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 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.

2.83 Banking Whole Blood for Research **(03/16/09)**

The National Cancer Institute is encouraging Cooperative Clinical Trial Groups including the Gynecologic Oncology Group to bank whole blood from women participating in clinical trials such that the blood specimens will be linked to clinical outcome data (progression-free survival, overall survival, response and adverse effects) and information regarding treatment. The purpose of this effort is to support research including pharmacogenomic and pharmacogenetic research such as the haplotype tagging SNP (htSNP) analysis of WNK lysine deficient protein kinase 1 (WNK1), G protein-coupled receptor kinase 4 (GRK4) and kallikrein B (KLKB1) to study genetic predictors of bevacizumab-induced hypertension (see Section 2.84).

Women who are candidates for this clinical trial or who have already been enrolled on GOG-0218 will be asked to give permission for 10 ml (2 teaspoons) of their blood to be collect for research to study DNA from normal cells. The women will also be asked GOG's standard future research questions asking permission for the following: the use of their specimens for future cancer research, the use of their specimens for future non-cancer research, the use of their clinical information for future research using their specimens, the use of their specimens for future research to study genetic material, and future contact to participate in research. Specific text is provided in the consent document describing that genetic material may be examined to study changes that are passed on in families or that are not passed on in families but are either natural or influenced by environment and lifestyle. These tests can focus on a section of genetic material (DNA); genetic material packaged into chromosomes, or examine all of the genetic material called the whole genome. The results can then be studied to identify changes in genetic material that influence the development of diseases including cancer, the effectiveness of specific treatments, or whether the person is at risk to experience an adverse event.

No matter what the women decide to do, it will not affect their care. The women can still participate in this GOG study even if they do not allow their specimens to be used for future research.

2.84 Genetic Predictors of Bevacizumab-Induced Hypertension **(03/16/09)**

Essential hypertension has been identified as the leading cause of cardiovascular and renal disease and affects more than 20% of the adult population in Westernized societies.[82] According to familial and twin studies, genes contribute 20–40% to the pathogenesis of essential hypertension.1 The role of the renin-angiotensin system (RAS) in blood pressure regulation has been well established.[83] When stimulated it leads to the production of angiotensin II, which causes vasoconstriction, aldosterone secretion, and increased sodium and water reabsorption by the kidneys, resulting in an increase in blood pressure. Therefore, components of the RAS are likely candidate genes that may predispose to essential hypertension. Angiotensinogen (AGT), bradykinin (BK), G protein β3 subunit (GNB3), β2 adrenergic receptor (ADRB2), and epithelial sodium channel α (ENaCα or SCNN1α) and others have all been investigated as candidate genes in the development of the disorder in many studies.[84-89]

Bevacizumab has been used as antiangiogenic therapy for a variety of tumors including renal cell, colorectal, lung, pancreatic, ovarian and breast carcinoma. The efficacy of bevacizumab as an anti-cancer agent relies on its inhibition of several actions of VEGF, including endothelial cell growth, vascular permeability and angiogenesis. Bevacizumab is currently FDA approved for treatment of colorectal carcinoma and non-small cell lung carcinoma, and has shown activity in a wide variety of other tumors as a single agent or in combination with cytotoxic agents. Studies with bevacizumab, a recombinant human monoclonal antibody to VEGF, have demonstrated that inhibition of VEGF induces or exacerbates hypertension in some patients and can also cause proteinuria, thrombosis, wound-healing complications, hemorrhage and gastrointestinal perforation. Grade 3 hypertension has been reported in 15-25% of patients receiving bevacizumab. Hypertension occurs more frequently in patients who received higher dosages.[90, 91] The incidence of hypertension for patients administered low-dose bevacizumab ranged from 2.7% to 32% and for those given high-dose from 17.6% to 36%. The relative risk of developing hypertension for low-dose administration was found to be 3.0 (95% CI, 2.2 to 4.2; $p<0.001$) and for high-dose 7.5 (95% CI, 4.2 to 13.4; $p<0.001$).[84] It is likely that genes which predispose to essential hypertension in the general population will also increase the likelihood of developing bevacizumab-induced hypertension.

