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PROTOCOL GOG-0218

A PHASE III TRIAL OF CARBOPLATIN AND PACLITAXEL PLUS PLACEBO VERSUS CARBOPLATIN AND PACLITAXEL PLUS CONCURRENT BEVACIZUMAB (NSC #704865, IND #7921) FOLLOWED BY PLACEBO, VERSUS CARBOPLATIN AND PACLITAXEL PLUS CONCURRENT AND EXTENDED BEVACIZUMAB, IN WOMEN WITH NEWLY DIAGNOSED, PREVIOUSLY UNTREATED, STAGE III OR IV, EPITHELIAL OVARIAN, PRIMARY PERITONEAL OR FALLOPIAN TUBE CANCER

NCI-SUPPLIED AGENT(S):

BEVACIZUMAB/ PLACEBO (NSC #704865, IND #7921) **(06/26/06) (08/06/07)(10/14/08)**

NCI Version Date: 08/05/08

Includes: Revisions 1-4

POINTS:
PER CAPITA –30
MEMBERSHIP - 6

TRANSLATIONAL RESEARCH PER CAPITA–Award based on specimen submissions. Distribution: Frozen tumor-3 points, tumor block-2 points (2nd choice tumor sections and scroll-1 point), frozen serum-0.5 point and frozen plasma-0.5 point.**(06/26/06)**

TRANSLATIONAL RESEARCH MEMBERSHIP - Bonus membership point will be awarded for submission of satisfactory frozen tumor, tumor block, frozen serum and frozen plasma. **(06/26/06)**

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This study is supported by the NCI Cancer Trials Support Unit (CTSU). **(08/06/07) (10/14/08)**

Institutions not aligned with GOG 0218 will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix. **See instructions in Appendix VIII for New Institutions prior to enrollment of first patient**

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://members.ctsu.org
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the GOG. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to GOG unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by GOG via GOG's web based system. Please send query responses and delinquent data to GOG as directed and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the GOG Statistical and Data center.

Patient enrollments from institutions that are not aligned with GOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to CTSU Data Operations unless otherwise specified in the CTSU logistical appendix. CTSU will use the GOG-0218 number as required for reporting to GOG and NCI and when registering patients through the GOG Registrar. CTSU participants and institutions will be instructed to use the GOG-0218 study number on all data forms.

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION (08/06/07)(10/14/08)

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone - 1-888-823-5923 Fax – 215-569-0206	CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 8:00 AM – 8:00 PM Eastern Time, Monday Friday (excluding holidays) [For CTSU patient enrollments that must be completed within approximately one hour or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]	GOG Statistical and Data Center at Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263 **Call GOG User support 716-845-7767 to obtain user name and password to submit electronic data** Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.

For patient eligibility or treatment-related questions contact the Study Chair of the Coordinating group. For questions unrelated to patient eligibility, treatment or data submission contact the CTSU Help Desk by phone or email:

All other questions (including forms-specific questions) should be communicated by phone or e-mail to:

CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Public Web site is located at: www.ctsu.org

The CTSU Registered Member Web site is located at http://members.ctsu.org

CTSU logistical information is located in Appendix VIII.. (08/06/07)

SCHEMA**(08/06/07)(10/14/08)**

ELIGIBILITY
•Epithelial ovarian, peritoneal primary or fallopian tube cancer
•FIGO Stage III with any gross (macroscopic or palpable) residual disease or FIGO Stage IV
(06/26/06)

Randomization (cycle = 21 days):

Arm I (standard chemotherapy)

Phase A Chemotherapy * day 1 every 21 days x 6 cycles
Placebo (for bevacizumab) ** day 1 every 21 days beginning with cycle 2 x 5 cycles

↓

Re-registration

↓

Phase B Placebo (for bevacizumab) ** day 1 every 21 days cycles 7 through 22 **(06/26/06)**

Arm II (concurrent bevacizumab)

Phase A Chemotherapy * day 1 every 21 days x 6 cycles
bevacizumab ** day 1 every 21 days beginning with cycle 2 x 5 cycles

↓

Re-registration

↓

Phase B Placebo (for bevacizumab) ** day 1 every 21 days cycles 7 through 22 **(06/26/06)**

Arm III (extended bevacizumab)

Phase A Chemotherapy * day 1 every 21 days x 6 cycles
bevacizumab ** day 1 every 21 days beginning with cycle 2 x 5 cycles

↓

Re-registration

↓

Phase B bevacizumab ** day 1 every 21 days cycles 7 through 22 **(06/26/06)**

*Paclitaxel 175mg/m^2 IV over 3 hours followed by Carboplatin AUC 6 IV over 30 minutes day 1 of cycles 1 through 6 only (Note: docetaxel 75mg/m^2 IV over 1 hour may be substituted for paclitaxel [see sections 2.65, 5.322, and 6.51].)

