Philip J. DiSaia, M.D.
President

Administrative Office
Four Penn Center
1600 John F. Kennedy Boulevard, Suite 1020
Philadelphia, Pennsylvania 19103
Phone: 215-854-0770 Fax: 215-854-0716

Laura L. Reese
Executive Director of Operations

GOG® FOUNDATION, INC.

Larry J. Copeland, M.D.
Vice President

Finance/Development Office
2127 Espey Court
Suite 100
Crofton, Maryland 21114
Phone: 410-721-7126 Fax: 301-261-3972

Mary C. Sharp
Chief Financial Officer

PROTOCOL GOG-0212

A RANDOMIZED PHASE III TRIAL OF MAINTENANCE CHEMOTHERAPY COMPARING 12, MONTHLY CYCLES OF SINGLE AGENT PACLITAXEL OR CT-2103 (IND# 70177) VERSUS NO TREATMENT UNTIL DOCUMENTED RELAPSE IN WOMEN WITH ADVANCED OVARIAN, PRIMARY PERITONEAL OR FALLOPIAN TUBE CANCER WHO ACHIEVE A COMPLETE CLINICAL RESPONSE TO PRIMARY PLATINUM/TAXANE CHEMOTHERAPY**(08/10/09)**

NCI Version: December 17, 2014

Includes Revisions: 1-15

POINTS:
PER CAPITA – 20**(10/25/06) (01/02/2013)**
MEMBERSHIP -12

TRANSLATIONAL RESEARCH PER CAPITA - Award based on specimen submissions.
Distribution: 0.5 point for a whole blood specimen.**(03/30/09).**
Points for the other specimens were included directly into the general Per Capita.
Lead Organization: NRG/NRG Oncology

STUDY CHAIR
LARRY J. COPELAND, M.D.
OHIO STATE UNIVERSITY
DEPT OB/GYN
DIVISION OF GYN ONC
3651 RIDGE MILL DRIVE
HILLIARD OH 43026
(614) 293-8697
EMAIL: larry.copeland@osumc.edu

STUDY CO-CHAIR
ROBERT A. BURGER, M.D.
FOXCHASECANCERCENTER
333 COTTMANAVENUE
PHILADELPHIA, PA19111
215-728-3150
215-728-2773
Robert.a.burger@fccc.edu**(03/30/09)**

QUALITY OF LIFE CO-CHAIR
DAVID CELLA, Ph.D.
"See GOG Website Directory"

STATISTICIAN
MARK F. BRADY, Ph.D.
"See GOG Website Directory"

TRANSLATIONAL RES.CO-CHAIR
MICHAEL BIRRER, M.D., Ph.D.
"See GOG Website Directory"

TRANSLATIONAL RES. SCIENTIST
KATHLEEN M. DARCY, Ph.D.
"See GOG Website Directory"

SCIENTIFIC COLLABORATOR
DORIS BENBROOK, Ph.D.
"See GOG Website Directory"

PATHOLOGIST
WILLIAM H RODGERS M.D., Ph.D.
"See GOG Website Directory"

NURSE CONTACT **(09/30/13)**
KORI FENNER, RN, BSN, OCN
OHIO STATE UNIVERSITY
GYN ONCOLOGY
3651 RIDGE MILL DRIVE
HILLIARD OH 43026
(614) 366-9582
FAX: (614) 366-1625
EMAIL: kori.fenner@osumc.edu

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Philip J. DiSaia, M.D.
Group Chair

Administrative Office
Four Penn Center
1600 John F. Kennedy Boulevard, Suite 1020
Philadelphia, Pennsylvania 19103
Phone: 215-854-0770 Fax: 215-854-0716

Laura L. Reese
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Gynecologic Oncology Group

Larry J. Copeland, M.D.
Group Vice Chair

Finance/Development Office
2127 Espey Court
Suite 100
Crofton, Maryland 21114
Phone: 410-721-7126 Fax: 301-261-3972

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MEMBERSHIP -12

SCHEMA**(09/30/05) (08/10/09)**

Patients diagnosed with primary peritoneal cancer or stage III or IV ovarian or fallopian tube cancer who have no symptoms suggestive of persistent cancer, normal physical exam, normal CT scan of the abdomen/pelvis and serum CA-125 antigen level after receiving 5-8 cycles of platinum-taxane therapy will be randomized to:

REGIMEN I: CT-2103 135mg/m^2 (10-20 minute infusion) q 28-days x 12

REGIMEN II: Paclitaxel 135mg/m^2 (3-hr infusion) q 28-days x 12

REGIMEN III: No further treatment until evidence of disease progression

Please see Section 7.2 as well as Appendix III (Specimen Procedures) and Appendix IV (Laboratory Procedures) for details regarding the specimen requirements and laboratory testing for this protocol. A new specimen requirement was added to this protocol **(03/30/09).**The collection of whole blood will apply to all of the patients who provide consent regardless of randomization and treatment including those already enrolled on GOG-0212. Women already enrolled on GOG-0212 will need to be re-consented for this collection. If the patient does not give permission, select "No" in the online Specimen Consent Application for the question "Did your patient give permission for her blood to be collected for submission and use for this research study" and enter "patient refusal" as the reason the specimen was not collected/submitted in item 5 on the SP Form for WB01.

OPEN TO PATIENT ENTRY MARCH 21, 2005; REVISED SEPTEMBER 30, 2005; REVISED FEBRUARY 6, 2006; REVISED OCTOBER 25, 2006; REVISED AUGUST 27, 2007; REVISED MARCH 10, 2008; REVISED MARCH 30, 2009; REVISED AUGUST 10, 2009; REVISED MAY 10, 2010; REVISED OCTOBER 4, 2010; REVISED JULY 18, 2011; REVISED AUGUST 27, 2012; REVISED AUGUST 19, 2013; REVISED SEPTEMBER 30, 2013; CLOSED TO PATIENT ENTRY JANUARY 13, 2014; REVISED

TABLE OF CONTENTS **(09/30/05) (08/27/07) (03/10/08)(03/30/09)(08/27/12)**

1.0 OBJECTIVES

1.1 Clinical Objectives **(08/10/09)**

1.11 To determine whether CT-2103 or paclitaxel, administered to women with advanced ovarian, primary peritoneal or fallopian tube cancer who have attained a clinically-defined complete response to primary platinum/taxane-based chemotherapy ("consolidation/maintenance therapy") will reduce the death rate, compared to re-treatment at the time of documented disease progression.

1.12 To determine if, in this clinical setting, CT-2103 produces a more favorable toxicity profile (with a particular focus on peripheral neuropathy as measured by the GOG NTX4) and superior quality-of-life (as measured by the FACT-O), compared to paclitaxel.

1.2 Translational Research Objectives **(03/30/09) (08/10/09)**

The overall goal of the translational research component of this protocol is to assess the clinical relevance of markers of angiogenesis in patients with advanced ovarian, primary peritoneal and fallopian tube cancer who achieve a clinically-defined complete response to primary platinum/taxane-based chemotherapy and are randomized to CT-2103, paclitaxel, or no treatment until the time of documented disease progression.

1.21 To explore the relationship between expression of several of the angiogenic markers and overall survival or progression-free survival in patients randomized to CT-2103, paclitaxel, or no treatment.

1.22 To assess the association among the various tissue and serum markers of angiogenesis, and compare the ability of different combinations of these markers to predict patient outcome including overall survival and progression-free survival in patients randomized to CT-2103, paclitaxel, or no treatment.

1.23 To bank DNA from whole blood for research and evaluate the association between single nucleotide polymorphisms (SNPs) and measures of clinical outcome including overall survival, progression-free survival and adverse events.

2.0 BACKGROUND AND RATIONALE

2.1 Overview **(08/10/09)**

Standard treatment of advanced ovarian, primary peritoneal and fallopian tube cancers includes the administration of a platinum agent and a taxane.[1-4] The combination of carboplatin and paclitaxel is the most frequently employed regimen due to ease of administration and the generally favorable side-effect profile.[2-4]

In women with advanced ovarian cancer who achieve a clinically-defined complete response following a platinum/paclitaxel regimen, recent data have revealed that continuation of single-agent paclitaxel on a monthly schedule for 12 cycles can significantly extend progression-free survival.[5] Unfortunately, due to the early closure of the randomized phase III trial it remains unknown if this "consolidation/maintenance" strategy favorably impacts overall survival in this clinical setting. Further, there is concern for the development of new, or worsening, of existing neurotoxicity associated with continuation of single-agent paclitaxel, and delivery of an alternative taxane (e.g., CT-2103) with a lessened risk of peripheral neuropathy has both the potential to reduce the toxicity of this approach, as well as permit more patients to be treated with (and successfully complete) this "consolidation/maintenance" program.

2.2 CT-2103

CT-2103 is a novel compound, resulting from the conjugation of paclitaxel to a proprietary poly-glutamate polymer.[6, 7] The drug has been shown in animal models to have a broad spectrum of activity.[8] Of note, CT-2103 is soluble in aqueous solution, and cremophor is not required.[9-12] The drug is administered as a 10-minute infusion, and preliminary safety data suggest the drug has a more favorable toxicity profile (hypersensitivity reactions, neurotoxicity, alopecia) compared to paclitaxel.

