principles of class prediction and class discovery as they apply to the molecular classification of human cancers were exemplified by Golub et al., who used oligonucleotide micro arrays to monitor gene expression in acute leukemias as a test case.[80] Class prediction identified and validated a subset of informative genes whose expression was highly correlated with previously defined classes. Further, subsequent studies have utilized these approaches to provide proof of the "molecular profiling principle" as well as to gain novel insights into clinical cancer problems. Using a specialized, lymphoid cell-specific cDNA microarray, Alizadeh et al. performed expression profiling of diffuse large B-cell lymphomas and identified two molecularly distinct forms of this malignancy that correlated with overall survival.[79]

We hypothesize that transcription profiling will provide us with gene signatures for advanced stage ovarian cancer patients who are likely to develop aggressive recurrent disease and shortened survival, and thus may need to be treated with unconventional regimens.

Thus, these new discoveries and technologies provide an ideal opportunity to determine the molecular and biochemical basis for the survival of patients with stage III-suboptimal and stage IV **(06/26/06)** epithelial ovarian and peritoneal primary cancers.

2.9 Reversible Posterior Leukoencephalopathy Syndrome (RPLS) or Similar Leukoencephalopathy Syndrome

RPLS or clinical syndromes related to vasogenic edema of the white matter have been rarely reported in association with bevacizumab therapy (< 1%). Clinical presentations are variable and may include altered mental status, seizure and cortical visual deficit. HTN is a common risk factor and was present in most (though not all) patients on bevacizumab who developed RPLS. MRI scans are key to diagnosis and typically demonstrate vasogenic edema (hyper intensity in T2 and FLAIR images and hypo intensity in T1 images) predominantly in the white matter of the posterior parietal and occipital lobes; less frequently, the anterior distributions and the gray matter may also be involved. RPLS should be in the differential diagnosis in patients presenting with unexplained mental status change, visual disturbance, seizure or other CNS findings. RPLS is potentially reversible, but timely correction of the underlying causes, including control of BP and interruption of the offending drug, is important in order to prevent progression to irreversible tissue damage. **(Date 2006)**

2.10 Inclusion of Women and Minorities

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

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

3.11 Patients with a histologic diagnosis of epithelial ovarian cancer, peritoneal primary carcinoma or fallopian tube cancer; FIGO stage III (Appendix I) with any gross (macroscopic or palpable) residual disease or FIGO stage IV (Appendix I), **(06/26/06)** defined surgically at the completion of initial abdominal surgery and with appropriate tissue available for histologic evaluation. The minimum surgery required was 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. If additional surgery was performed, it should have been in accordance with appropriate surgery for ovarian or peritoneal carcinoma described in the GOG Surgical Procedures Manual (https://www.gog.fccc.edu/manuals/pdf/surgman.pdf). However, the surgeon is not required to have performed all of the items contained in this section of the GOG Surgical Procedures Manual. 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." **(08/06/07)** Measurable disease on post- operative imaging studies is not required for eligibility.**(10/14/08)**

3.12 Patients with the following histologic epithelial cell types are eligible: Serous adenocarcinoma, endometrioid adenocarcinoma, mucinous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, transitional cell carcinoma, malignant Brenner's Tumor, or adenocarcinoma not otherwise specified (N.O.S.). However, the histologic features of the tumor must be compatible with a primary Müllerian epithelial adenocarcinoma. If doubt exists, it is recommended that the investigator should have the slides reviewed by an independent pathologist or, if necessary, the Pathology Co-Chair, prior to entry. 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.)**(10/14/08)**

3.13 Patients must have adequate:

3.131 Bone marrow function: Absolute neutrophil count (ANC) greater than or equal to 1,500/µl, equivalent to Common Toxicity Criteria for Adverse Events v3.0 (CTCAE) Grade1. This ANC cannot have been induced or supported by granulocyte colony stimulating factors. **(08/06/07)**