**bevacizumab / Placebo 15mg/kg IV day 1 of each cycle beginning with cycle 2

OUTCOME MEASURES **(10/14/08)**

•Primary Endpoint:
-Progression-free survival (PFS)

•Secondary Endpoints:
-Overall Survival (OS)
-Response Rate (RR)
-Toxicity
-Quality of Life
-Translational Research - Please see Section 7.2 as well as Appendix VI (Specimen Procedures) and Appendix VII (Laboratory Procedures) for details regarding the specimen requirements and laboratory testing for this protocol.

Patients treated on this trial will not be eligible for therapy on clinical trials evaluating consolidation or maintenance therapy while on or off study.

TABLE OF CONTENTS **(1-16-06)**

1.0 OBJECTIVES **(10/14/08)**

This is a phase III randomized study to evaluate new treatment programs for patients with International Federation of Gynecologic Oncology (FIGO, Appendix I) stages III and IV, epithelial ovarian, peritoneal primary or fallopian tube cancer. **(06/26/06) (08/06/07)**

1.1 Primary Objectives

1.11 To determine if the addition of 5 concurrent cycles of bevacizumab to 6 cycles of standard therapy (carboplatin and paclitaxel) [Arm II] increases the duration of progression-free survival (PFS) when compared to 6 cycles of standard therapy alone [Arm I] in women with newly diagnosed stage III (with any gross residual disease) and stage IV, epithelial ovarian, peritoneal primary or fallopian tube cancer. **(06/26/06) (08/06/07)**

1.12 To determine if the addition of 5 concurrent cycles of bevacizumab **(06/26/06)** plus extended bevacizumab for 16 cycles beyond the **(06/26/06)** 6 cycles of standard therapy (carboplatin and paclitaxel) [Arm III] increases progression-free survival when compared to 6 cycles of standard therapy [Arm I] in women with newly diagnosed stage III (with any gross residual disease) and stage IV, epithelial ovarian, peritoneal primary or fallopian tube cancer. **(06/26/06) (08/06/07)**

1.2 Secondary Objectives (10/14/08)

1.21 In the event that both Arm II and Arm III regimens are superior to the Arm I regimen with respect to progression-free survival, to determine whether the Arm III regimen prolongs progression-free survival when compared to the Arm II regimen.

1.22 To determine whether the Arm II or Arm III regimen increases the duration of overall survival when compared with the Arm I regimen.

1.23 To compare each of the experimental regimens to the Arm I regimen with respect to the incidence of severe toxicities or serious adverse events.

1.24 To determine the impact on Quality of Life (QOL, as measured by the **FACT-O TOI**) following treatment with the above regimens.

1.3 Translational Research Objectives

1.31 To assess the relationship between angiogenic markers and clinical outcome including tumor response, progression-free survival and overall survival in patients randomized to standard cytotoxic chemotherapy (paclitaxel and carboplatin) without bevacizumab, with concurrent bevacizumab or with extended bevacizumab.

1.32 To assess the predictive value of a set of genes whose expression correlates with survival of patients with stage III (with any gross residual disease) and stage IV, epithelial ovarian, peritoneal primary or fallopian tube cancer. **(06/26/06) (08/06/07)(10/14/08)**

2.0 BACKGROUND AND RATIONALE

2.1 Standard Management of Advanced Ovarian and Peritoneal primary Carcinoma

After initial surgical diagnosis, staging and cytoreduction, the standard primary systemic chemotherapy for women with advanced epithelial ovarian, and peritoneal primary cancer consists of chemotherapy with a platinum and taxane combination,[1,2] usually carboplatin[3-6] and paclitaxel. While significant advances have been made in patient management, this disease still carries the highest fatality to case ratio for all gynecologic malignancies diagnosed in the United States. It is estimated that in 2004, 25,580 new cases will have been diagnosed and 16,090 women will have died of the disease.[7] Over the past two decades, there have been only modest improvements in overall 5-year survival, and while 5-year survival has increased steadily from 30% to 50% overall, it has improved by only 5%, from 20% to only 25% for women with advanced-stage tumors. Clearly improvements are needed in primary therapeutic strategies.

2.2 New Therapeutic Strategies to Improve Outcomes

GOG-0182-ICON5 was a 5-arm randomized clinical trial comparing standard therapy (carboplatin and paclitaxel) with four investigational arms incorporating gemcitabine, topotecan and liposomal doxorubicin, either in combination or in sequence with paclitaxel and carboplatin. Major ovarian cancer clinical trials groups throughout the world participated in this study, including the MRC ICON investigators in the United Kingdom, European Institute of Oncology in Italy, and the Australia-New Zealand GOG Consortium. This international collaboration provided a unique opportunity to accrue large numbers of patients in a timely manner which facilitated the simultaneous evaluation of multiple agents in a prospective randomized trial. With international participation, accrual exceeded 1,200 patients per year, and the trial reached its targeted accrual goal within four years of activation.

