diphenhydramine 50mg IV, and an H2 receptor antagonist: cimetidine 300 mg IV, or ranitidine 50 mg IV, or famotidine 20 mg IV.

Paclitaxel, at the appropriate dose and dilution, will be given as a continuous IV infusion over 180 minutes + 15 minutes. 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), which are used to infuse parenteral Nitroglycerin. Nothing else other than 0.9% sodium chloride is to be infused through the line where paclitaxel is being administered.

7.2.1.2 Paclitaxel Storage and Stability

The intact vials should be stored under refrigeration (2-8°C). 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.

7.2.2 Carboplatin

7.2.2.1 Carboplatin Administration

Carboplatin is supplied as a sterile, pyrogen-free, 10mg/mL aqueous solution in multi-dose vials containing 50mg/5mL, 150mg/15mL, 450mg/45mL, or 600g/60mL of carboplatin. Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5mg/mL with 5% Dextrose in Water or 0.9% Sodium Chloride for Injection, USP.

Carboplatin infusion will be administered following paclitaxel, at the appropriate dose and dilution and will be given as a continuous IV infusion over 30 minutes + 15 minutes. Carboplatin will be administered via an infusion control device (pump) using non-PVC tubing and connectors.

7.2.2.2. Carboplatin Dosing

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.

The initial dose of carboplatin will be calculated using GFR. In the absence of new renal obstruction or other 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 be recalculated for subsequent cycles, but will be subject to dose modification as noted in the protocol.

Carboplatin doses are based on the patient's weight at baseline and will not be recalculated unless the patient has a weight change of greater than or equal to 10% from baseline.

In patients with abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance will be estimated using a minimum value of 0.7 mg/dl.

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

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

The maximum Carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min

The maximum allowed doses of Carboplatin are:

AUC 5 = 750 mg

AUC 4 = 600 mg

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

$$\text{Creatinine Clearance (mL/min)} = \frac{[140 - \text{age (yrs)}] \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dl)}}$$

Actual weight is used for estimation of GFR for patients with a BMI of less than 25. Adjusted weight is used for patients with a BMI of greater than or equal to 25.

Dose Modification for toxicity:

If the creatinine at the time of 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 ensures that the patient is actually receiving a dose reduction.

7.2.2.3 Carboplatin Storage and Stability

Unopened vials of carboplatin are stable to the date indicated on the package when stored at 25°C (77°F). Excursions from 15 to 30°C (59 to 86°F) are permitted. Protect from light. Carboplatin multi dose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries. When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C / 77°F). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded 8 hours after dilution.

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.

7.3 CONCOMITANT MEDICATIONS

Low-dose aspirin (≤ 325 mg/d) may be continued in subjects at higher risk for arterial thromboembolic disease. Subjects developing signs of arterial ischemia or bleeding on study should be evaluated for possible bevacizumab toxicity and dose modification per Section 7.4.2 Table 1, Bevacizumab Dose Management Due To Adverse Events.

7.4 DOSE MODIFICATIONS AND TOXICITY MANAGEMENT

7.4.1 General Modifications

7.4.1.1 Management of Hypersensitivity Reactions

In general, the occurrence of a hypersensitivity reaction to paclitaxel, carboplatin, or bevacizumab is not considered a

dose-limiting toxicity. Patients may be retreated at full doses after administration of medication to prevent hypersensitivity reactions, and adjustments to infusion rates should be made. 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.

7.4.1.1.1 Hypersensitivity to bevacizumab

Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. Subjects who experience a CTCAE Grade 3 or 4 allergic reaction / hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

The infusion should be slowed to 50% or less or interrupted for subjects who experience any infusion-associated symptoms not specified above. When the subject's symptoms have completely resolved, the infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle.

In the event of a prior bevacizumab hypersensitivity reaction, subsequent infusions should be delivered over 90 minutes, and the following prophylactic regimen is recommended upon re-exposure:

- H1 blocker (diphenhydramine 25-50 mg IVP or orally one hour prior to injection; or an equivalent dose of an alternate H1 blocker such as loratadine 10 mg or fexofenadine 60 mg).
- H2 blocker (famotidine 20 mg IVP or orally one hour prior to injection; or an equivalent dose of an alternate H2 blocker).
- Dexamethasone (10 mg administered PO 12 and 6 hours prior to bevacizumab injection).

7.4.1.1.2 Hypersensitivity to paclitaxel

Hypersensitivity reactions to paclitaxel or its vehicle (Cremophor) occur almost universally during the first few minutes of infusion. Continued treatment may be considered if the reaction was not life-threatening; however, patients must be cautioned of potential recurrences of the reaction. Should the patient decide to continue with treatment it is preferable that this be done on the same day of the occurrence.

A suggested procedure would be to repeat the patient's premedication with dexamethasone 20mg IV, cimetidine 300mg (or ranitidine 50mg) IV, and diphenhydramine 50mg IV 30 minutes before the paclitaxel reinfusion is to begin. Slowly infuse the paclitaxel by administering the drug first with 1 ml of the original IV solution diluted in 100 ml over one hour, then 5 ml in 100 ml over one hour, then 10 ml in 100 ml over one hour, and finally the original solution at the original infusion rate. No additional dose adjustments should be made for other hypersensitivity reactions.

7.4.1.2 General Guidelines for Hematologic Toxicity

7.4.1.2.1 Initial treatment modifications will consist of cycle delay and/or dose reduction as indicated below. The use of hematopoietic cytokines and protective reagents are restricted as noted:

7.4.1.2.2 Treatment decisions will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC).

7.4.1.2.3 Lower Limits for ANC and Platelet Count

Subsequent treatment with bevacizumab, carboplatin, and paclitaxel on Day 1 of each cycle will not be given until the ANC is ≥ 1500 cells/mm^3 (CTCAE Grade 1) and the platelet count is ≥ 100,000/ul. Therapy will be delayed for a maximum of three weeks until these values are achieved. Patients who fail to recover adequate counts within a three-week delay will be removed from study.

Treatment with weekly paclitaxel on Days 7 and 14 of each cycle will not be given unless ANC is ≥ 1000 cells/mm^3 and the platelet count is ≥ 75,000/ul. Paclitaxel therapy will be delayed for a maximum of three weeks until these values are achieved. Patients who fail to recover adequate counts within a three-week delay will be removed from study. If day 7 dosing criteria are not met, hold the paclitaxel dose and treat on day 14 as planned if toxicity has resolved. If day 14 dosing criteria are not met, hold the paclitaxel dose. Start the next full cycle (ie. Day 1 treatment) one week later if toxicity has resolved.

Exceptions:

- Patients who received G-CSF prior to the current cycle may begin with ANC ≥ 1000 cells/mm^3, if clinically appropriate, to allow for transient reductions in ANC after discontinuation of G-CSF.

- Patients who are delayed more than 7 days may begin with ANC ≥ 1000 cells/mm^3, if clinically appropriate, as they will receive G-CSF with subsequent therapy.