Preliminary analysis of phase I and phase II clinical trial experience reveals the following: (a) when employed in the *second-line setting*, single agent CT-2103 is active in the platinum-resistant and potentially platinum-sensitive sub-populations as well as taxane resistance;[12] (b) single agent CT-2103 is associated with minimal alopecia, infrequent mild to moderate peripheral neuropathy and infrequent hypersensitivity (patients are not routinely given prophylaxis for hypersensitivity reactions;[9-12] and (c) the drug can be safely combined with both cisplatin and carboplatin, with activity observed in the first-line and second-line settings.[13,14] (Many of these clinical trials remain in progress, with additional data forthcoming). Efficacy results are summarized in Table 1.

Table 1 Summary of Published Preliminary Efficacy Data

Dose (mg/m^2)	# of Patients Treated	PR	SD	PD	NA[1]
CTI 1052a: Phase I, single-agent, ascending dose Q2Week; study is complete[1]					
≤178	6	1	1	3	1
233	7		4		3
266	6		3	1	2
CTI 1052b: Phase I, single-agent, ascending dose Q1Week; study is complete[2]					
175/177	7	1		4	1
210	4		2	1	2
CTI 1055: Phase I, combination with 75 mg/m^{2}cisplatin, ascending dose Q1Week; study is complete[2]					
175	3	1	2		
210	6	1	3	2	
225	7	2	3	2	
250	6		2	4	
270	3			3	
CTI 1072: Phase I, combination with carboplatin, ascending dose Q3Week; study is complete[3]					
175 + carbo AUC 5	3		3		
210 + carbo AUC 5		1	2		
210 + carbo AUC 6	7		3	4	
225 + carbo AUC 6	6	2	2	2	
250 + carbo AUC 6	3		2	1	
PGT105: NSCLC, Phase I, single-agent, ascending dose Q3Week; study is ongoing[3]					
235	6			6	
270	6	1	2	3	
CTI 1069: Phase II, single agent, high-risk NSCLC; study is complete					
175	28	2	16	7	3
CTI 1071: Phase II, single agent relapsed/refractory ovarian, 1° peritoneal, fallopian carcinoma; study is complete[4]					
Platinum sensitive patients – 175	42	6	17	19	
Platinum resistant or refractory patients – 175	57	4	15	38	
CTI 1067: Phase II, single agent, resistant colorectal cancer; study is complete[3]					
210	60		17	41	2
CTI 1065: Phase II, single agent, breast cancer; study is complete[2]					
235	26	4	6	4	10

[1]NA = study ongoing, data not yet in-house or too early too evaluate
[2]Presented at ASCO 2003
[3]Presented at ECCO 2003
[4]Manuscript in preparation
PR = Partial Response, SD = Stable Disease, PD = Progressive Disease

2.21 Justification for Taxane dosage reduction: **(09/30/05) (03/30/09)**

Taxanes, specifically paclitaxel and CT-2103 have failed to demonstrate a dose response effect (e.g., increase dose with increase in response). Both CT-2103 and paclitaxel have demonstrated significant efficacy in the up front treatment of ovarian cancer in combination with platinum agents but neuropathy is a dose-limiting toxicity for many patients in the case of long term dosing strategies.

When originally conceived, GOG -0212 was to accomplish 12 months of single agent CT-2103 or paclitaxel therapy and compare these results to no maintenance therapy. In GOG-0212, the induction therapy appropriate to achieve a CR based on CA-125/CT scan, includes Carboplatin or Cisplatin/docetaxel or paclitaxel. Patients can have no greater than grade 1 neuropathy at study entrance. Based on the positions above and the GOG 9914 data, a dose of 135 mg/m^{2}of conjugated paclitaxel appears safe and seems appropriately efficacious and a dose of paclitaxel at 135 mg/m^{2}appears likewise efficacious as well. Clearly the incidence of neuropathy is less at this dose level for both drugs and is the primary consideration for recommending the dosage reduction for GOG-0212.[88]

2.3 Docetaxel

The SCOTROC study (Vasey, PA et al, Proceedings of ASCO, 2001 and 2002) compared carboplatin (AUC 5) combined with either docetaxel (DC) (75 mg/m^2/1 hr) or paclitaxel (PC) (175 mg/m^2/3 hr) in patients with newly diagnosed ovarian cancer. There were 1077 chemo-naive patients enrolled to this study between October-1998 and May-2000. The preliminary analyses indicate that these two regimens provide similar response rates (DC: 62% vs. PC: 66%) and progression-free survival. Myelosuppression was more severe on the docetaxel regimen, but this apparently did not compromise dose delivery or patient safety. However, the paclitaxel regimen produced much more grade 2 or more sensory neuropathy (DC: 10% vs. PC: 28%). The results from this study including an analysis of overall survival have recently been submitted for publication.

2.4 Targeting Angiogenesis with Taxanes

Angiogenesis is the biological process by which new blood vessels develop from established vasculature. The development of neovascular networks in tumors has been demonstrated to be a critical point in the development and spread of cancer.[15] Translational research studies have demonstrated that angiogenesis plays an important role in many types of cancers, including gynecologic cancers.[16] In ovarian cancer, active angiogenesis has been shown to be a marker of poor prognosis in both early and advanced stages.[17, 18] The inclusion of an inhibitor of angiogenesis into consolidation therapy may prevent growth of microscopic residual subclinical disease by preventing the switch to angiogenic tumor nodules and stimulating tumor dormancy. This would then be expected to translate to an increase in time to progression or recurrence that parallels the duration of the anti-angiogenic intervention. Taxanes are reasonable candidates to use in this setting based on their documented anti-angiogenic activity.[19, 20]

2.5 Markers of Angiogenesis

Angiogenesis in tumors has been studied by quantifying the tumor blood micro-vessel density (MVD) determined immunohistochemically using antibodies to CD31 or CD34, which are markers of vascular endothelial cells. MVD has been shown to predict the response of gastric adenocarcinomas to taxane-based therapy.[21]

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 addition to MVD, most angiogenesis studies also evaluate vascular endothelial growth factor (VEGF), which has been shown to promote neovascularization and stimulate endothelial cell survival.[22]

Circulating levels of VEGF in serum have been demonstrated to correlate with patient outcome in several types of cancer, including gynecologic.[23-28] VEGF levels were also found to correlate with MVD in endometrial and cervical, but not ovarian cancers.[29-31] In ovarian cancer, higher VEGF levels, but not MVD, were found to significantly correlate with decreased patient survival.[31] Multivariate analysis demonstrated that VEGF was an independent prognostic indicator of overall survival,[31] while the prognostic significance of MVD alone for ovarian cancer was less strong.[31,32] In endometrial cancer, univariate analysis found that VEGF significantly correlated with endometrial tumor characteristics and 10-year disease-free survival,[33] while both VEGF levels and MVD were found to correlate with advanced stage and metastases.[29] In cervical cancer, multivariate analysis found that MVD is an independent prognostic indicator of survival in stage IB,[34-37] and VEGF expression was found to be higher in adenocarcinoma than in squamous carcinoma.[30] In CIN, direct associations between MVD, VEGF and CD31 expression were observed with increasing grades of the lesions.[38] Progression of CIN to invasive cancer was found to correlate with VEGF expression and MVD.[34, 35] The human papillomavirus (HPV), which is a causative agent in cervical cancer, may contribute to tumor angiogenesis by direct stimulation of the VEGF gene.[39]

Another circulating cytokine, bFGF, is also elevated in patients with advanced cancer,[40] and appears to directly regulate tumor-associated vascular supply and cancer cell growth.[41,42] Angiogenin is also a potent mediator of neovascularization, which is likely secreted by both inflammatory cells and malignant cells within tumors.[43] Serum levels of this cytokine have been found to have a direct correlation with stage of disease in patients with endometrial[44] and cervical[45] carcinomas and an inverse correlation with prognosis in patients with pancreatic cancer.[46]

Angiogenesis is one of the cardinal processes leading to invasion and metastasis of solid tumors. The angiogenic-signaling pathway may be triggered by down-regulation of p53 function by E6, a regulatory protein encoded by HPV. Normally, p53 functions to inhibit angiogenesis by down-regulating the angiogenesis promoter vascular endothelial growth factor (VEGF), and up-regulating the angiogenesis inhibitor thrombospondin-1 (TSP-1). E6-mediated loss of p53 function may therefore be associated with a pro-angiogenic state. An immunohistochemistry (IHC) assay utilizing antibodies against VEGF or TSP-1 can be used to evaluate the level and localization of these soluble regulators of new blood vessel formation in tumor tissue. In addition, intratumoral angiogenesis may be evaluated through analysis of tumor vessel densities determined immunohistochemically using antibodies against CD31 or CD105 (endoglin). CD31 is a

protein expressed on the cell surface of endothelial cells and CD105 is a component of the TGF-beta-receptor complex that correlates with proliferation of tumor endothelial cells.[47]