3.132 Platelets greater than or equal to 100,000/µl. (CTCAE Grade 0-1).

3.133 Renal function: Creatinine ≤ 1.5 x institutional upper limit normal (ULN), CTCAE Grade 1.

3.134 Hepatic function:

3.1341 Bilirubin less than or equal to 1.5 x ULN (CTCAE Grade 1).

3.1342 SGOT and alkaline phosphatase less than or equal to 2.5 x ULN (CTCAE Grade 1).

3.135 Neurologic function: Neuropathy (sensory and motor) less than or equal to CTCAE Grade 1.

3.136 Blood coagulation parameters: PT such that international normalized ratio (INR) is ≤ 1.5 (or an in-range INR, usually between 2 and 3, if a patient is on a stable dose of therapeutic warfarin for management of venous thrombosis including pulmonary thrombo-embolus) **(08/06/07)** and a PTT < 1.2 times the upper limit of normal.

3.14 Patients with a GOG Performance Status of 0, 1, or 2.

3.15 Patients must be entered between 1 and 12 weeks after initial surgery performed for the combined purpose of diagnosis, staging and cytoreduction.

3.16 Patients with measurable (see Section 8.11) and non-measurable (see Section 8.12) disease are eligible. Patients may or may not have cancer-related symptoms.

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

3.18 An approved informed consent and authorization permitting release of personal health information must be signed by the patient or guardian.

3.19 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 or prior to disease progression. **(08/06/07)**

3.2 Ineligible Patients

3.21 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 **(10/14/08)**

3.22 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.

3.23 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. **(08/06/07)(10/14/08)**

3.24 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. **(06/26/06)**

3.25 Patients with synchronous primary endometrial cancer, or a past history of primary endometrial cancer, are excluded, unless all of the following conditions are met: Stage not greater than I-B; no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly differentiated subtypes, including papillary serous, clear cell or other FIGO Grade 3 lesions.

3.26 With the exception of non-melanoma skin cancer 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. **(08/06/07)**

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

3.28 Patients with serious non-healing wound, ulcer, or bone fracture. This includes history of abdominal fistula, gastrointestinal perforation or intra-abdominal abscess within 28 days. Patients with granulating incisions healing by secondary intention with no evidence of fascial dehiscence or infection are eligible but require weekly wound examinations (see Section 7.1).

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

3.30 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.

3.31 Patients with clinically significant cardiovascular disease. This includes:

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

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

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

3.314 Serious cardiac arrhythmia requiring medication. This does not include asymptomatic, atrial fibrillation with controlled ventricular rate. **(08/06/07)**

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

3.316 History of CVA within six months.

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

3.33 Patients with clinically significant proteinuria. Urine protein should be screened by urine protein-creatinine ratio (UPCR). The UPCR has been found to correlate directly with the amount of protein excreted in a 24 hour urine collection.[82-87] 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). Patients must have a UPCR < 1.0 to allow participation in the study.

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

3.341 Major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to the first date of bevacizumab/placebo therapy (cycle 2).

3.342 Major surgical procedure anticipated during the course of the study. This includes, but is not limited to abdominal surgery (laparotomy or laparoscopy) prior to disease progression as defined in section 8.3, such as colostomy or enterostomy reversal, interval or secondary cytoreductive surgery, or second look surgery. Please consult with the Study Chair prior to patient entry for any questions related to the classification of surgical procedures. **(08/06/07)**

3.343 Core biopsy, within 7 days prior to the first date of bevacizumab/placebo therapy (cycle 2).

3.35 Patients with GOG Performance Grade of 3 or 4.

3.36 Patients who are pregnant or nursing. 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.

3.37 Patients under the age of 18.

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

3.39 Patients with clinical symptoms or signs of gastrointestinal obstruction **and** who require parenteral hydration and/or nutrition **(06/26/06)**

3.40 Patients with medical history or conditions not otherwise previously specified which in the opinion of the investigator should exclude participation in this study. The investigator should feel free to consult the Study Chair or Study Co-Chairs for uncertainty in this regard.**(08/06/07)**.