7.4.1.2.4 Use of Hematopoeitic Cytokines and Protective Agents

- Patients will NOT receive prophylactic growth factors [filgrastim (GCSF), sargramostim (GM-CSF)] unless they experience recurrent neutropenic complications after treatment modifications specified below (Section 7.4.4). In particular, hematopoietic growth factors should not be used to avoid initial chemotherapy dose modifications as stipulated in the protocol. However, patients may also receive growth factors for management of neutropenic complications in accordance with clinical treatment guidelines. If required, it is recommended that growth factors be initiated the day after the last dose of chemotherapy and typically continuing until the ANC is sustained above > 1000/ mm^3. Growth factors should be discontinued if the ANC exceeds 10,000/mm^3 and should not be used within 72 hours of a subsequent dose of chemotherapy.
- Patients will not be eligible to receive PEG-filgrastim (Neulasta) on study due to the weekly dose schedule of paclitaxel.
- Patients will NOT receive prophylactic thrombopoietic agents unless they experience recurrent grade 4 thrombocytopenia after treatment modifications as specified below (Section 7.4.4).
- Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia. Treating physicians should be aware of the recent changes in prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen, and Procrit) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival and that these agents are administered only to avoid red blood cell transfusions. They do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts

should be consulted.
http://www.fda.gov/Medwatch/safety/2007/safety07.htm

- Patients may NOT receive amifostine or other protective agents.
- For first occurrence of febrile neutropenia, and/or documented grade 4 neutropenia persisting ≥ 7 days, add growth factors. In this circumstance, it is recommended that growth factors (G-CSF) at a dose of 5 µg/kg/day (or equivalent dose of sargramostim) will be administered subcutaneously starting the day after the last dose of chemotherapy and continuing through hematopoietic recovery. Growth factors should not be used within 72 hours of a subsequent dose of chemotherapy.

7.4.1.2.5 Dose modifications for the management of hematologic toxicity (Section 7.4.4) are applicable to carboplatin unless specifically indicated.

7.4.1.3 Special Modifications

7.4.1.3.1 For any CTCAE Grade 3 non-hematologic adverse event (except controllable nausea/emesis) considered to be at least possibly related to study treatment, protocol directed treatment should be held until symptoms resolve to <= CTCAE Grade 1. If a CTCAE Grade 3 adverse event persists for > three weeks or recurs after resumption of therapy, the patient may be taken off protocol directed treatment after consulting with the Study Chair.

7.4.1.3.2 For any CTCAE Grade 4 non-hematologic adverse event (except controllable nausea/emesis), the patient may be taken off protocol directed treatment therapy after consulting with the Study Chair.

7.4.1.3.3 Unanticipated Major Surgical Procedures – For any unanticipated (emergent/urgent or elective) major surgical procedure performed, patients will be removed from study. Treatment delay nor study removal is **not** required for minor procedures including a) cystoscopy, b) the removal or insertion of a central venous catheter, nephrostomy tube, or ureteral stent or c) thoracentesis or paracentesis for symptom relief in the absence of disease progression according to section 11.2.

7.4.1.3.4 Dose re-escalation will not be permitted if dose reduction is required for toxicity management.

7.4.1.3.5 It is recommended that routine medical measures be employed to manage nausea, emesis, constipation, and diarrhea.

7.4.2 Bevacizumab Dose Modification and Toxicity Management

There are no reductions in the bevacizumab dose. If adverse events occur that require holding bevacizumab, the dose will remain the same once treatment resumes.

Any toxicities associated or possibly associated with bevacizumab treatment should be managed according to standard medical practice. Discontinuation of bevacizumab will have no immediate therapeutic effect. Bevacizumab has a terminal half-life of 21 days; therefore, its discontinuation results in slow elimination over several months. There is no available antidote for bevacizumab.

Subjects should be assessed clinically for toxicity prior to, during, and after each infusion. If unmanageable toxicity occurs because of bevacizumab at any time during the study, treatment with bevacizumab should be discontinued.

Adverse events requiring delays or permanent discontinuation of bevacizumab are listed in Table 1.

Patients requiring permanent discontinuation of bevacizumab due to bevacizumab toxicities will continue on study with protocol-directed carboplatin and paclitaxel alone (unless otherwise indicated in Table 1), so long as a patient has not developed progressive cancer as per section 11.2 and has not yet received 6 cycles of carboplatin/paclitaxel therapy.

Table1:

Bevacizumab Dose Management Due to Adverse Events

Event	Action to be Taken
Hemorrhage	
Grade 1 or 2 Non-pulmonary and non-CNS events	No dose modification.
Grade 3 Non-pulmonary and non-CNS hemorrhage	Subjects experience CTCAE Grade 3 hemorrhage and who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab for the remainder of the study. All other subjects will have bevacizumab held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. If the above criteria are not met by 3 weeks after holding treatment with bevacizumab, treatment with bevacizumab should be discontinued for the remainder of the study. Subjects who experience a repeat Grade 3 hemorrhagic event will be discontinued from receiving bevacizumab for the remainder of the study.
Grade 4 non-pulmonary or non-CNS hemorrhage	Discontinue bevacizumab for the remainder of the study.
Grade 1 pulmonary or CNS hemorrhage	Subjects who are also receiving full-dose anticoagulation will be discontinued from receiving bevacizumab. All other subjects will have bevacizumab held until all of the following criteria are met: • The bleeding has resolved and hemoglobin is stable. • There is no bleeding diathesis that would increase the risk of therapy. • There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence. If the above criteria are not met by 3 weeks after holding treatment with bevacizumab, treatment with bevacizumab should be discontinued for the remainder of the study.
Grade 2, 3, or 4 pulmonary or CNS hemorrhage	Discontinue bevacizumab for the remainder of the study

Venous Thrombosis	
Grade 1 or 2	No dose modification.
Grade 3 or 4	Hold bevacizumab. If the planned duration of full-dose anticoagulation is ≤2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met: • The subject must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting evacizumab treatment. • The subject must not have had a Grade 3 or 4 hemorrhagic event while on anticoagulation. • The subject must not have pathological conditions that carry high risk of bleeding (ie. tumor involving major vessels). For patients with PT/INR > therapeutic range while on therapeutic warfarin, treatment with bevacizumab will be held until PT/INR is within the therapeutic range. Patients experiencing treatment delay > 3 weeks because of failure to meet the above criteria will be taken off bevacizumab for the remainder of the study.
Arterial Thromboembolic event (New onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, cerebrovascular accident, and any other arterial thromboembolic event)	
Any grade	Discontinue bevacizumab for the remainder of the study.
Congestive Heart Failure (Left ventricular systolic dysfunction)	
Grade 1 or 2	No dose modification.
Grade 3	Hold bevacizumab until resolution to Grade ≤ 1. Patients experiencing treatment delay > 3 weeks because of failure to meet the above criteria will be taken off bevacizumab for the remainder of the study.
Grade 4	Discontinue bevacizumab for the remainder of the study.
Proteinuria	
Grade 1 or 2 (UPCR <3.5)	No dose modification.
Grade 3 (UPCR ≥ 3.5)	Hold bevacizumab treatment until UPCR ratio recovers to <3.5. If therapy is held for > 2 months due to proteinuria, discontinue evacizumab.
Grade 4 (nephritic syndrome)	Discontinue bevacizumab for the remainder of the study.