In addition to known angiogenic cytokines, there is evidence implicating coagulation factors as biomarkers of angiogenesis. Cancer and its treatments are well-recognized risk factors for venous and arterial thromboembolism. Cancer patients are twice as likely to develop symptomatic thrombosis as other patients, with risk associated with tumor type, stage or extent of the cancer, and anti-neoplastic therapy. The pathophysiology of the pro-thrombotic state is thought to be related to tumor expression of tissue factor activity and proteases capable of activating coagulation factor X, as well as the host inflammatory response to the malignancy and treatment.[48, 49]

The protein C pathway is a primary regulator of coagulation and inflammation events.[50, 51] Protein C is activated on endothelial cells by the concerted activities of thrombin, thrombomodulin and the endothelial protein C receptor (EPCR). Activated protein C (APC) is a pleiotropic enzyme with multiple activities, including inactivation of critical coagulation cofactors, [50] enhancement of fibrinolysis,[52-54] inhibition of apoptosis,[55] and diminution of inflammatory responses by endothelium and monocytes.[56-59] Both the thrombomodulin and EPCR receptors are required for efficient protein C activation.[60] Normally, EPCR is expressed almost exclusively on endothelial cells and thrombomodulin expression is highest on the endothelial cells of the microvasculature.[61] EPCR is expressed in very high levels in endothelial cells and the placenta;[61,62] levels of the soluble receptor (see below) increase during pregnancy, probably due to shedding from the placenta.

Perhaps paradoxically, certain cancers also express increased levels of protein C pathway members, most notably thrombomodulin,[63-68] which may negatively influence tumor cell proliferation.[69] Two recent studies also demonstrate increased expression of EPCR on cancer cell lines and in some human tumor cells.[70,71] Over-expression of EPCR also was observed in adjacent endothelial vessels,[71] similar to that observed for thrombomodulin expression on vessels adjacent to gliomas.[72] The significance of these observations is not known with respect to either protein C pathway function or tumor survival and metastasis. Increased levels of a soluble form of thrombomodulin circulate in plasma in some cancer patients, attributable to endothelial damage by therapeutics.[73,74] A soluble form of EPCR (sEPCR) has been identified in plasma and serum using a patented and licensed ELISA assay for sEPCR.[75,76] These studies provide evidence to show that sEPCR levels report an endothelial response to injury, not just endothelial damage, because sEPCR levels respond to thrombin activity. As thrombin activity increases, sEPCR levels increase. In patients and normal volunteers, administration of warfarin reduces sEPCR levels and sEPCR levels return to pre-treatment levels after cessation of warfarin.[77] In a variety of healthy adults and patient populations, sEPCR levels are lower in women,[78] respond to anti-coagulant therapy (warfarin, heparin)[77] and are quite high in about 20-25% of a normal adult population (bimodal distribution).[78]

2.6 Rationale for Banking Whole Blood for Research**(03/30/09)**

The National Cancer Institute is encouraging Cooperative Clinical Trial Groups including the Gynecologic Oncology Group to bank whole blood from women participating in clinical trials such that the blood specimens will be linked to clinical outcome data (progression-free survival, overall survival, response and adverse effects) and information regarding treatment. The purpose of this effort is to support research including pharmacogenomic and pharmacogenetic research.

Women who are candidates for this clinical trial or who have already been enrolled on GOG-0212 will be asked to give permission for 10 ml of their blood to be collect for this research study and for future research. No matter what the women decide to do, it will not affect their care. The women can still participate in this GOG study even if they do not allow their blood to be collected and used for this research study and/or for future research. Women already enrolled on GOG-0212 will need to be re-consented for this collection.

2.7 Single nucleotide polymorphisms (SNPs) and SNP profiling**(03/30/09)**

It is well known that individual single nucleotide polymorphisms (SNPs) and SNP profilesare associated with many clinical aspects of cancer. This includes risk of developing invasive cancer, risk of recurrence of cancer, patient survival and chemotherapy toxicity. We propose to use genome wide SNP-association studies and individual SNP analyses to identify SNPs which correlate with a variety of clinical measures including but not limited to patient survival, recurrence of disease, response, and toxicity.

2.8 Quality of Life Rationale:

This trial will help determine whether the consolidation/maintenance strategy is associated with improved overall survival, and will enable comparison of two taxane maintenance strategies to be compared to observation. Patient-reported outcomes may differ between active consolidation versus observation, and even within active consolidation options if toxicities differ. When comparing active consolidation therapy for 12 cycles to observation, the critical issue to consider is the potential benefit of continued treatment on recurrence-free survival or overall survival and their associated patient-reported benefits, versus the drawbacks of toxicity. In a similarly designed study of metastatic breast cancer patients, [79] investigators found that observation with a plan to re-institute CMF chemotherapy upon recurrence led to worse quality of life compared to those patients treated continuously. Socinski and colleagues, studying a similar question in lung cancer using carboplatin and paclitaxel, found no difference in QOL between patients treated with four cycles of therapy and then followed for progression, versus patients treated until progression.[80] However, in fact despite schedule differences prescribed by protocol, there was no difference in actual length of treatment, as most patients progressed or otherwise came off therapy within four cycles. To our knowledge, this important question of treating with a consolidation strategy versus observation has not been asked from the QOL perspective in ovarian cancer, and available data from other tumor types, while limited, supports the hypothesis that consolidation, by virtue of extending time to progression, will be associated with better patient report of the physical dimensions of health-related quality of life. To address this, we propose use of the Trial Outcome Index of the Functional Assessment of

Cancer Therapy-Ovary (FACT-O TOI) .[81,82,84] 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.

When comparing consolidation therapy with paclitaxel to consolidation therapy with CT-2103, the critical issue relates to differences in toxicity. If, as expected, the patient-experienced toxicities are less with CT-2103, this should be detected indirectly with the FACT-O TOI endpoint. However, because of a specific interest in the concerns with peripheral neuropathy due to chronic administration of taxane (and platinum-based) therapy, we will add to the FACT-O TOI the FACT/GOG-Neurotoxicity scale which has been tested in the GOG on several thousand patients and has been found to be sensitive to developing peripheral neuropathy.[83-85] Although we will administer the complete 11-item scale, a 4-item subset will be used as the primary neurotoxicity endpoint and the main patient-reported endpoint to address the comparison between CT-2103 and paclitaxel treatments.

2.9 Inclusion of Women and Minorities

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

3.0 PATIENT ELIGIBILITY

3.1 Eligibility Criteria **(08/10/09)**

3.11 Patients with a histologic diagnosis of primary peritoneal carcinoma, or Stage III or IV epithelial ovarian or fallopian tube carcinoma, ,with either optimal (≤ 1 cm residual disease) or suboptimal residual disease following initial surgery. All patients must have had appropriate surgery for ovarian, primary peritoneal or fallopian tube carcinoma with appropriate tissue available for histologic evaluation to confirm diagnosis and stage.

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 N.O.S.

3.13 Patients must have completed treatment within the past 12 weeks with at least 5 cycles and not more than 8 cycles of a platinum (IV or IP) and paclitaxel or docetaxel-based combination chemotherapy and have no symptoms suggestive of persistent cancer, normal (no evidence of cancer) CT scan of the abdomen/pelvis and normal CA-125 following this therapy. **(09/30/05) (02/06/06)(07/18/11)**

3.131 Patients treated with neo-adjuvant platinum-taxane chemotherapy for a presumptive diagnosis of stage III or IV epithelial ovarian, primary peritoneal or, fallopian tube (by paracentesis, percutaneous biopsy or open biopsy) are eligible provided that they have undergone interval abdominal surgery after at least one but no more than six cycles of standard chemotherapy as defined in section 3.13. Such surgery must meet the same criteria as for those undergoing up front surgery, including tissue diagnosis for confirmation of primary tumor site and Stage III or IV disease. Also, patients must have received at least two cycles after interval abdominal surgery. **(08/27/07)**

3.14 Patients must have adequate: **(09/30/05)**

3.141 Bone marrow function: Absolute neutrophil count (ANC) greater than or equal to 1,500/ul, equivalent to Common Toxicity Criteria (CTCAE v3.0) grade 1. Platelets greater than or equal to 100,000/ul.

3.142 Renal function: creatinine less than or equal to 1.5 x institutional upper limit normal (ULN), CTCAE v3.0 grade 1.

3.143 Hepatic function: Bilirubin less than or equal to 1.5 x ULN (CTCAE v3.0 grade 1). SGOT and alkaline phosphatase less than or equal to 2.5 x ULN (CTCAE v3.0 grade 1).

3.144 Neurologic function: Neuropathy (sensory and motor) less than or equal to CTCAE v3.0 grade 1.

3.15 Patients must have a GOG Performance Status of 0, 1, or 2.

3.16 Patients must have signed an approved informed consent and HIPAA authorization.

3.17 Patients must complete pre-entry assessments as outlined in section 7.0.

3.2 Ineligible Patients **(08/10/09) (10/04/10)**

3.21 Patients with a current diagnosis of epithelial ovarian or fallopian tube tumor of low malignant potential (LMP) (Borderline carcinomas) are not eligible. Patients with a prior diagnosis of a low malignant potential tumor that was surgically resected and who subsequently develop invasive adenocarcinoma are eligible, provided that they have not received prior chemotherapy for their ovarian LMP tumor.