4.0 STUDY MODALITIES

4.1 Paclitaxel (NSC #673089)

4.11 Formulation: Paclitaxel is supplied as a 6mg/mL non-aqueous solution in multi dose vials containing 30mg/5mL, 100mg/16.7mL, or 300mg/50mL of paclitaxel. In addition to 6mg of paclitaxel, each mL of sterile non-pyrogenic solution contains 527mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

4.12 Storage: Unopened vials of paclitaxel are stable to the date indicated on the package when stored between 20 to 25°C (68 to 77°F). Protect from light.

4.13 Preparation: Paclitaxel must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride for Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C / 77°F) and room lighting conditions.

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

Paclitaxel should be administered through an inline filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® or IVEX-HP®, which incorporate short inlet and outlet PVC-coated tubing, has not resulted in significant leaching of DEHP.

All patients should be premedicated with corticosteroids, diphenhydramine, and H_2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Patients who experience severe hypersensitivity reactions to paclitaxel should not be re-challenged with the drug.**(10/14/08)**

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

4.15 Supplier: Commercially available both from Bristol-Myers Squibb Oncology as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

4.2 Carboplatin (Paraplatin® - NSC #241240)

4.21 Formulation: 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.

4.22 Storage: 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.

4.23 Preparation: 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. 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.

Calvert Formula for Carboplatin (AUC) Dosing

total dose (mg) = target AUC (in mg/mL/minute) * [GFR (in mL/minute) + 25]

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

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

4.25 Supplier: Commercially available both from Bristol-Myers Squibb Oncology as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

4.3 Bevacizumab (NSC #704865, IND #7921) or Placebo

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

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

4.32 How Supplied: "bevacizumab" and "placebo" are supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. For "bevacizumab", each 100mg (25mg/mL – 4mL fill) glass vial contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. For "Placebo", each 0mg (0mg/mL – 4mL fill) glass vial

contains phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. **DO NOT USE COMMERCIAL BEVACIZUMAB OR AVASTIN.**

Bevacizumab being provided in this study is for investigational use only and is not the commercially marketed product. The commercially available bevacizumab is marketed under the name Avastin. Investigational bevacizumab and commercially available Avastin may be produced at separate facilities. Although investigational bevacizumab and Avastin are expected to be very similar it is possible that some differences may exist. For further details and molecule characterization, see the updated bevacizumab Investigator Brochure. **(1-16-06) (06/26/06)**

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

4.34 Preparation: Bevacizumab should be prepared by a healthcare professional using aseptic technique. Vials contain no preservative and are intended for single use only. The calculated dose of bevacizumab should be diluted with sodium chloride (0.9%) solution for injection, up to a total volume ranging from 100 ml to 250 ml such that the final concentration of bevacizumab ranges between 1.4 and 16.5 mg/ml (the constituted solution is stable in this concentration range). Once diluted in 0.9% Sodium Chloride for Injection, the bevacizumab solution must be administered within 8 hours. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. **(08/06/07)**

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

4.36 Clinical Supplies: Bevacizumab (NSC 704865) and matching placebo will be provided free of charge by Genentech and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI). **DO NOT USE COMMERCIAL BEVACIZUMAB OR AVASTIN. (08/06/07)**

Bevacizumab and matching placebo will be supplied in 4 mL fill glass vials each containing 100 mg (bevacizumab) or 0 mg (placebo for bevacizumab) of bevacizumab. The blinded, patient-specific vials will be sealed in a cardboard box with a tamper-evident seal.