GI Perforation	Discontinue bevacizumab for the remainder of the study..
Fistula	
Any grade (TE fistula)	Discontinue bevacizumab for the remainder of the study..
Grade 4 fistula	Discontinue bevacizumab for the remainder of the study..
Bowel Obstruction*	
Grade 1	Continue patient on study for partial obstruction NOT requiring medical intervention.
Grade 2	Hold bevacizumab for partial obstruction requiring medical intervention. Patient may restart upon complete resolution.
Grade 3	Hold bevacizumab for complete obstruction. If surgery is necessary, patient will be removed from study.
Grade 4	Discontinue bevacizumab for the remainder of the study.
Wound dehiscence	
Prior to initiation of bevacizumab	In the event of superficial wound separation healing by secondary intention with no evidence of fascial dehiscence or infection, therapy with bevacizumab may be initiated with weekly wound examinations until closure.
After initiation of bevacizumab, any grade	Discontinue bevacizumab for the remainder of the study.
Reversible Posterior Leukoencephalopathy	
Any grade (confirmed by MRI)	Discontinue bevacizumab for the remainder of the study.
Other Unspecified Bevacizumab-Related Adverse Events	
Grade 3	Hold bevacizumab until recovery to ≤ Grade 1
Grade 4	Discontinue bevacizumab for the remainder of the study.

***** Since the development of intestinal obstruction could be a result of cancer progression, the investigator should take steps to evaluate such patients for the possibility of disease progression according to Section 11.2, using clinical, laboratory, and radiographic information as clinically indicated. In the event of disease progression as per Section 11.2, all protocol-directed therapy would be discontinued.

Hypertension

Patients should be monitored prior to each bevacizumab dose with measurement of blood pressure. Medication classes used for management of patients with Grade 3 hypertension receiving bevacizumab include angiotensin-converting enzyme inhibitors, beta blockers, diuretics, and calcium channel blockers. The goal for blood pressure control should be consistent with general medical practice guidelines (i.e. <140/90 mmHg). The use of anxiolytics in conjunction with specific anti-hypertensive agents is not prohibited.

- For controlled hypertension, defined as systolic <140 mm Hg and diastolic <90 mm Hg, continue therapy.
- For uncontrolled hypertension (systolic >140 mm Hg or diastolic >90) or symptomatic hypertension less than CTCAE Grade 4, hold bevacizumab and initiate or modify anti-hypertensive therapy as needed.
- If hypertension is controlled and symptomatic hypertension has resolved by one week after holding all therapy, continue all therapy.
- If hypertension remains uncontrolled or symptomatic hypertension less than CTCAE Grade 4 persists one week after holding treatment, the next treatment cycle should contain paclitaxel and carboplatin only with bevacizumab omitted. Patient may receive bevacizumab therapy if hypertension is controlled for subsequent treatment cycles.
- If uncontrolled or symptomatic hypertension has not resolved by 3 weeks after holding treatment with bevacizumab, treatment with bevacizumab should be discontinued for the remainder of the study.
- For any CTCAE Grade 4 hypertension (including hypertensive encephalopathy), discontinue bevacizumab for the remainder of the study.

7.4.3 Paclitaxel Treatment Modifications and Toxicity Management

Table A. Dose levels for paclitaxel

	-2	-1	0
Paclitaxel	60 mg/m2	70 mg/m2	80 mg/m2

7.4.3.1 Non-hematologic toxicity

7.4.3.1.1 Grade 2 (or greater) peripheral neuropathy requires reduction of one dose level and delay in all subsequent protocol-directed therapy course 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 3 weeks from time therapy is due, then patient will be removed from study.

7.4.3.1.2 Grade 3 (or greater) elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin requires reduction of one dose level and delay in subsequent therapy course for a maximum of 3

weeks until recovered to grade 1 or patient will be removed from study.

7.4.3.1.3 There will be no dose modifications for alopecia or fatigue.

7.4.3.1.4 It is expected that patients with nausea, emesis, diarrhea, or constipation will receive appropriate medical management without dose modification. However, patients with persistent (greater than 24 hours) grade 3 (or greater) toxicity in spite of optimal medical management require reduction of one dose level and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1 or patient will be removed from study.

7.4.3.1.5 Other non-hematologic toxicities with an impact on organ function of Grade 2 (or greater) require reduction of one dose level and delay in subsequent therapy for a maximum of 3 weeks until recovered to grade 1, or pre-therapy baseline or patient will be removed from study. If recovery is not reached as specified after a 3-week delay, the patient is taken off the study.

7.4.3.1.6 If a treatment had to be omitted during the preceding cycle due to toxicities mentioned in Section 7.4.3.1, the subsequent cycle will be given with a paclitaxel level 1 dose reduction.

7.4.3.1.7 If after a level 1 dose reduction again treatment had to be omitted due to toxicities mentioned in Section 7.4.3.1, the next cycle will be given with a paclitaxel level 2 dose reduction.

7.4.3.1.8 Patients requiring substitution of docetaxel instead of paclitaxel or greater than level 2 dose reduction will be removed from study.

7.4.4 Carboplatin Treatment Modifications and Toxicity Management

Table B. Dose levels for carboplatin

	-2	**-1**	**0**
Carboplatin	Off Study	AUC 4	AUC 5

7.4.4.1 Hematologic toxicity

Treatment modifications for the management of hematologic toxicity are applicable to carboplatin unless specifically indicated.

7.4.4.1.1 Dose-Limiting Neutropenia (DLT-ANC) is defined by the occurrence of febrile neutropenia or prolonged Grade 4 neutropenia persisting ≥ 7 days. There will

be no modifications for uncomplicated Grade 4 neutropenia lasting less than 7 days. Febrile neutropenia is defined within the CTCAE as fever with or without clinically or microbiologically documented infection with ANC less than 1,000/mm^3 and fever ≥ 38.5^0C.

7.4.4.1.2 Dose limiting thrombocytopenia (DLT-PLT) is defined by any occurrence of Grade 4 thrombocytopenia (<25,000/mm^3) or bleeding associated with Grade 3 thrombocytopenia (25,000 to <50,000mm^3). There will be no modifications for uncomplicated Grade 3 thrombocytopenia.

7.4.4.1.3 Initial occurrence of dose-limiting neutropenia or dose-limiting thrombocytopenia as defined in Sections 7.4.4.1.1 and 7.4.4.1.2 will be handled according to Table C using regimen modifications in Table B.