While the results of GOG-0182-ICON5 will help establish optimum chemotherapy for previously untreated patients with advanced ovarian and peritoneal primary cancer, the next generation of clinical trials will explore the impact of molecular targeted therapies in conjunction with chemotherapy. In particular, growth factor signal transduction inhibitors and anti-angiogenic agents as single agents and in combination with cytotoxic drugs are currently undergoing phase I and II trials in women with these tumors. Many of these agents have been shown to have cytostatic effects and have shown synergy with chemotherapy in experimental models of human cancer. In addition, since it is postulated that such biologic agents may also have a role in maintenance therapy, the

general approach in phase III trials will be the evaluation of the impact on outcome of active biologic agents in combination with standard cytotoxic therapy plus or minus extended single agent administration, compared with standard cytotoxic therapy alone, in patients with advanced disease.

2.3 Rationale for Angiogenesis -Targeted Therapeutics

Angiogenesis is one of the cardinal processes leading to invasion and metastasis of solid tumors. The angiogenic-signaling pathway may be triggered by the release of angiogenic promoters such as vascular endothelial growth factor (VEGF) from tumor cells into the local microenvironment. There is accumulating evidence that angiogenesis plays a central role in ovarian cancer disease progression and prognosis.[8-13] Given that a direct relationship has been demonstrated between the expression of biomarkers of angiogenesis and the behavior of epithelial ovarian cancer, it would seem implicit that pharmacological inhibitors of angiogenesis could arrest tumor progression.[14-17] Neutralizing anti-VEGF monoclonal antibodies have demonstrated therapeutic activity in a variety of pre-clinical solid tumor models.[18,19]

2.4 Role of Bevacizumab, an Anti-VEGF Monoclonal Antibody, in Epithelial Ovarian and Peritoneal primary Cancer Therapy (10/14/08)

Bevacizumab is a recombinant humanized version of a murine anti-human VEGF monoclonal antibody, named rhuMAb VEGF. Bevacizumab has been advanced into clinical development for use as a single agent to induce tumor growth inhibition in patients with solid tumors and for use in combination with cytotoxic chemotherapy to delay the time to disease progression in patients with metastatic solid tumors.[20]

The results of two single agent trials of bevacizumab for patients with recurrent epithelial ovarian and peritoneal primary cancer have been published.[21,22] GOG (GOG-0170-D) utilized two co-primary efficacy endpoints: clinical response by NCI RECIST criteria and proportion surviving progression-free for at least 6 months. 62 participants received bevacizumab at 15 mg/kg every 21 days until clinical or radiographic evidence of disease progression or development of unacceptable toxicity. The primary disease characteristics were typical of patients with recurrent ovarian cancer, and approximately 43% of patients were considered primarily platinum resistant. A 21% response rate was observed, and 40% were progression-free for at least 6 months, with a median PFS 4.7 months, compared with 1.8 months for a historical control based on previous negative phase II trials of cytotoxic agents in populations with similar clinical characteristics. Genentech AVF 2949 examined patients with a higher risk profile in terms of the potential for disease progression and adverse events, allowing only patients considered either primarily or

secondarily platinum resistant and having received 2 or 3 previous cytotoxic regimens. These differences in eligibility ultimately translated into a higher level of platinum resistance, a greater number of prior regimens and a slightly worse performance status profile in the AVF population. Forty four patients were treated at the same dose and schedule for bevacizumab as used in GOG 170-D. Seven (16%) responses were documented, and 12 (27%) were progression-free for at least 6 months.

The observed spectrum and degree of toxicity between these trials was not unexpected, for example with respect to arterial thrombotic and reno-vascular events. However, unlike GOG 170-D, in which no gastrointestinal perforations or fistulae were observed, 5 such events occurred in 44 patients enrolled to AVF 2949; these events led to early termination of AVF 2949 and an IND Action Letter in 2005. It is possible that the higher risk profile of AVF participants and imaging evidence of intestinal wall thickening as a precursor may account for this observation, but this is still speculative - some of these events occurred after discontinuing bevacizumab for disease progression, the natural history of gastrointestinal perforation and fistula in patients with advanced recurrent ovarian cancer is not well documented, and one cannot account for statistical variation without a controlled trial. That being said, Han et al. recently reviewed published data from phase II trials and historical cohort studies of open-label use of bevacizumab as a single agent and in combination with cytotoxic drugs. This review revealed an overall incidence rate of 5.2% in 308 patients, about double the rate seen in other solid tumor populations. While not all of these gastrointestinal perforations and fistulae have required open surgical management and most patients have recovered, prospective pre-clinical and clinical work is needed to identify mechanisms and risk factors. This is one of the goals for GOG 0218.

2.5 Experience with Combination Bevacizumab - Cytotoxic Therapy

Evidence from pre-clinical studies and recent phase II and III clinical trials in other solid tumors has demonstrated enhanced anti-tumor activity of traditional cytotoxic regimens, when combined with bevacizumab. For example, Devore and colleagues reported on a three-arm phase II randomized trial of carboplatin/paclitaxel at with or without bevacizumab (7.5 mg/kg or 15 mg/kg dose levels) every 21 days until disease progression, in 99 patients with stages IIIB and IV non-small cell lung cancer.[23] Response rates were 21.9 percent (7/32 patients) in the low dose and 42.9 percent (14/35 patients) in the high dose bevacizumab combination arms, compared to a response rate of 31.3 percent (10/32 patients) in the chemotherapy alone arm. A phase II/III trial

in this patient population has been conducted by ECOG; the final analysis of this study is pending.