For **Phase A (cycles 2 through 6)**, each box will be labeled with …

- the protocol number (i.e., "GOG-0218")
- the box number (i.e., "Box 1 of 2" and "Box 2 of 2")
- the number of vials (e.g., "48 vials")
- the patient ID number (e.g., "999-0218-001"; where "999" indicates the GOG – assigned institution code for the registering site, "0218" indicates the protocol number, and "001" indicates the patient sequence number for the registering site)
- the patient initials (i.e., first initial, middle initial, last initial [e.g., "FML"])
- the agent identification (i.e., "**Phase A** - bevacizumab 100 mg or Placebo")
- a blank line for the pharmacist to enter the patient's name
- storage instructions (i.e., "Store in refrigerator [2 – 8°C]. Do not freeze. Do not shake.")
- emergency contact instructions
- a Julian date

At the completion of chemotherapy cycle 6, ALL remaining PHASE A clinical supplies of bevacizumab / placebo should be returned to PMB (see "Drug Returns" below). DO NOT UTILIZE PHASE A DRUG SUPPLY FOR TREATMENT DURING PHASE B. (10/14/08)

For **Phase B (cycles 7 through 22)**, each box will be labeled with …

- the protocol number (i.e., "GOG-0218")
- the box number (i.e., "Box 1 of 2" and "Box 2 of 2")
- the number of vials (e.g., "48 vials")
- the patient ID number (e.g., "999-0218-001"; where "999" indicates the GOG – assigned institution code for the registering site, "0218" indicates the protocol number, and "001" indicates the patient sequence number for the registering site)
- the patient initials (i.e., first initial, middle initial, last initial [e.g., "FML"])
- the agent identification (i.e., "**Phase B** - bevacizumab 100 mg or Placebo")
- a blank line for the pharmacist to enter the patient's name
- storage instructions (i.e., "Store in refrigerator [2 – 8°C]. Do not freeze. Do not shake.")
- emergency contact instructions
- a Julian date

The Julian date indicates the day the box was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2005 = 05, 2006 = 06) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a box labeled and shipped on January 1, 2005 would have a Julian date of '05001' and a box labeled and shipped on December 31, 2006 would have a Julian date of '06365'. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will

recall all vials (i.e., both bevacizumab and placebo) shipped on or before that date thus eliminating any chance of breaking the blind.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (301) 496-5725 Monday through Friday between 8:30am and 4:30pm Eastern Time.

4.37 Drug Ordering: **(1-16-06)**

Note: Supplies of bevacizumab/placebo will be shipped by PMB to the investigator linked to the assigned patient ID number. The address used by PMB for shipments is the one specified in that investigator's currently filed NCI 1572 form. **(08/06/07)**

4.371 Phase A

Phase A - Begins with cycle 2 and continues through cycle 6 [during chemotherapy]. By definition, Phase A of treatment ends at the beginning of cycle 7. **(08/06/07)**

No blinded starter supplies will be available for this phase. Blinded, patient-specific supplies **for Phase A** will be sent to the registering investigator at the time of randomization. This randomization will be performed by the GOG Statistical and Data Center (SDC) in Buffalo, NY. The assigned patient ID number must be recorded by the registering institution for proper vial dispersion. Once a patient has been registered with the GOG SDC, the GOG SDC will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the GOG SDC the day the patient is registered and will be processed by the PMB the next business day and shipped the following business day. All shipments will be sent on blue ice by FedEx (generally one to two day delivery). Thus, if a patient is registered on Monday, GOG would enter a clinical drug request for that patient on Monday and PMB would process the request on Tuesday and ship the drug on Wednesday. Both United States and Canadian sites could expect to receive their order either Thursday or Friday. Note that PMB will only send blue ice shipments on Monday through Thursday for delivery on Tuesday through Friday. Thus, if a patient is registered on Wednesday, the order will be processed on Thursday and shipped the following Monday for delivery on Tuesday or Wednesday.

Request for Clinical Supplies for Phase A – *Submitted by the GOG SDC*

The web registration process for Phase A described in Section 5.11 will allow the GOG SDC to automatically submit an electronic request for the blinded, patient-specific clinical supplies of bevacizumab / placebo for Phase A of GOG-0218 to the PMB at the time of the initial registration / randomization. The Phase A clinical supplies should arrive at the clinical

site within approximately seven to ten days of randomization. This shipment will provide the entire patient-specific amount needed for each patient to complete cycles 2 through 6 of Phase A based on the order submitted to the PMB by the GOG SDC for Phase A. All drug orders will be shipped directly to the physician registering the patient.