7.4.4.1.4 For recurrent febrile neutropenia, and/or recurrent documented grade 4 neutropenia persisting ≥ 7 days (after initial dose reduction), continue growth factors and reduce carboplatin by one dose level on subsequent cycles.

7.4.4.1.5 There will be no dose modifications on the basis of uncomplicated granulocyte nadirs ≤ Grade 3 lasting less than 7 days.

Table C. Modification Instructions for Dose-Limiting Hematologic Toxicities

DLT ANC	DLT PLT	First Occurrence	Second Occurrence	Third Occurrence
Yes	**No**	Reduce carboplatin one dose level	Add G-GSF and maintain all current drug doses	Discontinue All Protocol-Directed Cytotoxic Therapy
Yes	**Yes**	Reduce carboplatin one dose level	Add G-GSF and decrease carboplatin one dose level	Discontinue All Protocol-Directed Cytotoxic Therapy
No	**Yes**	Reduce carboplatin one dose level	Decrease carboplatin one dose level	Discontinue All Protocol-Directed Cytotoxic Therapy

7.4.4.1.6 Carboplatin delay on the basis of neutropenia (Delay-ANC) is defined if the ANC is less than 1,500 cells/mm3 (CTCAE Grade 2 or worse) within 24 hours prior to scheduled therapy, or less than 1,000 cells/

mm3, if the patient received G-CSF during the previous cycle.

7.4.4.1.7 Carboplatin delay on the basis of thrombocytopenia (Delay-PLT) is defined if the platelet count is less than 100,000/ mm3 within 24 hours prior to scheduled therapy.

7.4.4.1.8 Modifications noted below are only required for management of delays in the absence of dose reductions stipulated by nadir DLT-ANC and/or DLT-PLT (as noted Table C). In other words, if the patient experiences DLT-ANC and Delay- ANC, make the modifications as indicated for the nadir counts without additional modifications based on delayed recovery.

Table D. Modifications for Delayed Hematologic Recovery

Category	Delay (days)	Modification
Delay-ANC	1-7	No change
	8-21	Add G-CSF to next cycle
	>21	Discontinue protocol-directed cytotoxic chemotherapy
Delay-PLT	1-7	No change
	8-21	Add G-CSF to next cycle
	>21	Discontinue protocol-directed cytotoxic chemotherapy

7.4.4.2 Non-hematologic toxicity

Renal toxicity (associated with reduction in GFR) is not expected as a direct complication of chemotherapy in this untreated patient population using the prescribed dose and schedule of each regimen. As such, there are no specific dose modifications for renal toxicity. However, the target AUC dose of carboplatin must be recalculated each cycle in any patient who develops renal insufficiency defined by non-IDMS serum creatinine greater than 1.5 x institutional upper limit normal (ULN), CTCAE Grade ≥ 2.

8.0 Study Calendar

	Pre-Study		During Chemotherapy Treatment		Off Study	
Observations & Tests	**Prior to Initial Study Treatment**	**Each Cycle**	**Day 8**	**Day 15**	**(within 4 weeks of last protocol-directed therapy)**	**Every 3 months**
Paclitaxel		X	X	X		
Carboplatin		X				
Bevacizumab		22				
Informed consent	X					
History & Physical Exam (including weight)	1	14			X	X
Pelvic exam	1	15			16	16
Vital signs	1	14	X	X	X	X
Toxicity Assessment	2	X			X	21
Performance status	1				X	X
CBC w/diff, plts	2	3	X	X	4	4
Serum chemistry (BUN/Cr, Magnesium, Calcium, SGOT, SGPT, Alkaline phosphatase, Total bilirubin, electrolytes)	2	3			5	5
PT/PTT/INR	1, 6	6			5, 6	5, 6
CA-125	1, 11	12			X	X
Radiographic Disease Assessment	18	9			9	5,9
EKG	1				5	5
CXR	1, 10				5	5
UPCR for proteinuria	2, 17	18			19	19
Serum Pregnancy Test (if childbearing potential exists)	2					
Incision check	2	13				
Blood draw for cytokine analysis	2	Pre cycle 3			20	
Biomarker evaluation of tumor tissue	23					24

[a] Patients who are considered inevaluable or patients who have disease progression or are non-responders as per Section 11.2 at time of off-study evaluation are not required to adhere to follow-up protocol.

1. Must be obtained within 28 days prior to initiating protocol therapy.

2. Must be obtained within 14 days prior to initiating protocol therapy.

3. Must be obtained within 4 days of re-treatment with protocol therapy.

4. Weekly until counts recover from nadir.

5. When clinically indicated.

6. For patients on prophylactic or therapeutic anticoagulation with warfarin, PT/INR should be monitored before each treatment. Treatment should be held for PT/INR of > 1.5 on prophylactic warfarin of > therapeutic range if on full-dose warfarin.

7. For patients with a history of hearing loss; repeat as clinically indicated.

8. An initial CT scan or MRI of at least the abdomen and pelvis is required to establish post-surgical baseline for the extent of residual disease within 4 weeks of registration and beginning of treatment.

9. Follow-up Radiographic Assessment of Disease. In the absence of disease progression by criteria in Section 11.2, imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation should be repeated with the following schedule, regardless of whether or not the patient had measurable disease on initial CT or MRI:

   a) Patients considered suboptimal will receive radiographic disease assessment after completion of 3 cycles of study therapy and within 4 weeks after completion of protocol directed chemotherapy.

   b) Patients considered optimal will receive radiographic disease assessment after completion of protocol directed chemotherapy.

   c) All patients, during or after completion of all protocol therapy, may receive radiographic disease assessment as clinically indicated at any time for clinical suspicion of progressive disease.

   If based on any of these evaluations a response (CR or PR) is documented, a same modality imaging study should be performed after no less than 4 weeks in order to confirm persistence of response by RECIST criteria.[51] Imaging assessments as part of this protocol should be discontinued if disease progression is confirmed according to guidelines in Section 11.2, regardless of means of confirmation, except that 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 two weeks that such progression is documented.

10. Not required if CT or MRI of chest already performed at pre-treatment baseline.

11. Baseline pre-chemotherapy value is required. When available, also include pre-surgical value.

12. Progression can be based upon serum CA-125, only during the period following completion of cytotoxic chemotherapy, if one of the three conditions is 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 8.4).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.

13. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection are eligible but require weekly would examinations until complete closure. Any occurrence of fascial dehiscence or deterioration related to the incision should be addressed according to guidelines for treatment modification (Section 7.4.2) and Adverse Events reporting (Section 12.0).
14. Within one week before and as close to the beginning of the next applicable course as possible.
15. Pelvic examination is required only if this method is used to evaluate measurable disease or for clinical suspicion of disease progression or recurrence.
16. Pelvic examination is required during follow-up to evaluate for disease progression or recurrence.
17. Urine protein should be screened by UPCR (see Section 5.3.16 for details). Patients must have a UPCR < 1.0 to allow participation in the study.
18. Patients receiving bevacizumab should be monitored by urine analysis for urine protein: creatinine (UPCR) ratio prior to every other dose of bevacizumab:

UPCR ratio < 3.5	Continue bevacizumab.
UPCR ratio ≥ 3.5	Hold bevacizumab until UPCR ratio recovers to < 3.5. If therapy is held for > 2 months due to proteinuria, discontinue bevacizumab
Grade 4 or nephrotic syndrome	Discontinue bevacizumab.