3.22 Germ cell tumors, sex cord-stromal tumors, carcinosarcomas, mixed mullerian tumors or carcinosarcomas, metastatic carcinomas from other sites to the ovary and low malignant potential tumors including so called micropapillary serous carcinomas are not eligible.

3.23 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 3 years prior to registration, and the patient remains free of recurrent or metastatic disease.

3.24 Patients who have received investigational therapies, and/or biological therapies (i.e. Bevacizumab or Erlotinib) for their epithelial ovarian, primary peritoneal or fallopian tube cancers or for any other abdominal or pelvic tumor, are ***not*** excluded. However, biologics cannot be continued concurrent with the GOG-012 maintenance treatment (or observation). Patients who have received prior chemotherapy for any other abdominal or pelvic tumor (except as noted above) are excluded. Patients may have received prior adjuvant chemotherapy for localized breast cancer, provided that it was completed more than 3 years prior to registration, and that the patient remains free of recurrent or metastatic disease. (08/10/09)**(07/18/11)**

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:

3.251 Stage not greater than I-B

3.252 Less than 3 mm invasion without vascular or lymphatic invasion

3.253 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 5 years or whose previous cancer treatment contraindicates this protocol therapy are excluded.

3.27 Patients with acute hepatitis, or known chronic hepatitis.

3.28 Patients with an active infection that requires antibiotics.

3.29 Patients with ongoing gastrointestinal bleeding requiring blood product support.

3.30 Patients whose circumstances at the time of entry onto the protocol would not permit completion of study or required follow-up.

3.31 Patients with unstable angina or those who have had a myocardial infarction within the past six months. Patients with evidence of abnormal cardiac conduction (e.g. bundle branch block, heart block) are eligible if their disease has been stable for the past six months.

3.31 Patients are excluded who have had prior therapy with CT-2103.

3.32 Patients with active bleeding or an unexplained PT or PTT > institutional upper limit normal (ULN).

3.33 Patients who are pregnant or nursing are excluded; patients who may become pregnant must practice an effective method of birth control.

4.0 STUDY MODALITIES

4.1 CT-2103 (IND Sponsor: GOG IND #70177) (09/30/05)(03/30/09)

4.11 Physical and Chemical Description: CT-2103 drug substance is the ester conjugate of α-poly (L-glutamic acid) (PGA) and paclitaxel bound at the 2′hydroxy site on paclitaxel. The apparent average molecular weight of CT-2103 is approximately 40,000 Daltonsand the base PGA polymer is approximately 17,000 Daltons (apparent average molecular weight as determined by aqueous gel permeation chromatography with detection by multi angle laser light scattering). Paclitaxel is present in the bound form at approximately 35% by weight in the conjugate, equivalent to about one paclitaxel ester linkage per 11 monomer units of the polymer. The drug substance is a white to off-white amorphous powder. The pKa is approximately 4.5. CT-2103 is soluble in 0.10 M Na_2HPO_4, 0.26 M phosphate buffer, 0.10 M NaOH, and ethanol; freely soluble in dimethylsulfoxide, and dimethylformamide; sparingly soluble in methanol; and practically insoluble in 0.1 M HCl, acetonitrile, and ether.

CT-2103 for Injection is supplied as a white to off-white lyophilized cake containing 94 mg paclitaxel as an ester conjugate of α-poly(L-glutamic acid) in a 20 mL clear, glass, stoppered, single-use vial with a flip-off seal. Each vial contains:

Active ingredient: Approximately 269 mg paclitaxel poliglumex (9 mg/mL conjugated paclitaxel when reconstituted)

Inactive ingredients:50 mg Poloxamer 188201 mg dibasic sodium phosphate, anhydrous162 mg monobasic sodium phosphate, monohydrate

Unopened vials of CT-2103 are to be stored protected from light in a refrigerator at 2 to 8°C (36 to 46°F). Stability testing is being performed to support the use of the drug product for a minimum of 24 months after the date of manufacture.**(09/30/05)**

4.12 Directions for Reconstitution and Dilution: CT-2103 must be reconstituted and diluted before administration. The formulation has no preservative and is intended for single use only; infusion solutions should be prepared and transferred using aseptic technique in a biological safety cabinet.

Reconstitution to a solution containing 9 mg/mL conjugated paclitaxel should be accomplished by quickly adding 10 mL Sterile Water for Injection to the vial, directing the stream at and wetting the entire cake, followed by swirling to disperse the water throughout the cake, and agitating until the contents are fully dissolved. Once the diluent has been added to a vial of lyophilized product, the contents should be swirled *immediately* to disperse the water throughout the cake. In the event that more than one vial of CT-2103 will be reconstituted, the procedure for product reconstitution should be followed through the initial

mixing for each vial individually. The only diluent to be used to reconstitute the product is 10 mL Sterile Water for Injection. Reconstituted CT-2103 solutions are stable for 4 hours at room temperature and for 24 hours when refrigerated at 2°C to 8°C.

The reconstituted solution should be a clear, colorless solution. The solution and any foam should be inspected carefully to confirm the absence of visible particulates. This is best accomplished by holding the vial at an angle under a fluorescent light and inspecting the contents from the bottom end up.

The required volume of 9 mg/mL solution to produce the appropriate dose per square meter of body surface area is to be withdrawn (excluding any foam) and transferred to a sterile polyolefin-based plastic IV bag(polyethylene or copolymer ofethylene and propylene) or PVC plastic IV bag containing 100 mL sterile 5% Dextrose Injection in water (D5W), 0.9% (w/v) sodium chloride for injection, or lactated Ringer's solution.Do not withdraw diluent to make room for the reconstituted CT-2103; the entire 100 mL of solution should be used. Reconstituted and diluted drug solutions (0.9 mg conjugated paclitaxel/mL) in the IV bag are stable for 24 hours refrigerated at 2°C to 8°C or at room temperature.

4.13 Administration :**(03/10/08)**(10/04/10)

CT-2103 contains paclitaxel, and hypersensitivity reactions have been observed in some patients treated to date. Injectable steroids, antihistamines and epinephrine should be immediately available to provide prompt treatment of any hypersensitivity reactions that may occur during or following study treatment.

The diluted solution should be administered with a non-PVC administration set or a PVC administration set as a 10 minuteinfusion. A 0.2 μm pore-size filter(polyethersulfone, cellulose acetate or acrylic membrane)should be used in the administration set.The infusion may take longer due to individual patient considerations. The infusion may be administered using gravity feed or an IV infusion pump which is compatible with the recommended infusion sets.

A central line is not required for administration ofCT-2103, which may be given via a peripheral vein; however, if the patient has a central line in place, drug may be administered via that central line. Patients should not be discharged from the clinic until vital signs are stable.

4.131 Antiemetic Regimens

The following representative antiemetic regimens are suggested:

- Ondansetron 8-32 mg IV 30 minutes prior to administration of chemotherapy and dexamethasone 10-20 mg IV 30 minutes prior to drug administration or,

- Granisetron 10 mcg/kg IV (or 2 mg PO) 30 minutes prior to chemotherapy, with or without lorazepam 0.5-2.0 mg IV 30 minutes prior to chemotherapy.

4.132 Maximum body surface area used for dose calculations will be 2.0 m^2 as per GOG Protocol Procedures Manual.

4.14 Adverse Effects Associated with CT-2103: **(10/04/10) (08/19/13)**

More than 1500 patients have been treated with CT-2103 in phase I to III studies. Almost all reported serious adverse events were disease-related. The most common toxicities related to the administration of CT-2103 as a single-agent (occurringin ≥ 10% of patientswere nausea (24.5%), fatigue (19.8%), neutropenia (18.2%), peripheral sensory neuropathy (12.6%), vomiting (12.4%), anemia (11.6%), peripheral neuropathy (10.4%), and anorexia (10.2%). No grade 3 or 4 treatment-related AEs occurred in ≥ 10% of patients. Grade 3 neutropenia (6.3%) and grade 4 neutropenia (6.4%) were the only treatment-related grade 3 or 4 AEs reported in ≥ 5% of patients.

Alopecia is infrequent and no complete hair loss has been observed.

Neuropathy: In heavily pretreated patients peripheral neuropathy appears to be dose-limiting after repeated cycles. Prior taxane use and the number of cycles of drug are associated with an increased risk of neuropathy. Neuropathy was reported at a higher frequency in the breast and ovarian cancer studies than in other phase I and II studies and is probably related to prior exposure to neurotoxic agents. Patients must be carefully monitored for the presence of neuropathy and dose modification and discontinuation criteria in protocols should be carefully followed.

Neutropenia may occur, especially at higher doses. The neutrophil nadir occurs on days 7-15 and should be monitored carefully during these times.

Hypersensitivity reactions have been observed infrequently; when they occur, they are usually mild to moderate reactions that are easily controlled with routine medications.