More importantly, a recently reported phase III trial, AVF2107, of over 800 previously untreated patients with previously untreated metastatic colorectal cancer randomized to receive either bevacizumab for one year plus the Saltz chemotherapy regimen (5-FU/Leucovorin/CPT-11, IFL) or the Saltz regimen plus placebo for one year met its primary endpoint of improving overall survival.[24] The magnitude of benefit observed far exceeded what the study was designed to demonstrate. The trial also met the secondary endpoints of progression-free survival, response rate, and duration of response (see table below).

	IFL/ bevacizumab (n = 403)	**IFL/ placebo (n = 412)**	**Hazard Ratio (p-Value)**
Response Rate	44.9%	34.7%	(0.0029)
Median TTP	10.6 months	6.2 months	(0.00001)
Median Survival	20.3 months	15.6 months	0.65 (0.00003)

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

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

These included hypertension and bleeding as more predominant in the bevacizumab arm.[25]

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

2.6 Rationale for Clinical Trial Design

Bevacizumab was selected for evaluation in combination with standard chemotherapy based on preliminary phase II single agent data obtained in patients with recurrent epithelial ovarian and peritoneal primary cancers (see Section 2.4) and results from a phase III clinical trial in patients with metastatic colorectal cancer demonstrating a survival benefit to patients receiving bevacizumab with standard cytotoxic chemotherapy compared with patients receiving standard chemotherapy alone (see Section 2.5). Based on the mechanism of action of bevacizumab, there may be benefit of extended therapy with this agent until disease progression, in extending PFS or OS in this patient population. However, it is unclear whether additional benefit of bevacizumab beyond the general duration of standard primary chemotherapy exists. Therefore, two experimental arms were selected to compare with standard cytotoxic chemotherapy with paclitaxel and carboplatin: one incorporating 5 cycles of bevacizumab (concurrent bevacizumab) and the other with bevacizumab for an additional 16 cycles after completion of chemotherapy with paclitaxel and carboplatin **(06/26/06)** (extended bevacizumab).

This is a double-blind, placebo-controlled phase III trial in order to preserve the integrity of the progression-free survival and overall survival endpoints by eliminating biases in disease assessment monitoring, the declaration of disease progression and the institution/selection of future therapies. Therefore, it is understood that investigators, patients and research personnel will not know whether or not patients have received bevacizumab or placebo. Because of the intent-to-treat analysis, this rule applies to patients who enter the study and then are later found to be ineligible. The only indication for unblinding to treatment arm is a serious adverse event in which it is determined by the Study Chair that unblinding would improve patient safety. The justification for maintaining the blind even after disease progression is the absence of evidence that such knowledge would provide increased benefit. For example, there is no evidence that prior exposure to bevacizumab would exclude subsequent use/benefit of bevacizumab or other VEGF targeted agents. **(08/06/07)**

2.61 Study Population

A study population limited to those patients with stage III-suboptimal and

stage IV **(06/26/06)** tumors was initially selected because this group carries the poorest prognosis of those with advanced disease and would allow conservation of sample size needed to demonstrate a survival benefit associated with bevacizumab therapy. However, the accrual rate through the first 18 months of study was less than half that projected. A systematic survey of the study sites revealed that the majority of patients with epithelial ovarian cancer or primary peritoneal cancer undergoing up front surgery are optimal (have no more than 1 cm maximal diameter residual tumor implants) and that a major obstacle to enrollment has been the exclusion of such patients. Furthermore, the results of the trial would be better generalized to the population at large with epithelial ovarian and primary peritoneal cancers with the inclusion of the largest subset of these patients. That being said, a decision was made to limit enrollment of patients with stage III optimal cancers to only those with macroscopic residual disease at the completion of initial surgery; this is because those with no gross (macroscopic or palpable) residual disease are felt to be at too low a risk for relapse and death to justify their inclusion (see revisions to section on Statistical Considerations). **(08/06/07).** Although Mullerian adenocarcinomas of the fallopian tube are much less common than epithelial ovarian and primary peritoneal cancers, due to similarities in response to treatment and prognosis, this disease has been grouped with epithelial ovarian and primary peritoneal cancers in National Cancer Institute trials. This study will evaluate these cancers as well. **(10/14/08)**

2.62 Sample Size Considerations **(10/14/08)**

The sample size of the proposed study was estimated with progression-free survival (PFS) as the primary endpoint, while taking steps to protect the integrity of overall survival (OS) as a secondary endpoint. At the recently held 3rd International Ovarian Cancer Consensus Conference, September 2004, in Black Forest, Germany, an agreement was reached that PFS is a reproducible surrogate of overall survival in this population.[26]