19. Check UPCR at first post-treatment visit. Check the UPCR at subsequent post-treatment follow-up intervals only if the value is > 1.0.
20. Performed only at the first follow-up evaluation in patients who have received at minimum two cycles of bevacizumab.
21. Patients discontinued from the treatment phase of the study for any reason will be evaluated ~30 days (28–42 days) after the decision to discontinue treatment (see Section 7.4.2) unless patients are discontinued from the study due to an ongoing bevacizumab-related Grade 4 or serious adverse event. These patients will continue to be followed until resolution of the event or until the event is considered irreversible.
22. Bevacizumab dosing will start on Day 1 of Cycle 2.
23. Tissue from the tumor bank repository will be stored at the time of initial cytoreductive surgery if the patient consented to tumor bank storage prior to surgery.
24. Genetic analyses of tumor tissue samples will be conducted after disease progression has been determined or after 24 months of follow-up, whichever comes first.

9.0 SUBJECT DISCONTINUATION

Subjects who meet the following criteria should be discontinued from study treatment:

1. Completed protocol-directed treatment
2. Inability to tolerate the lowest doses because of toxicity.
3. The patient may withdraw from the study at any time for any reason.
4. Patients with deterioration of performance status may be removed from study at the investigator's discretion
5. Non-compliance
6. Subjects who experience a CTCAE Grade 3 or 4 allergic reaction / hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade)
7. Radiographic evidence of disease progression (see section 11.2.1)
8. Grade 4 hypertension or Grade 3 hypertension not controlled with medication
9. Reversible posterior leukoencephalopathy syndrome (RPLS)
10. Nephrotic syndrome
11. Grade ≥ 2 pulmonary or CNS hemorrhage; any Grade 4 hemorrhage
12. Symptomatic Grade 4 venous thromboembolic event (for lung protocols: any venous thromboembolic event requiring full dose warfarin or equivalent (i.e., unfractionated or low molecular weight heparin)
13. Any grade arterial thromboembolic event
14. Grade 4 congestive heart failure
15. Gastrointestinal perforation
16. Tracheoesophageal fistula (any grade) or Grade 4 fistula
17. Grade ≥ 2 bowel obstruction that has not fully recovered despite medical or surgical intervention
18. Wound dehiscence requiring medical or surgical intervention
19. Unwillingness or inability of subject to comply with study requirements
20. Determination by the investigator that it is no longer safe for the subject to continue therapy
21. All Grade 4 events thought to be related to bevacizumab by the investigator
22. Patients requiring surgery for any reason while receiving protocol-related therapy

    Patients who have an ongoing bevacizumab-related Grade 4 or serious adverse event at the time of discontinuation from study treatment will continue to be followed until resolution of the event or until the event is considered irreversible.

10.0 STUDY DISCONTINUATION

Patients will receive treatment until disease progression, the development of adverse events requiring discontinuation of protocol treatment, or completion of 6 cycles of protocol-directed treatment, whichever comes first. No form of therapy targeted against a patient's cancer other than that specified in this protocol will be administered while on study.

11.0 STATISTICAL CONSIDERATIONS

11.1 Determination of Sample Size

We will enroll and evaluate a minimum of 15 patients with a target completed sample size of 30 patients. Patients will be enrolled at a rate of 1-2 patients per month. Our primary outcome is treatment success, defined as a patient completing at least 4 cycles of combination therapy (Bevacizumab with Carboplatin and weekly Paclitaxel) regardless of delay or dose modification. Our target treatment success rate is 60%.

We will employ a Bayesian monitoring rule following the example of Thall and Simon.[52] We will stop the trial early if Pr(treatment success rate $\geq$ 60% | data from the trial) < 0.05. That is, given the outcomes from the patients who have already been evaluated, if we determine that there is less than a 5% chance that the treatment success rate is 60% or more we will stop the trial. This decision rule gives the following stopping rule. We assume a uniform prior distribution for the treatment success rate. Stop the trial if

[# of pts with treatment success / # of pts evaluated]

≤ 5/15, 6/16, 7/18, 8/20, 9/22, 10/24, 11/26, 12/27, 13/29

The operating characteristics of this study design are shown in Table 1.

Table 1. Operating Characteristics of Feasibility Monitoring Rule

Success Rate	Probability of Stopping Early	Sample Size		
		P_{25}	P_{50}	P_{75}
0.35	0.929	15	15	18
0.40	0.819	15	16	27
0.45	0.649	15	22	30
0.50	0.446	18	30	30
0.55	0.249	30	30	30
0.60	0.125	30	30	30
0.65	0.046	30	30	30
0.70	0.014	30	30	30

Once we have completed the study we will estimate the treatment success rate with 90% credible interval. If we find 23 of the 30 patients with treatment success, then our 90% credible interval for the treatment success rate will be 61.7% to 86.5%. We will also report the posterior probability that the treatment success rate is 60% or

more. For example, if we complete the trial with 21 of 30 patients with treatment success, the posterior probability that the treatment success rate is at least 60% will be 0.857.

11.2 Planned Efficacy Evaluations

11.2.1 Efficacy Variables

11.2.1.1 Parameters of Response – RECIST Criteria Version 1.1

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 ≥10 mm when measured by conventional techniques, including caliper measurements on clinical exam, CT, and MRI, or ≥20 mm by chest x-ray.[51] PET scanning information will not be evidence of disease progression or measurable disease. PET CT Fusion studies may not meet technical requirements.

To be considered pathologically enlarged and measurable, a lymph node should be ≥15mm by short axis on CT scan.

11.2.1.2 Baseline Documentation of "Target" and "Non-Target" Lesions

- All measurable lesions up to a maximum of 2 lesions per organ and 5 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 diameters for all target lesions will be calculated and reported as the baseline sum. Only the short axis of lymph nodes classified as measurable will contribute to the baseline sum. The baseline sum 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), including pathological lymph nodes ≥ 10 to <15 mm short axis, 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.
- Tumor lesions that are situated in previously irradiated area might or might not be considered measurable.

11.2.1.3 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.

- Complete Response (CR) is disappearance of all *target* and *non-target* lesions and no evidence of new lesions documented by two disease assessment. Any pathological lymph node (whether target or non-target) must have reduction in short axis to <10mm.
- Partial Response (PR) is at least a 30% decrease in the sum of diameters of all *target* measurable lesions taking as reference the baseline sum of diameters. There can be no unequivocal progression of *nontarget* 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.
- Increasing Disease is at least a 20% increase in the sum of diameters of *target* lesions taking as references the smallest sum on study. In addition to the 20% relative increase, the sum must also have an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progressive disease. 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.
- 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.
- Stable Disease is any condition not meeting the above criteria.
- 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*.