It is not clear whether there are any predisposing factors (such as prior exposure to taxanes or prior hypersensitivity reactions to taxanes) that could predict the occurrence of these events. Female patients who have received prior chemotherapy (of any type) and who have received ≥ 4 cycles of CT-2103 may have a slightly higher rate of reactions. The clinical relevance of this observation is unclear as several of the reactions occurred in one investigator sponsored trial in patients with metastatic breast cancer.

As with any chemotherapy agent, hypersensitivity reactions can be life-threatening and caution should be exercised when treating a patient.

Routine premedication to prevent hypersensitivity reactions, nausea and vomiting is not routinely employed in CT-2103 trials and should be left to the investigator's discretion. Patients who experience hypersensitivity reactions may

continue receiving CT-2103 at the investigator's discretion, but must receive standard premedication in accordance with institutional practices before each subsequent treatment. Beginning with cycle 4 administration, if systemic signs or symptoms (grade 1-2), such as nausea, vomiting, dizziness, chest pain, shortness of breath or flushing develop, the infusion should be interrupted until the symptoms are treated and fully resolved. If any of the symptoms are severe (grade 3 or 4), treatment should be discontinued. (10/25/06)

Baseline Laboratory Findings: CT-2103 is a long-acting taxane whose active ingredient is paclitaxel, and its metabolism may be prolonged in the face of hepatic or biliary dysfunction. Patients with baseline bilirubin ≥1.5 x ULN (NCI CTC grade 2 or greater) should not receive CT-2103. Patients with transaminase (AST and ALT) ≥ 2.5 x ULN (CTC Grade 1) should not receive CT-2103 unless liver metastases are present, in which case a patient should not have AST and ALT >5 x ULN (CTC Grade 2). Patients with alkaline phosphatase > 2.5 x ULN should not receive CT-2103 unless a bone origin of the alkaline phosphatase is documented. Elevations in AST and ALT have been observed with CT-2103. These elevations are generally low grade, transient, and resolve without clinical sequelae.

Potential Anticoagulation Interaction: Paclitaxel, the active moiety of CT-2103, is primarily metabolized by CYP2C8 and C3A4 enzymes, drugs that are substrates or inhibitors of these enzymes (e.g., warfarin, ketoconazole) should be given to patients with caution. Warfarin is one such drug; the concomitant administration of CT-2103 and warfarin could result in a more pronounced anticoagulant effect. Routine coagulation parameters such as prothrombin time (PT), international normalized ratio (INR), and aPTT should be assessed in all patients before beginning treatment with CT-2103. Patients who are on anticoagulation therapies such as warfarin, should have careful monitoring, as the dose of warfarin may need to be adjusted. Routine monitoring of coagulation parameters after CT-2103 dosing in patients who are not receiving anticoagulant therapy is not required.

Studies on the procoagulant inhibitory properties of CT-2103 suggest that for the first 48 hours after infusion with CT-2103, results of standard laboratory measurements of coagulation may be prolonged. Current data suggest that CT-2103 is a non-competitive inhibitor of Factor Xa and thrombin. In randomized, comparator phase III trials, no pattern of increased bleeding was observed during this time period.

Patients on anticoagulation therapy or patients with abnormal PT or aPTT should be carefully monitored. Caution should be exercised in patients who undergo surgery or experience significant trauma, particularly head trauma, within 48 hours after dosing with CT-2103.

Please reference the CT-2103 Investigator Brochure for complete information regarding adverse effects of the drug.

4.141 Investigator Brochure:**(09/30/05)**
To obtain an Investigator Brochure, please e-mail requests to **gog0212ib@gog.org**. Please provide in the request, the name of

Institution, name of requester and contact information (address, phone number and e-mail address). Once this information is received, GOG will distribute the IB and a Signature Acknowledgement Receipt Letter.

4.15 Supplier: Cell Therapeutics, Inc., Seattle, WA

4.16 IND Sponsor: GOG-IND# 70177**(09/30/05)(05/10/10)**

4.161 Industry Contact:
Archana Sah
Cell Therapeutics, Inc.
501 Elliott Ave West, Suite 400
Seattle, WA98119
(206) 272-4659
asah@ctiseattle.com

Sponsor Medical Liaison:
Jack Singer, MD
Cell Therapeutics, Inc.
501 Elliott Ave. West, Suite 400
Seattle, WA98119
(206) 272-4405

4.17 Drug Distribution: CT-2103 will be distributed by **CTI**. CTI requires a minimum of up to 5 working days advanced notification for shipping drug. Please refer to the Study Drug Information Packet (see the regulatory forms link to download) for drug distribution procedures for initial and subsequent shipments. The initial and subsequent drug request forms are available in the regulatory forms link. NOTE: Initial drug shipment requests are made through the GOG, and subsequent request for shipments should be sent directly to CTI**. (03/10/08)**

4.18 Precautions in Handling: Standard institutional procedures for handling investigational antineoplastic agents should be followed. The eye and skin irritation, mutagenic, carcinogenic, and teratogenic potentials of CT-2103 have not been studied.

In rabbits, CT-2103 caused minimal to mild concentration-dependent irritation when administered intravenously, perivenously, or subcutaneously. In the case of extravasation during IV infusion, institutional practice should be followed. Spills of either the drug product or the diluted solutions can be washed with warm soapy water and the cleaning materials disposed of according to local, state, and federal regulations

4.19 Drug Accountability: All study drugs must be accounted for during the course of this study. Sites must maintain a NCI accountability log (or an accountability form containing the equivalent information at a minimum).

4.20 Drug Return: Please download the "Study Drug Information Packet" from the regulatory forms link for information regarding CT-2103 return. **(08/27/07) (03/10/08)**

4.2 Paclitaxel (NSC #673089)

4.21 Formulation: Paclitaxel is a poorly soluble plant product from the western yew, Taxus brevifolia. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water.

4.22 Supplier/How Supplied: Commercially available from Bristol-Myers Oncology. A sterile solution concentrate, 6 mg/ml, in 5 ml vials (30 mg/vial) or 17 ml vials (100 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use.

4.23 Solution Preparation: Paclitaxel, at the appropriate dose, will be diluted in 500-1000 cc of 0.9% Sodium Chloride injection, USP or 5% Dextrose injection, USP (D_5W) (500 cc's is adequate if paclitaxel is a single agent). Paclitaxel must be prepared in glass, polypropylene, or polyolefin containers and non-PVC-containing (nitroglycerin) infusion sets should be used. A small number of fibers (within acceptable limits established by the USP) have been observed after dilution. Solutions exhibiting excessive particulate formation should not be used.

NOTE: Formation of a small number of fibers in solution (within acceptable limits established by the USP Particulate Matter Test for LVPs) have been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: IVEX-II, IVEX-HP or equivalent) into the IV fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

4.24 Storage: The intact vials should be stored between 2-25°C (36-77°F).

4.25 Stability: Commercially available paclitaxel will be labeled with an expiration date. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

4.26 Intravenous Administration of Paclitaxel: Paclitaxel, at the appropriate dose and dilution, will be given as a 3-hour continuous IV infusion. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the IV administration sets (polyethylene or polyolefin) which are used to infuse parenteral Nitroglycerin. Nothing else other than 0.9% sodium chloride is to be infused through the line where paclitaxel is being administered.

4.27 Adverse Effects:

Hematologic: Myelosuppression
Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis
Heart: Arrhythmia, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia
Pulmonary: Pneumonitis
Blood Pressure: Hypotension, hypertension (possibly related to concomitant medication--Dexamethasone)
Neurologic: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy
Skin: Infiltration: erythema, induration, tenderness, rarely ulceration, radiation-recall reactions, erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)
Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus
Liver: Increased SGOT, SGPT, bilirubin and alkaline phosphatase, hepatic failure, hepatic necrosis
Other: Alopecia, fatigue, arthralgia, myalgia, light-headedness, myopathy
Other, Vision: Sensation of flashing lights, blurred vision, scintillating scotomata
Note: See FDA- Approved Package Insert for a comprehensive list of adverse events associated with paclitaxel.

4.3 Specimen Requirements and Laboratory Testing

A summary of the specimen requirements and laboratory testing for this protocol is provided in Section 7.2.

5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE **(09/30/05) (08/27/07)(03/10/08)**

Before patient entries will be accepted, submit the following documents to the GOG Administrative Office via mail **(Attn: Regulatory Department, Protocol GOG-0212)**:

- IRB approval*
- IRB-approved informed consent
- IRB Membership list or FWA assurance letter
- Study-specific signed original FDA Form 1572 for institution PI**
- Current CV (signed and dated within one year) for institution PI and all sub-investigators listed on FDA Form 1572
- Medical license for institution PI and sub-investigators listed on the FDA Form 1572
- Lab license, certificates, and required Normal Lab Values (NLV) for labs listed on FDA Form 1572
- Signed original GOG Investigator Signature Page for PI**
- Signed original GOG Financial Disclosure Form for all investigators listed on FDA Form 1572**
- Initial Study Drug Request Form**

Please allow 7-10 days for processing of regulatory documents before screening the first patient. All copies of the above should be filed into a study-specific regulatory binder at your institution.