4.372 Phase B

Phase B - Begins with cycle 7 [first cycle post chemotherapy] and continues through cycle 22 [approximately **(06/26/06)** 15 months total treatment duration]

In order to obtain Phase B clinical supplies, **patients must be re-registered** with the GOG SDC (see section 5.12) after completing the administration of all drugs on day 1 of cycle 6 of treatment which signals the completion of chemotherapy (cycle 6) for logistical purposes. **No blinded starter supplies will be available for this phase.** Blinded, patient-specific supplies **for Phase B** will be sent to the registering investigator at the time of re-registration. This re-registration will be performed by the GOG SDC.. **The patient ID number will NOT change.** Once a patient has been re-registered with the GOG SDC, the GOG SDC will electronically transmit a clinical drug request for that patient to the PMB. This request will be entered and transmitted by the GOG SDC the day the patient is re-registered and will be processed by the PMB the next business day and shipped the following business day. All shipments will be sent on blue ice by FedEx (generally one to two day delivery). Thus, if a patient is re-registered on Monday, GOG would enter a clinical drug request for that patient on Monday and PMB would process the request on Tuesday and ship the drug on Wednesday. Both United States and Canadian sites could expect to receive their order either Thursday or Friday. Note that PMB will only send blue ice shipments on Monday through Thursday for delivery on Tuesday through Friday. Thus, if a patient is registered on Wednesday, the order will be processed on Thursday and shipped the following Monday for delivery on Tuesday or Wednesday.

Initial Request for Clinical Supplies for Phase B - *Submitted by the GOG SDC*

The web re-registration process for Phase B described in Section 5.12 will allow the GOG SDC to automatically submit an electronic request for blinded patient-specific clinical supplies of bevacizumab / placebo for Phase B to the PMB at the time of the completion of chemotherapy / re-registration. The Phase B clinical supplies should arrive at the clinical site within approximately seven to ten days of re-registration. The initial request for Phase B will provide a patient-specific amount needed for each patient to complete cycles 7 through 10 of Phase B based on the initial request submitted to the PMB by the GOG SDC for Phase B. All drug orders will be shipped directly to the physician re-registering the patient.

Institutions enrolling patients through CTSU, refer to Appendix VIII for special instructions for Phase B completion of chemotherapy / re-registration.

Re-Order Request for Clinical Supplies for Phase B - *Submitted by the Institution*

The institution will need to re-order clinical supplies three times to complete Phase B. Complete an NCI Clinical Drug Request form and fax it to the PMB at 301-480-4612. The NCI Clinical Drug Request form is available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The assigned patient ID number (e.g., "999-0218-001"), the patient initials (e.g., "FML"), the number of vials remaining from the prior shipment, and the patient's weight (in KG) should be entered on each order. Each re-order request submitted to the PMB by the institution for clinical supplies for Phase B will provide a patient-specific amount needed for each patient to complete four cycles of Phase B.

- The first re-order request submitted by the institution to PMB immediately after completion of cycle 10 will provide a patient-specific amount needed for each patient to complete cycles 11 through 14 of Phase B.
- The second re-order request submitted by the institution to PMB immediately after the completion of cycle 14 will provide a patient-specific amount needed for each patient to complete cycles 15 through 18 of Phase B.
- The third re-order request submitted by the institution to PMB immediately after the completion of cycle 18 will provide a patient-specific amount needed for each patient to complete cycles 19 through 22 of Phase B.