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

- Progression Based on Serum CA-125:

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

  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

  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.

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

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

- In some cases a discrepancy may exist between trends in CA-125 levels and data from either imaging or physical examination. In such cases, disease status by CT or MRI (and physical examination) should take precedence over CA-125. For example, if there is evidence of disease on CT, MRI, or physical examination, and none of these areas

demonstrate any progression then rising CA-125 levels would be insufficient to determine disease progression.

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

11.2.1.4 Confirmatory Measurement/Duration of Response

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

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

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

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

11.2.1.5 Progression-Free Survival

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

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

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

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

11.2.1.5.3 For disease progression defined by CA125 criteria alone, the date of progression will be

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

11.2.1.5.4 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.

11.2.1.5.5 Death due to disease without prior objective documentation of progression.

11.2.1.5.6 Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression.

11.2.1.6 Overall Survival

Overall Survival is the observed length of life from entry into the study to death, regardless of cause or the date of last contact.

11.2.1.7 Subjective Parameters

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

11.2.2 Methods of Analysis

- This is a traditional phase II study and, hence, no randomization or comparison group is involved.
- The principal parameters employed to evaluate the efficacy of each agent are:

11.2.2.1 Progression-free survival (PFS)

We will estimate the PFS with the Kaplan-Meier product-limit estimator stratified by debulking status (optimal, sub-optimal).[53] We will use the Cox proportional hazards regression model [54] to assess the association of gene expression and cytokines with PFS as described below.

11.2.2.2 The frequency and duration of objective response.

We will estimate the frequency of objective response with a 95% confidence interval separately for optimally debulked patients and sub-optimally debulked patients.

For those patients who achieve an objective response we will estimate the duration of objective response with a 95% confidence interval separately for optimally debulked patients and sub-optimally debulked patients. We will use logistic regression methods to assess the association between cytokines and objective response.

The frequency and severity of observed adverse effects.

We will tabulate the frequency and severity of observed adverse events separately for optimally debulked patients and sub-optimally debulked patients, as well as for all patients together.

11.3 Genomic Data Analyses

Expression arrays will be quantified using Robust Multichip Analysis.[55] After quantification, we will fit Cox proportional hazards models on a gene by gene basis, with gene expression levels and debulking status as covariates; we seek cases where the gene expression coefficients are significant. We will adjust for multiple comparisons using beta-uniform mixture (BUM) models [56], and seek genes that remain significant at a false discovery rate (FDR) of 0.2. Given the mechanism of action for bevacizumab, this analysis will be repeated with attention restricted to the subset of genes associated with angiogenesis according to Gene Ontology.

11.4 Cytokine Evaluation Analyses

We anticipate profiling the paired pre and post-treatment plasma samples for the expression levels of a small number of cytokines (on the order of 20 to 50). We are primarily interested in relating two quantities with PFS: (1) baseline cytokine levels at time of initial measurement, and (2) post-pre differences in cytokine levels. In both cases, we will assess significance by fitting Cox proportional hazards models with debulking status as an additional covariate, and looking at the significance of the cytokine coefficient term. We will correct for multiple testing using a conservative Bonferroni adjustment, dividing the target p-value for significance by the total number of tests performed.

12.0 SAFETY REPORTING OF ADVERSE EVENTS

12.1 ADVERSE EVENT REPORTING AND DEFINITIONS

In the event of an adverse event the first concern will be for the safety of the subject.

Investigators are required to report to Genentech Drug Safety ANY serious treatment emergent adverse event (STEAE) as soon as possible.

A STEAE is any sign, symptom or medical condition that emerges during Bevacizumab treatment or during a post-treatment follow-up period that (1) was not present at the start of Bevacizumab treatment and it is not a chronic condition that is part of the patient's medical history, OR (2) was present at the start of Bevacizumab treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory serious criteria:

- Results in death
- Is life-threatening
- Requires or prolongs inpatient hospitalization
- Is disabling
- Is a congenital anomaly/birth defect
- Is medically significant or requires medical or surgical intervention to prevent one of the outcomes listed above.

12.2 REPORTING OF SERIOUS TREATMENT EMERGENT ADVERSE EVENTS

All STEAEs should be recorded on a MedWatch 3500a Form and faxed to:

1) Genentech Drug Safety Fax: (650) 225-4682 or (650) 225-5288

AND

2) Judith Wolf, Principal Investigator Phone: (713)792-7310 Fax: (713)745-8276

AND

3) MDACC IRB Contact: Mary Fields or Barbara Groves Fax: (713) 794-4589

Please use safety reporting fax cover sheet in Appendix G for your fax transmission.

MedWatch 3500a Reporting Guidelines:

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500a form:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)

- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information:

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500a report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500a form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report)

Occasionally Genentech may contact the reporter for additional information, clarification, or current status of the subject for whom and adverse event was reported.

Assessing Causality:

Investigators are required to assess whether there is a reasonable possibility that bevacizumab caused or contributed to an adverse event. The following general guidance may be used.

Yes: if the temporal relationship of the clinical event to bevacizumab administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: if the temporal relationship of the clinical event to bevacizumab administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

12.3 Safety Reporting Requirements for IND Exempt Studies

For **Investigator Sponsored IND Exempt Studies**, there are some reporting requirements for the FDA in accordance with the guidance set forth in 21 CFR 314.80.

Postmarketing 15-Day "Alert Report":

The Sponsor-Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is **unexpected and assessed by the investigator to be possibly related to the use of Bevacizumab**. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be submitted to the FDA (2 copies)

at the following address: Central Document Room, 12229 Wilkins Avenue, Rockville, MD 20852.

All Postmarketing 15-Day "Alert Reports" submitted to the FDA by the Sponsor-Investigator must also be faxed to: Genentech Drug Safety

Fax: (650) 225-4682 or (650) 225-5288 (Please use the safety reporting fax cover sheet attached to this document for your fax transmission)

For questions related to safety reporting, contact:

Genentech Drug Safety

Tel: 1-888-835-2555

or

Fax: (650) 225-4682 or (650) 225-5288

(Please use the safety reporting fax cover sheet attached to this document for your fax transmission)

13.0 RETENTION OF RECORDS

We will retain all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for at least 2 years after the investigation is completed.

REFERENCES

[1] Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, Thun MJ. Cancer statistics, 2008. CA Cancer J Clin 2008;58:71-96.

[2] Cannistra SA. Cancer of the ovary. N Engl J Med 2004;351:2519-29.

[3] Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA, Mannel RS, DeGeest K, Hartenbach EM, Baergen R. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2003;21:3194-200.