* When submitting the IRB approval to the GOG, the CTSU IRB Certification Form must be used (form can be downloaded at www.ctsu.org). All initial, continuing and amendment reviews must be sent to the GOG Administrative Office.

** Please see GOG-0212 protocol documentation page to download forms by clicking on the "Regulatory Forms" link.

The GOG Administrative Office will receive, review, and approve all regulatory documents. The GOG will notify CTI of institution approval for drug shipment (See Section 4.17 for drug distribution procedures). **All regulatory documents must be approved before patient entries can be accepted onto the study.**

5.1 Registration

When a suitable candidate has been obtained for protocol entry, the following steps should be taken:

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

5.12 All eligibility requirements indicated in 3.0 must be satisfied.

5.13 The Fast Fact Sheet data for this protocol must be gathered.

5.14 The institution must register the patient using the web-based registration application or by phone.

5.141 Instructions for web-based registration can be found on the GOG Web menu page. Select "Start/finish a patient registration" then select "Directions" found on the left side of the page. **(09/30/05)**

5.142 Alternatively, patient registration can take place by phoning the GOG Statistical and DataCenter at: 1-800-523-2917, Monday through Friday, 9 a.m. to 5 p.m. EST/EDT. Entry/Randomization will take place on the telephone after consideration of Fast Fact Sheet data.

5.15 The institution must enter the patient's name, and GOG patient study ID, in the appropriate place in their Log Book to verify the patient's entry.

5.2 Treatment Plan

5.21 Drug-specific plan: Eligible patients will be randomized equally to one of the following treatment arms:

Regimen I: CT-2103 (135 mg/m^2 over 10-20 minutes) q-28 days x 12

Versus

Regimen II: Paclitaxel (135 mg/m^2 over 3 hours) q 28-days x 12

Versus

Regimen III: No anti-cancer treatment until evidence of disease progression.

Submit monthly D2R and T forms to include required CA-125 value and pertinent history/physical information. For Regimen III the cycle number should equal the number of months since registration (i.e. Third months Surveillance equals cycle 3).

The randomization will be stratified by the following factors:

1. Disease stage (stage III vs. IV)
2. Presence of macroscopic disease following initial debulking surgery (yes vs. no)
3. Prior taxane treatment (induction regimen included docetaxel or paclitaxel only)
4. Route of prior platinum treatment (intraperitoneal vs. intravenous) **(09/30/05)**

5.22 Preparative Regimen for Paclitaxel

Paclitaxel will be administered as a 3-hour infusion on this study. It is recommended that a preparative regimen be employed to reduce the risk associated with hypersensitivity reactions. This regimen should include dexamethasone (either IV or PO), anti-histamine H1 (such as diphenhydramine) and anti-histamine H2 (such as cimetidine, ranitidine, or famotidine).

5.23 Initiation of "consolidation/maintenance" therapy **(09/30/05) (10/12/05) (02/06/06)**

Starting no more than 12 weeks after the final cycle of primary platinum/taxane chemotherapy, patients meeting the eligibility criteria (described in Section 3.1) will receive either (a) single agent CT-2103 once each month (q-28 days) for 12 months (Regimen I) or (b) single agent paclitaxel (Regimen II) or (c) no further treatment until progression (Regimen III).

5.3 Specimen Requirements and Laboratory Testing

A summary of the specimen requirements and laboratory testing for this protocol is provided in Section 7.2.

6.0 TREATMENT MODIFICATIONS**(09/30/05)**

Study Drug	**2 Level reduction**	**1 Level reduction**	**Initial dose level**
Paclitaxel	80 mg/m^2	100 mg/m^2	135 mg/m^2
CT-2013	80 mg/m^2	100 mg/m^2	135 mg/m^2

6.1 Hematologic toxicity

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

6.111 Patients will NOT receive prophylactic growth factors [filgrastim (G-CSF), sargramostim (GM-CSF), pegfilgrastim (Neulasta)] unless they experience recurrent neutropenic complications after treatment modifications specified below.

6.112 Patients may receive erythropoietin for management of anemia AFTER documentation of hemoglobin less than 10 g/dl (CTCAE v3.0 grade 2). **(09/30/05)**

6.113 Patients may NOT receive amifostine or other protective reagents.

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

6.13 Subsequent cycles of therapy will not begin until the ANC is ≥ 1500 cells/mm^3 (CTCAE v3.0grade 1) and the platelet count is ≥ 100,000/ul. Therapy will be delayed for a maximum of two weeks until these values are achieved. Patients who fail to recover adequate counts within a two-week delay will be removed from study but follow up will continue. **(09/30/05)**

6.14 For first occurrence of febrile neutropenia, and/or documented grade 4 neutropenia persisting ≥ 7 days, reduce chemotherapy by one dose level on subsequent cycles.

6.15 For recurrent febrile neutropenia, and/or recurrent documented grade 4 neutropenia persisting ≥ 7 days (after initial dose reduction), add prophylactic growth factors. In this circumstance, it is recommended that G-CSF at a dose of 5 μg/kg/day (or equivalent dosing of pegfilgrastim or sargramostim) will be administered subcutaneously starting the day after the last dose of chemotherapy (normally day 13) and continuing through hematopoietic recovery. Growth factors should not be used within 72 hours of a subsequent dose of chemotherapy.

6.16 Patients with grade 4 thrombocytopenia will have a 1 level dose reduction.

6.17 There will be no dose modifications on the basis of uncomplicated granulocyte nadirs lasting less than 7 days.

6.2 Non-hematologic toxicity

6.21 Development of persistent (2 weeks beyond dosing date) grade 1 peripheral neuropathy requires reduction of one dose level in subsequent therapy until recovery to grade 0. Grade 2 peripheral neuropathy requires reduction of one dose level in subsequent therapy until recovered to grade 1 and may not be re-escalated. Patients with persistent grade 3 peripheral neuropathy should be taken off treatment.

6.22 Grade 2 (or greater) renal toxicity requires reduction of one dose level and delay in subsequent therapy for a maximum of 2 weeks until recovered to grade 1.

6.23 Grade 3 (or greater) elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin requires reduction of one dose level and delay in subsequent therapy for a maximum of 2 weeks until recovered to grade 1.

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

6.25 It is expected that patients with nausea, emesis, diarrhea, or constipation will receive appropriate medical management without dose modification. However, patients with persistent (greater than 24 hours) grade 3 (or greater) toxicity in spite of optimal medical management require reduction of one dose level and delay in subsequent therapy for a maximum of 2 weeks until recovered to grade 1.

6.26 Other non-hematologic toxicities with an impact on organ function of Grade 2 (or greater) require reduction of one dose level and delay in subsequent therapy for a maximum of 2 weeks until recovered to grade 1, or pre therapy baseline.

6.3 Dose escalations

There will be no dose escalations or re-escalations on this study.

7.0 STUDY PARAMETERS & SERIAL OBSERVATIONS

7.1 Observations and Tests **(09/30/05) (10/04/10)(08/19/13) (09/30/13)**

The following observations and tests are to be performed and recorded on the appropriate form(s). **Specimen requirements are summarized in Section 7.2.**

	During Treatment			**Yearly Post Treatment**
Tests and Observations	**Prior to Study**	**Nadir (8-12 days)**	**Prior to Each Course or Monthly During 1st year**	**q 3 Months for 2 years & q 6 months for 10 years**
History	5		6	X
Physical Exam	5		6	X
CBC & Differential	3	X	4	1
Platelets	3	X	4	1
Serum Creatinine	3		4	1
Bilirubin, SGOT, Alkaline Phosphatase	3		4	1
CA-125	3		6	10
Negative serum pregnancy test in women of child-bearing potential	3			
Chest X-Ray	5		1	1
EKG	2			
Coagulation Profile (PT, PTT, INR)	3		8	
CT scan of abdomen/pelvis	5		6	6
Quality of Life (FACT-OTOI/, GOG-NTX), coversheet	X		7	7
Subsequent regimens				9

1. When clinically indicated.
2. Baseline EKG required within 28 days prior to initiating protocol therapy.
3. Must be obtained within 14 days prior to initiating protocol therapy.
4. Must be obtained within 4 days of re-treatment with protocol therapy.
5. Must be obtained within 28 days prior to initiating protocol therapy. Not required if CT or MRI of chest already performed at pre-treatment baseline.**(08/10/09)**
6. History, physical exam and CA-125 are assessed prior to each cycle of treatment or monthly during the first year for those randomized to the surveillance arm or those removed from study treatment prior to disease progression. Patients with symptomatic changes or progressing disease based on rising CA-125 must have a CT scan of the abdomen and pelvis performed.
7. Quality of Life will be assessed with the FACT-OTOI/GOG-NTX at Baseline (prior to randomization), and again prior to course 3 (2 months), course 5 (4 months), course 7 (6 months), end of treatment (11-12 months), and one year post completion of consolidation (2 years for all patients). Times in parentheses are included for patients on the observation arm, and for all patients who discontinue protocol therapy for any reason, including those who go on to other therapies. That is, all living patients should be followed 6 times (baseline and five follow up evaluations) for QOL for two years regardless of treatment or disease status.
8. Obtain weekly and at the end of study visit only in patients with baseline abnormal coagulation parameters or patients who are on anti-coagulant treatment

9. For those patients who progress on study and are placed on second or subsequent chemotherapy regimen(s), CA-125 values and list of drug(s) are to be collected during the post-study treatment period until allchemotherapy is terminated. Any CT scan results done following the first progression of disease are to be reported.
10. CA-125 measurements will be obtained every 3 months for 2 years, every 6 months for a total of 12 years.