The International HapMap Project recently completed and released phase II of its data, which delineate the common patterns of genetic variation across the genome.[92] This project has been instrumental in elevating the potential for and quality of disease association studies. For hypertension related genes, the block structure and haplotype tagging single nucleotide polymorphisms, or htSNPs, have been identified by both the HapMap Project and others.[84, 86, 87] In general, specific haplotype blocks are thought to contain genetic variants involved in susceptibility to disease.[93-95] This method of analysis has resulted in the

publication of a series of studies that examine potential genetic contributions to common diseases including prostate cancer, breast cancer, diabetes and coronary artery disease.[96] Haplotype analyses can identify both genetic predisposition to disease and elucidate mechanisms of tumorigenesis. This project will take a haplotype-based approach to the candidate genes indicated above that may be associated with bevacizumab induced hypertension.

To date, patients with solid tumors treated with bevacizumab in combination with other therapy were identified from one of six clinical trials at Memorial Sloan Kettering Cancer Center. Haplotype-tagging (ht) SNPs for 10 candidate genes (see below) associated with hypertension were identified through the International Hapmap Project. Germline DNA from FFPE normal tissue was genotyped for 103 htSNPs using Sequenom® mass spectrometry assays. Bevacizumab toxicities were identified from clinical trial reports and graded according to common toxicity criteria. Bayesian statistical methods were used to reconstruct haplotypes from diploid genotyping data. Single loci genotypes and haplotype frequencies were compared using standard two-sided statistical tests.

Candidate Systems	Candidate Genes
Renin-Angiotension-Aldosterone System	Angiotensinogen (AGT) Angiotensin II receptor, type I (AGTR1) Aldosterone synthase (CYP11B2) Angiotensin 1 converting enzyme (ACE)
Bradkinin	Bradykinin receptor B1 (BDKRB1) Kallikrein B (KLKB1)
Sodium Regulation	WNK lysine deficient protein kinase I (WNK1) G protein-coupled receptor kinase 4 (GRK4) Sodium channel, nonvoltage-gated 1 alpha (SCNN1A) G protein, beta-3 subunit (GNB3)
Vascular Permeability	Vascular endothelial grotwh factor A (VEGF-A)

The study population included 102 patients with the following solid tumors: breast cancer, 53; non-small cell lung cancer, 25; serous ovarian cancer, 11; and other, 13. Of these patients, 28 developed grade 1-4 bevacizumab-induced hypertension. Of the 10 hypertension-associated candidate genes, WNK1 was found to be most strongly associated with bevacizumab-induced HTN. Single loci testing identified 2 of 22 WNK1 htSNPs, rs11064560 and rs2158501, that were individually associated with bevacizumab-induced hypertension ($p = 0.0026$ and $p = 0.013$, respectively; trend test). Haplotype analyses of WNK1 identified three risk haplotypes for bevacizumab-induced hypertension. Patients who carried at least one of these risk haplotypes had an increased risk of bevacizumab-induced hypertension (OR, 4.7; $p = 0.002$; 95% CI, 1.67-13.1). We have also identified multiple markers in GRK4 and KLKB1 that are associated with bevacizumab-induced hypertension.

GRK4 encodes a member of the guanine nucleotide-binding protein (G protein)-coupled receptor kinase subfamily of the Ser/Thr protein kinase family. The protein phosphorylates the activated forms of G protein-coupled receptors thus initiating its deactivation. This gene has been linked to both genetic and acquired hypertension. The WNK1 gene encodes a cytoplasmic serine-threonine kinase expressed in distal nephron. KLKB1 is a serine protease that catalyzes release of bradykinin, a potent vasodilator. The data suggest that of the genes investigated, genetic variation in WNK1 is most strongly associated with bevacizumab-induced hypertension. WNK1, GRK4 and KLKB1 are biologically plausible mediators due to their role in blood pressure control. Genetic predisposition to bevacizumab-induced hypertension can help to risk stratify patients prior to initiating therapy. The findings described above presented at the 2008 ASCO Annual Meeting.[97]

The protocol is being amended to add a translational research objective to study natural changes in three genes that regulate hypertension to determine if genetic variations in genes associated with essential hypertension including WNK lysine deficient protein kinase 1 (WNK1), G protein-coupled receptor kinase 4 (GRK4) and kallikrein B (KLKB1) predict which patients are likely to develop bevacizumab-induced hypertension.[98-101]

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

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, Fallopian tube **(03/16/09)** 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.[102-107] **(03/16/09)** 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,