[4] Neijt JP, Engelholm SA, Tuxen MK, Sorensen PG, Hansen M, Sessa C, de Swart CA, Hirsch FR, Lund B, van Houwelingen HC. Exploratory phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer. J Clin Oncol 2000;18:3084-92.

[5] Wu CH, Yang CH, Lee JN, Hsu SC, Tsai EM. Weekly and monthly regimens of paclitaxel and carboplatin in the management of advanced ovarian cancer. A preliminary report on side effects. Int J Gynecol Cancer 2001;11:295-9.

[6] Sehouli J, Stengel D, Mustea A, Camara O, Keil E, Elling D, Ledwon P, Christiansen B, Klare P, Gebauer G, Schwarz M, Lichtenegger W. Weekly paclitaxel and carboplatin (PC-W) for patients with primary advanced ovarian cancer: results of a multicenter phase-II study of the NOGGO. Cancer Chemother Pharmacol 2008;61:243-50.

[7] Pignata S, Breda E, Scambia G, Pisano C, Zagonel V, Lorusso D, Greggi S, De Vivo R, Ferrandina G, Gallo C, Perrone F. A phase II study of weekly carboplatin and paclitaxel as first-line treatment of elderly patients with advanced ovarian cancer. A Multicentre Italian Trial in Ovarian cancer (MITO-5) study. Crit Rev Oncol Hematol 2008;66:229-36.

[8] Havrilesky LJ, Alvarez AA, Sayer RA, Lancaster JM, Soper JT, Berchuck A, Clarke-Pearson DL, Rodriguez GC, Carney ME. Weekly low-dose carboplatin and paclitaxel in the treatment of recurrent ovarian and peritoneal cancer. Gynecol Oncol 2003;88:51-7.

[9] Isonishi S, Yasuda M, Takahashi F, Katsumata N, Kimura E, Aoki D, Jobo T, Terauchi F, Tsuda H, Sugiyama T. Randomized phase III trial of conventional paclitaxel and carboplatin (c-TC) versus dose dense weekly paclitaxel and carboplatin (dd-TC) in women with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer: Japanese Gynecologic Oncology. J Clin Oncol 2008 (abstr 5506);26.

[10] Kikuchi A, Sakamoto H, Yamamoto T. Weekly carboplatin and paclitaxel is safe, active, and well tolerated in recurrent ovarian cancer cases of Japanese women previously treated with cisplatin-containing multidrug chemotherapy. Int J Gynecol Cancer 2005;15:45-9.

[11] Loesch D, Robert N, Asmar L, Gregurich MA, O'Rourke M, Dakhil S, Cox E. Phase II multicenter trial of a weekly paclitaxel and carboplatin regimen in patients with advanced breast cancer. J Clin Oncol 2002;20:3857-64.

[12] Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat Med 1995;1:27-31.

[13] Fidler IJ, Ellis LM. The implications of angiogenesis for the biology and therapy of cancer metastasis. Cell 1994;79:185-8.

[14] Yoneda J, Kuniyasu H, Crispens MA, Price JE, Bucana CD, Fidler IJ. Expression of angiogenesis-related genes and progression of human ovarian carcinomas in nude mice. J Natl Cancer Inst 1998;90:447-54.

[15] Hollingsworth HC, Kohn EC, Steinberg SM, Rothenberg ML, Merino MJ. Tumor angiogenesis in advanced stage ovarian carcinoma. Am J Pathol 1995;147:33-41.

[16] Gasparini G, Bonoldi E, Viale G, Verderio P, Boracchi P, Panizzoni GA, Radaelli U, Di Bacco A, Guglielmi RB, Bevilacqua P. Prognostic and predictive value of tumour angiogenesis in ovarian carcinomas. Int J Cancer 1996;69:205-11.

[17] Kim KJ, Li B, Winer J, Armanini M, Gillett N, Phillips HS, Ferrara N. Inhibition of vascular endothelial growth factor-induced angiogenesis suppresses tumour growth in vivo. Nature 1993;362:841-4.

[18] Luo JC, Toyoda M, Shibuya M. Differential inhibition of fluid accumulation and tumor growth in two mouse ascites tumors by an antivascular endothelial growth factor/permeability factor neutralizing antibody. Cancer Res 1998;58:2594-600.

[19] Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, Berlin J, Baron A, Griffing S, Holmgren E, Ferrara N, Fyfe G, Rogers B, Ross R, Kabbinavar F. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.

[20] Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542-50.

[21] Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D, Davidson NE. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007;357:2666-76.

[22] Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, Schwartz MA, Benson AB, 3rd. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007;25:1539-44.

[23] Ozcan C, Wong SJ, Hari P. Reversible posterior leukoencephalopathy syndrome and bevacizumab. N Engl J Med 2006;354:980-2; discussion 980-2.

[24] Glusker P, Recht L, Lane B. Reversible posterior leukoencephalopathy syndrome and bevacizumab. N Engl J Med 2006;354:980-2; discussion 980-2.

[25] Hambleton J, Skillings J, Kabbinavar F, Bergsland E, Holmgren E, Holden SN, Hurwitz H, Scappaticci F. Safety of low-dose aspirin (ASA) in a pooled analysis of 3 randomized, controlled trials (RCTs) of bevacizumab (BV) with chemotherapy (CT) in patients (pts) with metastatic colorectal cancer (mCRC). J Clin Oncol (Meeting Abstracts) 2005;23:3554.

[26] Scappaticci FA, Fehrenbacher L, Cartwright T, Hainsworth JD, Heim W, Berlin J, Kabbinavar F, Novotny W, Sarkar S, Hurwitz H. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. J Surg Oncol 2005;91:173-80.

[27] Miller KD, Chap LI, Holmes FA, Cobleigh MA, Marcom PK, Fehrenbacher L, Dickler M, Overmoyer BA, Reimann JD, Sing AP, Langmuir V, Rugo HS. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 2005;23:792-9.

[28] Karp JE, Gojo I, Pili R, Gocke CD, Greer J, Guo C, Qian D, Morris L, Tidwell M, Chen H, Zwiebel J. Targeting vascular endothelial growth factor for relapsed and refractory adult acute myelogenous leukemias: therapy with sequential 1-beta-d-arabinofuranosylcytosine, mitoxantrone, and bevacizumab. Clin Cancer Res 2004;10:3577-85.

[29] Wedam SB, Low JA, Yang SX, Chow CK, Choyke P, Danforth D, Hewitt SM, Berman A, Steinberg SM, Liewehr DJ, Plehn J, Doshi A, Thomasson D, McCarthy N, Koeppen H, Sherman M, Zujewski J, Camphausen K, Chen H, Swain SM. Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer. J Clin Oncol 2006;24:769-77.

[30] D'Adamo DR, Anderson SE, Albritton K, Yamada J, Riedel E, Scheu K, Schwartz GK, Chen H, Maki RG. Phase II study of doxorubicin and bevacizumab for patients with metastatic soft-tissue sarcomas. J Clin Oncol 2005;23:7135-42.