7.2 Translational Research **(03/30/09)**

7.21 Specimen Requirements

Please see below for a summary of the specimen requirements for GOG-0212if the patient gives permission for her tumor if available from a previous surgery and some of her blood to be submitted to the GOG Tissue Bank for research. Refer to Appendix II for a description of the Specimen Procedures for this protocol, including instructions for obtaining a GOG Bank ID, submitting SP Forms as well as preparing, shipping, banking and distributing the GOG-0212 specimens.**The banking of whole blood for future research will apply to all of the patients who provide consent regardless of randomization and treatment including those already enrolled on GOG-0212.**

Quick Scan Summary of the Specimen Requirements for GOG-0212.

Required Specimens (Specimen Codes)[1]	**Form SP Label in Forms Tracking System**[2]	**Collection Time Points and Requirements** *	**Deadlines and Recommendations**[2]
Archival Formalin-Fixed and Paraffin-Embedded (FFPE) PrimaryTumor (FP01):[3] block or 20 unstained sections (FP01)	SP-FP01-0212	Tumor from a previous surgery.	Ship FP01 to the GOG Tissue Bank using your own shipping container via US Postal Mail at your own expense within 8 weeks of study entry. [3] Form SP for FP01 must be submitted to the GOG Statistical and Data Center (SDC) online using the SDC Electronic Data Entry System (SEDES) within 8 weeks of study entry.
Pre-Cycle Serum (SB01) with Platelet Count [4]	SP-SB01-0212	Collect prior to starting cycle 1 of therapy for Regimen I (CT-2103) or II (paclitaxel), or within 1 week of study enrollment for Regimen III (no treatment).	**Ship SB01 and SB02 together to the GOG Tissue Bank when possible.**[4] Submit a copy of Form SP for SB01 to SDC within 12 weeks of study enrollment to allow two serum specimens to be shipped to the Bank.
Pre-Cycle 2 Serum (SB02) with Platelet Count [4]	SP-SB02-0212	Collected prior to starting cycle 2 of therapy for Regimen I (CT-2103) or II (paclitaxel), or 4-6 weeks after study enrollment for Regimen III (no treatment).	
Whole Blood (WB01) [5] **to extract DNA for SNP analysis** - draw 10 ml of blood into a standard purple-top Vacutainer® tube with EDTA Whole Blood (WB01)[5]	SP-WB01-0212	Collect prior to or after starting treatment on this phase III trial or at any time during follow up. Collect on a Monday through Friday schedule. **Do not collect this blood the day before a holiday**	**Ship WB01 to the GOG Tissue Bank in Columbus, OHthe day the blood is drawn**.[5] Form SP for WB01 must be submitted to the SDC online using SEDES the day the blood is collected.

* If the patient gives permission for some of her tumor if available from a previous surgery or biopsy and some of her blood to be submitted to the GOG Tissue Bank for this research.

[1] Label each specimen with the protocol number (GOG-0212), a GOG Bank ID (# # # # - # # – G # # #), a specimen code (see above) and the collection date (mm/dd/yyyy).

[2] Please complete Form SP for EACH specimen and include a copy when the specimen is submitted to the GOG Tissue Bank as described in Appendix II.

[3] The block or 20 unstained slides of primary tumor (FP01) must be shipped to the GOG Tissue Bank in your own shipping container using the US Postal Service at your expense. GOG Tissue Bank / Protocol GOG-0212, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, E-mail: gogbank@nationwidechildrens.org.Refer to Section IV and Section VIII in Appendix II for important instructions for preparing and shipping the archival FFPE primary tumor specimens to the GOG Tissue Bank for GOG-0212.In the event that it is not possible to submit the archival FFPE tumor specimen, submit the SP form via SEDES with the reason the specimen was not collected in item 5 (e.g., patient refused, not enough tumor for research, referring site won't release tumor).

[4] Two serum specimens for GOG-0212 **MUST** be shipped to the GOG Tissue Bank (address provided above) with a completed SP Form for SB01 and SB02. Twofrozen serum specimens can be shipped in a Single-Chamber Specimen Kit with excess dry ice on a Monday through Thursday schedule for Tuesday through Friday delivery using the GOG Tissue Bank's Federal Express Account Number (1290-2562-0). If your institution does not have access to approved ultra-cold storage conditions for the frozen serum, you will not be able to batch the pre-cycle 1 and pre-cycle 2 serum specimens into one Single-Chamber Specimen Kit but instead will need to ship the pre-cycle 1 or the pre-cycle 2 serum in separate Single-Chamber Kits on the day the serum is prepared if possible. Refer to Section V and Section VIII in Appendix II for important instructions for preparing and shipping the serial serum specimens to the GOG Tissue Bank for GOG-0212. In the event that it is not possible to submit the serum specimens, submit the SP form via SEDES with the reason the specimen was not collected in item 5 (e.g., patient refused, tried but not able to draw blood or non-US site logistically infeasible).

[5] Whole blood specimen for GOG-0212**MUST** be shipped to the GOG Tissue Bank (address provided above) with a completed SP Form for WB01. The blood must be shipped using your own shipping container at ambient temperature the blood the day is collected as it will be immediately processed upon receipt at the GOG Tissue Bank. Whole blood will need to be shipped to the GOG Tissue Bank for next morning delivery on a Monday through Friday schedule for Tuesday through Saturday delivery using the GOG Tissue Bank's Federal Express Account Number (1290-2562-0).**Do not collect blood the day before a holiday**as staff will not be available at the Bank to receive or process the blood. Refer to Appendix II for instructions on how to pack the whole blood for shipment as the GOG Tissue Bank can not provide Shipping Kits for submitting the whole blood specimen for this protocol. In the event that it is not possible to submit the whole blood specimens, submit the SP form via SEDES with the reason the specimen was not collected in item 5 (e.g., patient refused, tried but not able to draw blood or non-US site logistically infeasible).

7.22 Laboratory Testing

Staff at the GOG Tissue Bank will coordinate with the Chairs of the GOG Committee for Experimental Medicine and the Tissue Utilization Subcommittee as well as staff in the GOG Statistical and Data Center to distribute appropriate specimens to approved investigators for testing for this trial (see Appendix III and below for details). Investigators will be responsible for completing the approved testing and transferring appropriate laboratory data with accurate specimen identifiers to the GOG Statistical and DataCenter for analysis. The study chair for GOG-0212 will coordinate study co-chairs, scientific collaborators and members of the GOG Statistical and Data Center as needed to perform appropriate statistical analysis and to prepare abstracts, presentations, reports and manuscripts.

7.221 Immunohistochemistry Assays

Unstained sections of FFPE primary tumor from conventional blocks and/or tissue microarrays (TMA) created by the GOG Tissue Bank for GOG-0212 will be distributed to Dr. Robert Burger at FoxChaseCancerCenterand Dr. Bradley Monk at the University of Californiaat IrvineMedicalCenter to examine the immunohistochemical expression of CD-31, TSP-1, CD-105, and VEGF expression as

described in Appendix III. Immunohistochemistry assays and the evaluation of the stained slides will be performed blinded to all of the clinical data.

7.222 Immunoassays

An aliquot of pre-cycle 1 serum and pre-cycle 2 serum will need to be distributed to Dr. Robert Burger at Fox Chase Cancer Center, Dr. Bradley Monk at the University Of California at Irvine Medical Center, Dr. Doris Benbrook at the University of Oklahoma Health Sciences Center, and Drs. Debbie Stearns-Kurosawa and Shinichiro Kurosawa at at the Oklahoma Medical Research Foundationto quantify the circulating levels of specific angiogenic markers as described in Appendix III. Enzyme-linked immunosorbent assays will be used to quantify the expression of VEGF, bFGF, angiogenin, and sEPCR. In addition, an angiogenesis antibody array will be used to examine the levels of VEGF, angiogenin, bFGF, EGF, EAN-78, GRO, IFN-γ, IGF-1, IL-6, Leptin, MCP-1, PDGF-BB, PIGF, RANTES, TGF-β1, TIMP-1, TIMP-2, thrombopoietin, and VEGF-D levels. Each of the immunoassays will be performed blinded to all of the clinical data.

7.223 SNP Analysis

The 10 ml of whole blood (WB01) drawn into a standard purple-top Vacutainer® tube with EDTAwill be shipped to the GOG Tissue Bank in Columbus, OH for immediate processing, extraction of DNA and Q/C assessments. Staff at the GOG Tissue Bank will distribute When appropriate, the GOG Tissue Bank staff will be responsible for shipping an appropriate quantity of DNA with corresponding Q/C data to Dr. Michael Birrer at MGHCancerCenter and/or CEM-approved investigator(s)for whole genome SNP-associations studies and/or evaluation of individual SNPs.