2.63 Optimum Number of Cytotoxic Chemotherapy Cycles

It has become common practice to administer six to eight cycles of initial chemotherapy in phase III clinical trials for patients with advanced-stage ovarian cancer. The optimal number of cycles has not been defined, but there is no evidence that more than 4 cycles is associated with an improvement in long-term outcomes. Length of therapy has not been prospectively evaluated with a combination of platinum and paclitaxel. From available data, it is reasonable to conclude that the absolute number of cycles within a clinically relevant range of between 6 and 8 is unlikely to have a measurable impact on long-term disease control. At present, there are no prospective data to indicate that dose intensity,

cumulative dose delivery, or number of cycles has an impact on long-term outcomes following primary therapy with platinum and paclitaxel. There is, however, evidence of increased risk of severe adverse effects of treatment with the combination of paclitaxel and carboplatin beyond the traditional 6 cycles. These effects include cumulative platelet toxicity and increased risks of severe hypersensitivity, particularly related to carboplatin, as well as increased risk of high Grade neuropathy related to paclitaxel. The above counterbalancing factors serve as the rationale for 6 cycles of induction chemotherapy in the current trial.

2.64 Wound Healing Issues

2.641 Delay of Initial Treatment with bevacizumab

Because of the concern of potential wound complications related to bevacizumab, in this trial bevacizumab/placebo therapy will begin at the start of cycle number 2 of carboplatin and paclitaxel combination chemotherapy.

2.642 Management of Incisions Healing by Secondary Intention

It is not uncommon for patients recovering from initial cytoreductive surgery for advanced epithelial ovarian or primary peritoneal cancer to have granulating incisions healing by secondary intention. Excluding such patients would therefore be discriminatory, and conclusions of this trial could not be validly generalized to the population with these tumors. If inhibition of further healing in patients with uncomplicated incisions healing by secondary intention occurred in patients receiving bevacizumab, it would be extremely unlikely for such interruption in the healing process to lead to CTC Grade 3 or Grade 4 events (e.g. requirement of additional surgery for failure to heal or wound re- opening, infection requiring systemic antibiotics). Therefore, patients with uncomplicated wound separations healing by secondary intention without evidence of fascial dehiscence, active infection or fistula will be eligible to participate in this trial and receive bevacizumab/placebo. As an additional safeguard for such patients, weekly wound examinations will be required until complete wound closure, with specific chart and case report form documentation. In the event of deterioration, bevacizumab/placebo would be discontinued. **(06/26/06)**

2.65 Selected Substitution of Docetaxel for Paclitaxel

Publication of results from GOG Protocol 0111 [27] and a confirmatory European trial [28] led to adoption of paclitaxel and carboplatin as the standard primary therapy for patients with advanced epithelial and peritoneal primary cancer. However, it is estimated that on the order of 5% of patients in the population eligible for participation in the current trial will develop peripheral neuropathy

or refractory acute hypersensitivity infusion reactions which would necessitate discontinuation of paclitaxel.

Docetaxel is a novel taxane with reduced potential for neurotoxicity compared with paclitaxel. In addition, docetaxel has been safely substituted for paclitaxel in patients experiencing severe acute hypersensitivity to paclitaxel refractory where re-challenge is either unsuccessful or deemed unsafe.

With regard to efficacy, there is evidence that docetaxel is an alternative treatment option to paclitaxel for patients with epithelial ovarian and peritoneal primary cancer. Docetaxel has been combined with cisplatin or carboplatin extensively in phase II and III clinical trials. These studies have demonstrated activity in a variety of tumor types (non-small cell lung, breast, head and neck, bladder, gastric, and gynecologic malignancies) and show that combinations of these drugs are safe and feasible.[29-55] Docetaxel has substantial activity against platinum-refractory ovarian carcinoma [56] and is also active as primary therapy in ovarian cancer.[32,45,51,53] A phase III randomized trial (SCOTROC) of docetaxel and carboplatin versus paclitaxel and carboplatin in patients with advanced epithelial ovarian cancer has recently been published.[52] In this trial, patients received carboplatin at an AUC of 5 with either docetaxel at 75 mg/m^2 1-hour IV infusion or paclitaxel at 175 mg/m^2 3-hour IV infusion. Results of this trial demonstrated no significant difference in median progression-free survival (15.0 months versus 14.8 months), two year overall survival (64.2% versus 68.9%) or objective tumor response (58.7% versus 59.5%) for the combination of docetaxel and carboplatin versus the combination of paclitaxel and carboplatin, respectively. While docetaxel and carboplatin produced more neutropenia (Grade 3-4 neutropenia 94% for docetaxel and carboplatin versus 84% for paclitaxel and carboplatin, $p < .001$) and neutropenic complications than treatment with paclitaxel-carboplatin, the docetaxel and carboplatin regimen was significantly less neurotoxic (Grade ≥2 neurosensory toxicity in 11% for docetaxel and carboplatin versus 30% for paclitaxel and carboplatin, $p < .001$).