GOG-0218 Shipment Schedule

Patient Randomized with GOG	Initial e-Order Transmitted by GOG	Initial e-Order Received and Approved by PMB	Initial Order Shipped By PMB	Initial Order Received at Site *
Monday	Monday	Tuesday	Wednesday	Thursday
Tuesday	Tuesday	Wednesday	Thursday	Friday
Wednesday	Wednesday	Thursday	Monday	Tuesday
Thursday	Thursday	Friday	Monday	Tuesday
Friday	Friday	Monday	Tuesday	Wednesday

***arrival time approximate / shipments sent by Federal Express**

4.38 Drug Transfers: Vials **MAY NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the principal investigator at a given clinical site changes) must be approved

in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 301-402-0429) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The patient ID number (e.g., "999-0218-001") and the patient initials (e.g., "FML") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "**GOG-0218**").

4.39 Drug Returns: Only unreconstituted drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed **Phase A** vials remaining when a patient completes cycle 6, sealed **Phase A or Phase B** vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The patient ID number (e.g., "999-0218-001") and the patient initials (e.g., "FML") should be entered in the "Lot Number" field. A separate line item is required for EACH patient ID number returned.

4.310 Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "999-0218-001") on this protocol.

4.311 Emergency Unblinding: In the event of an emergency during normal business hours (Monday through Friday 9:00 am to 5:00 pm Eastern Time), contact the GOG Statistical and Data Center by phone at 1-800-523-2917. At all other times, call: 716-901-2853. If there is no answer, leave a message including a telephone number for a return call. A staff member from the GOG Statistical and Data Center will return your call. **Remember, this is only in the event of an emergency!** This procedure is to be used by the physician when the physician needs to know whether the patient is taking bevacizumab or a placebo to manage the acute illness. Patients should be instructed that if they have any questions or symptoms they should contact the treating physician's office.

The GOG Statistical and Data Center will require the protocol number (i.e., "GOG-0218"), the patient ID number (e.g., "999-0218-001"), and the patient initials (e.g., "FML") to unblind the patient.

4.312 Comprehensive Adverse Events and Potential Risks List (CAEPR) For Bevacizumab (NSC #704865) **(1-16-06) (06/26/06) (10/14/08)**

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This

subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/reporting/adeers.html for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for bevacizumab.

Category (Body System)	Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)	'Agent Specific Adverse Event List' (ASAEL)
ALLERGY/IMMUNOLOGY		
	Allergic reaction/hypersensitivity (including drug fever)	***Allergic reaction/hypersensitivity (including drug fever)***
	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	***Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)***
BLOOD/BONE MARROW		
	Hemoglobin	***Hemoglobin***
	Leukocytes (total WBC)	***Leukocytes (total WBC)***
	Neutrophils/granulocytes (ANC/AGC)	***Neutrophils/granulocytes (ANC/AGC)***
CARDIAC ARRHYTHMIA		
	Supraventricular arrhythmia NOS	***Supraventricular arrhythmia NOS***
	Ventricular fibrillation	
CARDIAC GENERAL		
	Cardiac ischemia/infarction	***Cardiac ischemia/infarction***
	Cardiac troponin I (cTnI)	
	Hypertension	***Hypertension***
	Hypotension	
	Left ventricular diastolic dysfunction	
	Left ventricular systolic dysfunction	
CONSTITUTIONAL SYMPTOMS		
	Fatigue (asthenia, lethargy, malaise)	***Fatigue (asthenia, lethargy, malaise)***
	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)	***Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10^9/L)***
	Rigors/chills	***Rigors/chills***
	Weight loss	
DERMATOLOGY/SKIN		
	Pruritus/itching	***Pruritus/itching***
	Rash/desquamation	***Rash/desquamation***
	Ulceration	
	Urticaria (hives, welts, wheals)	***Urticaria (hives, welts, wheals)***
	Wound complication, non-infectious	
GASTROINTESTINAL		
	Anorexia	***Anorexia***
	Colitis	
	Constipation	***Constipation***
	Diarrhea	***Diarrhea***
	Fistula, GI - Select	
	Heartburn/dyspepsia	***Heartburn/dyspepsia***
	Ileus (functional obstruction of bowel, i.e., neuroconstipation)	
	Leak (including anastomotic), GI: large bowel	
	Mucositis/stomatitis (functional/symptomatic) - Select	***Mucositis/stomatitis (functional/symptomatic) - Select***
	Nausea	***Nausea***
	Perforation, GI - Select	
	Ulcer, GI - Select	
	Vomiting	***Vomiting***
HEMORRHAGE/BLEEDING		
	Hemorrhage, GI - Select	***Hemorrhage GI - Select***
	Hemorrhage, CNS	***Hemorrhage, CNS***
	Hemorrhage, GU: vagina	***Hemorrhage, GU: vagina***
	Hemorrhage, pulmonary/upper respiratory: lung	***Hemorrhage, pulmonary/upper respiratory: lung***
	Hemorrhage, pulmonary/upper respiratory: nose	***Hemorrhage, pulmonary/upper respiratory: nose***
INFECTION		
	Infection with normal ANC or Grade 1 or 2 neutrophils - Select	