[31] Golub TR, Slonim DK, Tamayo P, Huard C, Gaasenbeek M, Mesirov JP, Coller H, Loh ML, Downing JR, Caligiuri MA, Bloomfield CD, Lander ES. Molecular classification of cancer: class discovery and class prediction by gene expression monitoring. Science 1999;286:531-7.

[32] Bonome T, Lee JY, Park DC, Radonovich M, Pise-Masison C, Brady J, Gardner GJ, Hao K, Wong WH, Barrett JC, Lu KH, Sood AK, Gershenson DM, Mok SC, Birrer MJ. Expression profiling of serous low malignant potential, low-grade, and high-grade tumors of the ovary. Cancer Res 2005;65:10602-12.

[33] Tsai JP, Chen HW, Cheng ML, Liu HK, Lee YP, Hsieh CL, Luh KT, Wu CW, Hsu LH, Chao TY, Wang WH, Chang CM, Ting CC. Analysis of host versus tumor interaction in cancer

patients: opposing role of transforming growth factor-beta1 and interleukin-6 in the development of in situ tumor immunity. Immunobiology 2005;210:661-71.

[34] Lambeck AJ, Crijns AP, Leffers N, Sluiter WJ, ten Hoor KA, Braid M, van der Zee AG, Daemen T, Nijman HW, Kast WM. Serum cytokine profiling as a diagnostic and prognostic tool in ovarian cancer: a potential role for interleukin 7. Clin Cancer Res 2007;13:2385-91.

[35] Nilsson MB, Langley RR, Fidler IJ. Interleukin-6, secreted by human ovarian carcinoma cells, is a potent proangiogenic cytokine. Cancer Res 2005;65:10794-800.

[36] Merritt WM, Lin YG, Spannuth WA, Fletcher MS, Kamat AA, Han LY, Landen CN, Jennings N, De Geest K, Langley RR, Villares G, Sanguino A, Lutgendorf SK, Lopez-Berestein G, Bar-Eli MM, Sood AK. Effect of interleukin-8 gene silencing with liposome-encapsulated small interfering RNA on ovarian cancer cell growth. J Natl Cancer Inst 2008;100:359-72.

[37] Shen GH, Ghazizadeh M, Kawanami O, Shimizu H, Jin E, Araki T, Sugisaki Y. Prognostic significance of vascular endothelial growth factor expression in human ovarian carcinoma. Br J Cancer 2000;83:196-203.

[38] McMeekin DS, Sill MW, Benbrook D, Darcy KM, Stearns-Kurosawa DJ, Eaton L, Yamada SD. A phase II trial of thalidomide in patients with refractory endometrial cancer and correlation with angiogenesis biomarkers: a Gynecologic Oncology Group study. Gynecol Oncol 2007;105:508-16.

[39] McMeekin DS, Sill MW, Darcy KM, Stearns-Kurosawa DJ, Webster K, Waggoner S, Benbrook D. A phase II trial of thalidomide in patients with refractory leiomyosarcoma of the uterus and correlation with biomarkers of angiogenesis: a gynecologic oncology group study. Gynecol Oncol 2007;106:596-603.

[40] Burger RA, Sill MW, Monk BJ, Greer BE, Sorosky JI. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:5165-71.

[41] Cannistra SA, Matulonis UA, Penson RT, Hambleton J, Dupont J, Mackey H, Douglas J, Burger RA, Armstrong D, Wenham R, McGuire W. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. J Clin Oncol 2007;25:5180-6.

[42] Sweeney CJ, Miller KD, Sissons SE, Nozaki S, Heilman DK, Shen J, Sledge GW, Jr. The antiangiogenic property of docetaxel is synergistic with a recombinant humanized monoclonal antibody against vascular endothelial growth factor or 2-methoxyestradiol but antagonized by endothelial growth factors. Cancer Res 2001;61:3369-72.

[43] Wildiers H, Guetens G, De Boeck G, Verbeken E, Landuyt B, Landuyt W, de Bruijn EA, van Oosterom AT. Effect of antivascular endothelial growth factor treatment on the intratumoral uptake of CPT-11. Br J Cancer 2003;88:1979-86.

[44] Chura JC, Van Iseghem K, Downs LS, Jr., Carson LF, Judson PL. Bevacizumab plus cyclophosphamide in heavily pretreated patients with recurrent ovarian cancer. Gynecol Oncol 2007;107:326-30.

[45] Cohn DE, Valmadre S, Resnick KE, Eaton LA, Copeland LJ, Fowler JM. Bevacizumab and weekly taxane chemotherapy demonstrates activity in refractory ovarian cancer. Gynecol Oncol 2006;102:134-9.

[46] Han ES, Monk BJ. What is the risk of bowel perforation associated with bevacizumab therapy in ovarian cancer? Gynecol Oncol 2007;105:3-6.

[47] Micha JP, Goldstein BH, Rettenmaier MA, Genesen M, Graham C, Bader K, Lopez KL, Nickle M, Brown JV, 3rd. A phase II study of outpatient first-line paclitaxel, carboplatin, and bevacizumab for advanced-stage epithelial ovarian, peritoneal, and fallopian tube cancer. Int J Gynecol Cancer 2007;17:771-6.

[48] Perez DG, Suman VJ, Fitch TR, Amatruda T, 3rd, Morton RF, Jilani SZ, Constantinou CL, Egner JR, Kottschade LA, Markovic SN. Phase 2 trial of carboplatin, weekly paclitaxel, and biweekly bevacizumab in patients with unresectable stage IV melanoma: a North Central Cancer Treatment Group study, N047A. Cancer 2009;115:119-27.

[49] Ginsberg JM, Chang BS, Matarese RA, Garella S. Use of single voided urine samples to estimate quantitative proteinuria. N Engl J Med 1983;309:1543-6.

[50] Schwab SJ, Christensen RL, Dougherty K, Klahr S. Quantitation of proteinuria by the use of protein-to-creatinine ratios in single urine samples. Arch Intern Med 1987;147:943-4.

[51] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.

[52] Thall PF, Simon R. Practical Bayesian guidelines for phase IIB clinical trials. Biometrics 1994;50:337-49.

[53] Kaplan E, Meier P. Nonparametric estimation from incomplete observations. Journal of the American Statistical Association 1958;53:457-481.

[54] Cox DR. Regression models and life tables (with discussion). Journal of the Royal Statistical Society 1972;34:187-220.

[55] Irizarry RA, Hobbs B, Collin F, Beazer-Barclay YD, Antonellis KJ, Scherf U, Speed TP. Exploration, normalization, and summaries of high density oligonucleotide array probe level data. Biostatistics 2003;4:249-64.

[56] Pounds S, Morris SW. Estimating the occurrence of false positives and false negatives in microarray studies by approximating and partitioning the empirical distribution of p-values. Bioinformatics 2003;19:1236-42.

[57] Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.