The results of the SCOTROC trial have led many oncologists to select substitution of docetaxel for paclitaxel in first line therapy for patients with advanced epithelial and peritoneal primary cancer. Thus, in order to optimize cytotoxic therapy in all arms of the current trial, reduce the likelihood of protocol violations and avoid imbalances in the type of taxane utilized in each treatment arm, in the current trial docetaxel will be selectively substituted for paclitaxel in circumstances in which peripheral neuropathy or hypersensitivity warrants discontinuation of paclitaxel (Section 6.51 and Section 6.62, respectively).

2.66 Post-Remission Therapy (10/14/08)

It is expected that all of the chemotherapy regimens employed in this trial will achieve an overall response rate of greater than 75%. However, as many as 90% of patients with stage III and stage IV **(06/26/06)** epithelial ovarian, peritoneal primary and fallopian tube cancer in clinical complete remission will ultimately recur and die of disease. Therefore, a number of strategies are under active consideration to delay or prevent recurrence. Among these strategies include "consolidation" treatment with cytotoxic, hormonal, or biologic targeted agents.

For example, recent data have revealed that continuation of single-agent paclitaxel on a monthly schedule for 12 cycles significantly extended progression-free survival.[57] Certainly consolidation therapy has been implemented variably in clinical practice outside clinical trials with the decision based on physician and patient preference, with no evidence that overall survival is influenced by either treatment of patients in complete clinical remission or for that matter, at the time of clinical disease progression.

Due to the lack of evidence that any current consolidation approach is associated with an improvement in overall survival, and our desire to preserve the integrity of the progression-free interval, **(10/14/08)** the current trial design will control for the potential use of consolidation therapies, including agents unique to the experimental regimen, as well as the potential for investigator assessment bias. In order to accomplish this goal, the arms will be placebo-controlled. Based on the mechanism of action of bevacizumab, there may be benefit of extended therapy with this agent, justifying the inclusion of an extended therapy arm in the current trial. Specifically, a total of 22 cycles **(06/26/06)** of treatment was chosen since it approximates the 15 months **(06/26/06)** median PFS in this population of women with stage III-suboptimal and stage IV **(06/26/06)** epithelial and peritoneal primary cancer , based on data from recent GOG phase III trials (see Section 11.0). While it was considered important for the placebo control to be maintained for this entire duration in all three arms of the trial, at the same time extending a placebo beyond 15 months was felt to be impractical, unethical and cost-prohibitive. Finally, patients treated on this trial will not be eligible for therapy on clinical trials evaluating consolidation or maintenance therapy while on or off study.

2.67 Role of Secondary Surgery

Continued uncertainty exists as to whether second-look surgical procedures contribute to the overall management of patients with ovarian cancer. Some investigators and institutions do not recommend a second-look operation whereas other investigators feel that, in some patients, a second-look procedure may be useful to identify patients with small-volume residual disease who are candidates for additional treatment. The uncertain benefit of second-look surgery has been reflected in current treatment guidelines, where it has been designated as an optional procedure (NCCN). In community practice outside of clinical trials, the frequency of second-look surgery has declined. The non-uniform application of second-look surgery and the ability to document "sub-clinical" residual disease has the potential for confounding primary endpoints on this clinical trial, such as determination of the PFS. In the absence of clear evidence that this procedure provides benefit, second-look surgery for patients in clinical complete remission will not be permitted on the current study.

Based on results from GOG-0152 demonstrating that interval secondary cytoreductive surgery did not improve progression-free or overall survival in patients with advanced disease who had previously undergone maximal primary cytoreduction,[58] and the potential for increased surgical morbidity from delayed wound healing in patients who undergo major surgical procedures while on treatment with bevacizumab, interval cytoreductive surgery will not be

permitted for patients enrolled on the current trial.

2.68 CA-125 as a Biologic Marker of Progressive Disease

Serum levels of CA-125, a tumor-associated glycoprotein antigen, are elevated in 80% of patients with epithelial ovarian cancer.[59] CA-125 has been monitored, often on a frequent basis, to verify response to therapy, presence of residual disease, and as early evidence of recurrence. However, CA-125 is not entirely tumor specific, and can be elevated in a variety of benign conditions, such as endometriosis, uterine fibroids, and pelvic inflammation; this is particularly true in pre-menopausal women. In addition, levels of CA-125 can be discordant with tumor response, both as false-positive and false-negative trends; the influence of biologic agents on these inaccuracies is unclear. Nonetheless, because imaging modalities such as contrast computed tomography appear to be relatively insensitive in detecting disease progression, it has been standard practice for patients and physicians interpret a progressive rise in CA-125 post-therapy as evidence of recurrent or progressive disease, and will make therapeutic decisions based solely on the CA-125. This has complicated the assessment of PFS in prior randomized trials, as patients will receive new therapy prior to clinical documentation of progressive disease on the basis of physical examination or radiographic findings. The current randomized trial will employ a conservative formula to define progressive disease based on serial elevation of CA-125 [60-64] (in addition to other standard definitions in the management of solid tumors), but only following completion of initial chemotherapy. Although imperfect, it is preferable to apply uniform criteria that include CA-125 rather than absorb uncharacterized events that would compromise the secondary endpoint of PFS. Progression during the period of cytotoxic chemotherapy will require radiographic or physical confirmation.