Category (Body System)	Adverse Events with Possible Relationship to Bevacizumab (CTCAE v3.0 Term)	'Agent Specific Adverse Event List' (ASAEL)
	Infection with normal ANC or Grade 1 or 2 neutrophils - Select (pelvis, peritoneal cavity, rectum, scrotum, skin, wound)	
METABOLIC/LABORATORY		
	Alkaline phosphatase	***Alkaline phosphatase***
	ALT, SGPT (serum glutamic pyruvic transaminase)	***ALT, SGPT (serum glutamic pyruvic transaminase)***
	AST, SGOT (serum glutamic oxaloacetic transaminase)	***AST, SGOT (serum glutamic oxaloacetic transaminase)***
	Bilirubin (hyperbilirubinemia)	***Bilirubin (hyperbilirubinemia)***
	Creatinine	
	Proteinuria	***Proteinuria***
NEUROLOGY		
	CNS cerebrovascular ischemia	***CNS cerebrovascular ischemia***
	Dizziness	***Dizziness***
	Neurology - Other: (Leukoencephalopathy syndrome including reversible posterior leukoencephalopathy syndrome [RPLS])	
PAIN		
	Pain - abdomen NOS	***Pain - abdomen NOS***
	Pain - chest/thorax NOS	***Pain - chest/thorax NOS***
	Pain - head/headache	***Pain - head/headache***
	Pain - joint	***Pain - joint***
	Pain - muscle	
	Pain - NOS	
PULMONARY/UPPER RESPIRATORY		
	Bronchospasm, wheezing	
	Cough	***Cough***
	Dyspnea (shortness of breath)	***Dyspnea (shortness of breath)***
	Fistula, pulmonary/upper respiratory - Select	
	Nasal cavity/paranasal sinus reactions	***Nasal cavity/paranasal sinus reactions***
	Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)	***Voice changes/dysarthria (e.g., hoarseness, loss or alteration in voice, laryngitis)***
	Pulmonary/Upper Respiratory - Other (nasal-septal perforation)	
RENAL/GENITOURINARY		
	Fistula, GU - Select	
	Renal failure	
SYNDROMES		
	Cytokine release syndrome/acute infusion reaction	***Cytokine release syndrome/acute infusion reaction***
VASCULAR		
	Thrombosis/thrombus/embolism	***Thrombosis/thrombus/embolism***
	Visceral arterial ischemia (non-myocardial)	

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

Additional selected AEs reported on bevacizumab trials but with the relationship to bevacizumab still undetermined:

Blood/Bone Marrow – hemoglobin; idiopathic thrombocytopenia purpura; platelets
Cardiac general – cardiac arrest; pericardial effusion
Coagulation – DIC
Death – sudden death (cause unknown)
Dermatology/Skin – hypopigmentation
Gastrointestinal – small bowel obstruction; rectal abscess/necrosis; taste alteration
Metabolic/Laboratory –hyperglycemia; hypoglycemia; hypomagnesemia; hyponatremia
Musculoskeletal/Soft Tissue – aseptic necrotic bone; gait/walking; myasthenia gravis
Neurological – aseptic meningitis; confusion; encephalopathy; peripheral neuropathy; seizure; syncope
Ocular/Visual – cataract; watery eye
Pulmonary/Upper Respiratory – ARDS; pneumonitis/pulmonary infiltrates; pneumothorax
Renal/Genitourinary – urinary frequency
(for a more complete listing of reported AEs, please refer to the Investigator's Brochure)

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

4.3121 General Information on Adverse Effects of Bevacizumab

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

The following is a description of major adverse events associated with bevacizumab therapy. A list of Comprehensive Adverse Events and Potential Risks (CAEPR) in NCI-CTCAE v3.0 terms is included above. Reference may also be made to the Investigators' Brochure and the FDA package insert (www.fda.gov/cder/foi/label/2004/125085lbl.pdf).

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

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

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

Hemorrhage: The incidence of hemorrhage is increased with bevacizumab therapy. Epistaxis is common, occurring in 20-40% of patients, but it is generally mild and rarely requires medical intervention. Life-threatening and fatal hemorrhagic events have been observed in bevacizumab studies and included pulmonary hemorrhage, CNS bleeding and gastrointestinal (GI) bleeding. In a phase 2 study in non-small cell lung cancer, 6 cases of life-threatening hemoptysis or hematemesis were reported among 66 patients treated with bevacizumab and chemotherapy; 4 of these events were fatal.[88] In the pivotal phase 3 trial in advanced colorectal cancer, the rate of GI hemorrhage (all grades) was 24% in the IFL/bevacizumab arm compared to 6% in the IFL arm; grade 3-4 hemorrhage was 3.1% for IFL/bevacizumab and 2.5% for IFL. Serious GI hemorrhage has also been observed in clinical trials with bevacizumab in patients with pancreatic cancer or varices treated with bevacizumab.

Arterial Thromboembolic Events: The risk of arterial thromboembolic events is increased with bevacizumab therapy, and such events included cerebral infarction, transient ischemic attack (TIA), myocardial infarction and other peripheral or visceral arterial thrombosis. In the pivotal trial in CRC (AVF2107), the incidence of arterial thromboembolic events was 1% in the IFL/placebo arm compared to 3% in the IFL/ bevacizumab arm. A pooled analysis of five randomized studies showed a two-fold increase in these events (4.4% vs 1.9%). Certain baseline characteristics, such as age and prior arterial ischemic events, appear to confer additional risk.[89] In patients $\geq$ 65 years treated with bevacizumab and chemotherapy, the rate of arterial thromboembolic events was approximately 8.5%.

Gastrointestinal Perforation/Fistula: GI perforations/fistulas were rare but occurred at an increased rate in bevacizumab -containing therapies. The majority of such events required surgical intervention and some were associated with a fatal outcome. In the pivotal phase 3 trial in CRC (AVF2107), the incidence of bowel perforation was 2% in patients receiving IFL/ bevacizumab and 4% in patients receiving 5-FU/ bevacizumab compared to 0.3% in patients receiving IFL alone. GI perforation has also been reported in patients with gastric/esophageal cancer, pancreatic cancer, ovarian cancer or comorbid GI conditions such as diverticulitis and gastric ulcer. Fistulae (e.g. tracheo-esophageal, recto-vaginal) have also been observed. A review of published data from phase II trials of bevacizumab and historical cohort studies of open-label use of bevacizumab as a single agent and in combination with cytotoxic drugs specifically for treatment of epithelial ovarian and primary peritoneal cancer revealed an overall incidence rate of 5.2% in 308 patients, about double the rate seen in other solid tumor populations.[90] While not all of these GI perforations and fistulae required open surgical management and most patients recovered, prospective pre-clinical and clinical work is needed to identify mechanisms and risk factors (10/14/08) **GI perforation**