2.7 Quality of Life (QoL) (10/14/08)

This trial will help determine if anti-VEGF therapy, when combined with standard chemotherapy, prolongs OS and PFS after suboptimal cytoreductive surgery of epithelial ovarian and peritoneal primary cancer. In addition, this study will determine the optimal schedule of anti-VEGF therapy. Patient-reported outcomes may differ when anti-VEGF therapy is added to standard paclitaxel and carboplatin chemotherapy. Specifically, the primary objective of measuring QoL in this trial is to determine if the addition of anti-VEGF therapy reduces disease related symptoms (improves QoL) more quickly and for more prolonged periods of time than chemotherapy alone. In addition, other objectives of measuring QoL include determining if anti-VEGF therapy alters QoL as a result of treatment related toxicity not captured though traditional physician-reported measures.

Data from GOG Protocol 0170-D suggest that bevacizumab may, among responders, not only reduce tumor volume as measured though traditional disease response monitoring, but may also clear ascites and pleural effusions leading to reduced abdominal bloating and pain thus improving QoL. Indeed, VEGF appears to be obligatory for ascites formation by increasing vascular permeability.[65] Thus, neutralization of VEGF activity could perhaps dramatically improve QoL after just one or two doses of bevacizumab by reducing malignant ascites formation. Moreover, since

taxanes have anti-angiogenesis activity, it is hypothesized that a combination of bevacizumab and paclitaxel could be synergistic.[66] Unfortunately, QoL was not closely monitored in GOG Protocol 0170-D and future trials such as the current clinical trial studying bevacizumab in ovarian cancer require QoL measures to evaluate these important endpoints.[67]

Since most women with stage III and stage IV epithelial ovarian, primary peritoneal **(06/26/06)** and fallopian tube cancer will succumb to their malignancy and since many regimens have similar efficacy, differences in QoL may help determine the optimal treatment regimen in this setting. In addition, systematic documentation of QoL among those enrolled onto this trial may assist in providing information to future non-trial patients regarding the expected effects of therapy as they make their treatment choices. To date, four completed phase III studies in the upfront treatment of ovarian cancer have implemented QoL outcome measures in their study design, and in every instance QoL was helpful in determining the best regimen. For example, OV.10 established the benefit of paclitaxel in treating ovarian carcinoma,[28,68] the AGO trial established the benefit of carboplatin,[69] and the SCOTROC trial established the role of docetaxel [52] and in all of these studies QoL was an important endpoint. More recently, GOG-0152 was the first prospective trial to study QoL in ovarian cancer performed in the GOG. This study included **(06/26/06)** patients similar to the current study and demonstrated the feasibility of obtaining high quality QoL data from this population within this cooperative group.[70] GOG-0152 again illustrated the critical importance of measuring QoL. This study showed that endpoints useful in evaluating optimal therapies in the upfront management of ovarian cancer may be missed if only physician reported endpoints are measured. For example, this study found important difference in neurotoxicity between regimens by measuring QoL and demonstrated that baseline QoL (as measured by the FACT-O) was prognostic of overall survival. Importantly, the recently completed study, GOG-0182, which was the predecessor to the currently proposed study, did not contain a QoL component. If this trial shows no difference in the anti-tumor activity between the six regimens studied in this clinical trial, the opportunity to pick the best regimen will be missed because QoL was not measured.

In the current trial, QoL will be assessed using the Trial Outcome Index of the Functional Assessment of Cancer Therapy-Ovary (FACT-O TOI).[71,72] This 26-item summary score captures the FACT-G QOL dimensions of Physical Well-Being (7 items), Functional Well-Being (7 items), and the Ovarian Cancer Subscale (12 item). By combining these three subscales, one is assured of capturing the full range of physical aspects of QOL in advanced ovarian cancer, including pain, fatigue, abdominal symptoms and functional status. By combining questions GP4, O1, and O3, which assess abdominal pain, swelling and cramps respectively, a comprehensive patient reported assessment of disease related abdominal symptoms including ascites can be evaluated. Also, the abdominal pain module piloted in GOG Protocol 0172 will be included.

The timing of the QoL assessments is critical to capture data useful in discriminating subtle differences between regimens. This is complicated by the fact that the acute affects of cytotoxic therapy may cause a decrease in QoL. In order to capture early difference in QoL as a result of anti-angiogenesis therapy with bevacizumab, assessment time points during this trial will be weighted toward the early part of this study. In addition, since some subjects may only complete a few cycles of therapy, it is

important to have early assessment points. Finally, in order to avoid the confounding affects of acute chemotherapy related toxicity, questionnaires will be completed just before (21 days after the last dose) the next cycle of chemotherapy and focus on QoL within the last seven days. Thus, assessments will be made:

1. Prior to cycle 1 (t = 0 weeks)
2. Prior to cycle 4 (after 3 doses of chemotherapy and 2 doses of bevacizumab/placebo, t= 9 weeks), to assess immediate changes in QoL
3. Prior to cycle 7 (after 6 doses of chemotherapy and 5 doses of bevacizumab/placebo, t= 18 weeks) to assess intermediate changes in QoL
4. Prior to cycle 13 (t= 36 weeks), 6 months after chemotherapy
5. Prior to cycle 22 (t= 60 weeks), completion of study therapy
6. 6 months after completion of study therapy (t= 84 weeks)

2.8 Translational Research Related to Anti-VEGF Therapy

2.81 Markers of Angiogenesis

Angiogenesis is one of the cardinal processes leading to invasion and metastasis of solid tumors. There are more than 19 known angiogenic growth factors and at least 30 known angiogenesis inhibitors in the body, and more than 300 exogenous angiogenesis inhibitors have been discovered to date. Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) are among the most well studied angiogenic growth factors. In tumors, angiogenesis has been studied by quantifying the tumor blood micro-vessel density (MVD) determined immunohistochemically using antibodies to CD31, a protein expressed on the surface of vascular endothelial cells. MVD has been shown to predict the response of gastric adenocarcinomas to taxane-based therapy.[73] In addition to MVD, most angiogenesis studies also evaluate VEGF, which has been shown to promote neovascularization and stimulate endothelial cell survival.[74] VEGF levels were also found to correlate with MVD in endometrial and cervical, but not ovarian cancers.[75,77] In ovarian cancer, higher VEGF levels, but not MVD, were found to significantly correlate with decreased patient survival.[76] Multivariate analysis demonstrated that VEGF was an independent prognostic indicator of overall survival,[76] while the prognostic significance of MVD alone for ovarian cancer was less strong.[76,78]

Immunohistochemistry will be utilized to evaluate the expression of CD-31 and VEGF in previously untreated primary or metastatic tumor tissue. Expression of these angiogenic markers will be examined in conventional unstained tumor sections compared with tissue micro arrays (TMAs). An analysis will be undertaken to assess the relationship between tumor tissue expression of angiogenic markers and clinical outcome including tumor response, progression-free survival and overall survival in this patient population in the TMAs created for GOG-0218 if appropriate. If not, conventional unstained tissue sections will be used to examine the relationship between the angiogenic markers and clinical outcome in patients participating in this randomized treatment protocol. Immunoassays will be performed to quantify the concentration of angiogenic markers including VEGF in serum and plasma. Plasma is being added as an optional specimen for GOG-0218 based on recent observations from GOG-

0229B and GOG-0231B suggesting that the pre-treatment concentration of VEGF in plasma not serum was associated with progression-free survival and overall survival in patients with persistent or recurrent endometrial cancer and in patients with persistent or recurrent leiomyosarcoma of the uterus (manuscripts in preparation). The exact choice of biomarkers to be evaluated and assays to be performed in tumor, serum and plasma specimens will be reevaluated based on evolving data in the field. **(1-16-06) (06/26/06)**

The GOG has embarked on a programmatic examination of angiogenic markers as predictors of clinical outcome including tumor response and survival in ovarian and cervical cancer. The first part of this plan incorporated exploratory translational research objectives into Phase II (GOG-0170D, GOG-0229B and GOG-0231-B) and Phase III (GOG-0157, GOG-0175 and GOG-0191) treatment protocols, a pilot protocol (GOG-9911) and a GOG Tissue Bank project. The laboratory data for these studies will continue to be analyzed, reported and published during the next few years. The second part of this plan will incorporate research hypotheses generated from these exploratory studies into definitive translational research objectives that can be tested and validated in randomized phase III treatment protocols activated or under development in ovarian cancer and cervical cancer including GOG-0198, GOG-0212, GOG-0213, GOG-0218, and GOG-0219. At the appropriate time, the current translational research objectives in GOG-0218 will be amended to incorporate a definitive translational research objective regarding angiogenic markers that can be tested and validated using the specimens submitted for this protocol. A summary of the relevant laboratory data will also be provided to establish the background and rationale for that amendment.

2.82 Genomic Analysis

The genomic research component of this protocol will focus on the refinement and validation of genes whose expression predict for survival in patients with advanced stage ovarian cancer. Despite the fact that 80% of advanced ovarian cancers (stages III/IV) respond to primary treatment with surgery and chemotherapy, the disease usually recurs and is ultimately fatal. Though most patients die within two years of diagnosis, a subset of patients, even with clinically and morphologically indistinguishable diseases, develop a more chronic form of ovarian cancer, and may survive five years or more with treatment. It is possible that patients with indolent cancer should be monitored and treated differently from patients with rapidly progressing ovarian cancer. At this point, clinicians do not have the tools to predict the clinical course of the disease at the time of initial diagnosis.

Transcription profiling is a large-scale gene-expression analysis-technology, which has been widely used to identify differentially expressed genes and molecular signatures in many biological processes.[79-81] In the past five years, over 600 manuscripts on expression profiling of cancers using microarray technology have been published, illustrating the recognized utility of this approach in exploring questions of tumor biology and clinical correlates. The