7.23 Future Research**(03/30/09)**

See the last section of Appendix II for important details regarding the banking and distribution of residual specimens after completion of GOG-0212 for future research.

8.0 EVALUATION CRITERIA

8.1 Definition of progression or recurrence and survival

Patients must have no clinical evidence of disease when they are enrolled onto this protocol including normal CA-125, and normal CT scan.

8.11 Progression or recurrence is defined as increasing clinical, radiological or histological evidence of disease since study entry or two serum values of CA-125 greater than or equal to two times the upper limits of normal (ULN) performed at least one week apart, regardless of CT scan results. Since disease progression based only on rising CA-125 involves two observations on two different dates, the date of progression will be defined as the first date on which the CA-125 was greater than or equal to two times the upper limit of normal. In the event of increasing symptoms and no elevation of CA-125, a CT scan will be performed to evaluate for progression. Patients with progressing disease based on rising CA-125 must have CT scan of the abdomen and pelvis performed.**(03/10/08)(05/10/10)**

8.12 Progression-Free Interval (PFS) or Recurrence-Free Interval (RFS) will be defined as date from entry onto the protocol to the date of first clinical, biochemical, or radiological evidence of progression or death due to any cause. PFS will be censored at the last assessment of disease progression for living patients who have not progressed.

8.13 Overall Survival (OS) will be defined as observed length of life from entry onto the protocol to death due to any cause, or for living patients, date of last contact (regardless of whether or not this contact is on a subsequent protocol).

8.2 When progression or recurrence occurs, second line and third line regimens will be collected, as well as CA-125 levels documenting treatment effects at least on a monthly basis until the end of the study. Any CT scan results obtained in evaluation of apparent disease progression should be recorded.

8.3 Results of the Laboratory Testing

Procedures are provided in Appendix III (Laboratory Procedures) for data acquisition and evaluation for CD-31, TSP-1, CD-105, and VEGF expression in primary tumor tissue and for VEGF, bFGF, angiogenin, sEPCR, EGF, EAN-78, GRO, IFN-γ, IGF-1, IL-6, Leptin, MCP-1, PDGF-BB, PIGF, RANTES, TGF-β1, TIMP-1, TIMP-2, Thrombopoietin, and VEGF-D levels in serial serum specimens.

9.0 DURATION OF STUDY **(08/19/13)**

9.1 Patients will remain on the treatment program until disease progression, unacceptable toxicity or they complete the planned treatment program.

9.2 All patients will be followed (with completion of all required case report forms) until disease progression. In addition, following disease progression, patients will be monitored for delayed toxicity, types of subsequent chemotherapy administered, CA-125, CT scan results, and survival with Q forms submitted to the GOG Statistical and DataCenter, unless consent is withdrawn.

10.0 STUDY MONITORING & REPORTING PROCEDURE

10.1 This study is being conducted under GOGIND #70,177. **(08/27/07)**

10.2 ADVERSE EVENT REPORTING FOR AN INVESTIGATIONAL AGENT(09/30/05) (03/30/09)(08/27/12)

10.21 Definition of Adverse Events (AE)

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that occurs in a patient administered a medical treatment, whether the event is considered related or unrelated to the medical treatment.

10.22 Reporting Adverse Events**(03/30/09)**

Depending on the phase of the study, use of investigational or commercial agents, and role of the pharmaceutical sponsor, an expedited AE report may need to reach multiple destinations. For patients participating on a GOG trial, all expedited AE reports should be submitted by using the CTEP automated system for expedited reporting (AdEERS). All AdEERS submissions are reviewed by GOG prior to final submission. Submitting a report through AdEERS serves as notification to GOG, and satisfies the GOG requirements for expedited AE reporting. All adverse reactions will be immediately directed to the Study Chair for further action.

The requirement for timely reporting of adverse events to the study sponsor is specified in the Statement of Investigator, Form FDA-1572. In signing the FDA-1572, the investigator assumes the responsibility for reporting AEs to the NCI. In compliance with FDA regulations, as contained in 21 CFR 312.64, AEs should be reported by the investigator.

10.23 Phase 2 and 3 Trials Utilizing an Investigational Agent under a non-CTEP IND (GOG IND): AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of the Investigational Agent.

Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Investigational Agent:
From the period of protocol activation through September 30, 2011, Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (CTCAE v3.0) are utilized for defining and grading specific adverse events reported through the AdEERS system. **(08/27/12)**

Beginning October 1, 2011, the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will be utilized for AE reporting through the AdEERS system. CTCAE v 4.0 is located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of this Version of CTCAE. CTCAE v 4.0 definition is also available on the GOG member web site (https://gogmember.gog.org under MANUALS). **(08/27/12)**

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	24-Hrs; 3 Calendar Days	Not Required	24-Hrs; 3 Calendar Days	24-Hrs; 3 Calendar Days	24-Hrs; 3 Calendar Days	Not Required	24-Hrs; 3 Calendar Days	24-Hrs; 3 Calendar Days
Possible Probable Definite	Not Required	24-Hrs; 3 Calendar Days	Not Required	24-Hrs; 3 Calendar Days	24-Hrs; 3 Calendar Days	24-Hrs; 3 Calendar Days	Not Required	24-Hrs; 3 Calendar Days	24-Hrs; 3 Calendar Days

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a non-CTEP IND (GOG IND) require reporting as follows:
AdEERS 24-hour notification followed by complete report within 3 calendar days for:
- Grade 3 unexpected event with hospitalization or prolongation of hospitalization
- Grade 4 and Grade 5 unexpected events
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under the section entitled, "Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a non-CTEP IND (GOGIND)."

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via AdEERS

within 24 hours of learning of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported to GOG via AdEERS if the event occurs following treatment with an agent under a non-CTEP IND (GOG IND).

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a non-CTEP IND (GOG IND):

- Please refer to the Investigator Brochure for information regarding adverse effects when determining expectedness of an event for the purpose of expedited reporting via AdEERS.

10.3 ADVERSE EVENT REPORTING FOR A COMMERCIAL AGENT **(03/30/09)**

10.31 Phase 2 and 3 Trials Utilizing a Commercial Agent: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of AnyCommercial Study Agent

Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Commercial Agent on Phase 2 and 3 Trials

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days
Possible Probable Definite	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days	7 Calendar Days	Not Required	24-Hrs; 3 Calendar Days	7 Calendar Days

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with a commercial agent require reporting as follows:

AdEERS 24-hour notification followed by complete report within 3 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 7 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

Please see exceptions below under the section entitled, "Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent." March 2005

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 3 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.

  "7 calendar days" – A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported to GOG via AdEERS if the event occurs following treatment

with a commercial agent.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent:

- Uncomplicated grade 4 neutropenia that does not result in hospitalization will not be considered an SAE, but should be recorded on the Form T.

10.4 Procedures for Expedited Adverse Event Reporting:**(03/30/09)**

10.41 AdEERS Expedited Reports: Expedited reports are to be submitted using AdEERS available at http://ctep.cancer.gov. The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.

Up until September 30, 2011, AML/MDS events must be reported via AdEERS (in addition to your routine AE reporting mechanisms). In CTCAE v3.0, the event can be reported as: "Secondary malignancy-Other (specify)". **(08/27/12)**

Starting October 1, 2011 when use of CTCAE v4.0 begins: AML/MDS events must be reported via AdEERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplatic syndrome, or 3) Treatment related secondary malignancy.**(08/27/12)**

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to GOG by telephone at: 215-854-0770. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted.**(03/10/08) (10/04/10)**

10.42 Reporting to the Pharmaceutical Company: CTI requires reporting of all serious adverse events, as defined by 21 CFR 312.32(a), that are considered possibly, probably, or likely to be related to study therapy, regardless of NCI CTC grade. The GOG Regulatory Department will forward the AdEERS form to CTI Pharmacovigilance within 24 hours of becoming aware of the event. The AdEERs form willbe sent to CTI Pharmacovigilancevia email at: drugsafety@ctiseattle.com.

10.43 Reporting to the FDA: The GOG Regulatory Department will notify FDA and all participating investigators in a written IND safety report of any adverse event associated with the use of the drug that is both serious and unexpected. Each notification shall be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information. Each written notification will be submitted on FDA Form 3500A (MedWatch).

10.44 Recording and Follow-up of Adverse Events (08/10/09)

10.441 All adverse events that occur from the time of study drug administration through 30 days after the final treatment will be recorded. Duration, severity, and outcome for each adverse event will be recorded on the Form T and treatments administered will be recorded on the Form D2R. Drug related adverse events will be followed until resolved, until no further improvement is expected, until a non-study antitumor therapy is initiated, or for 30 days after last study treatment, whichever comes first (with the exception of neuropathy, which must be followed until resolution to ≤ grade 1 or until stable for 60 days).

10.4411 Conditions that were present at the study start and that worsen during the study should be reported as beginning on the date the event worsened, not the date it began pre-study. Event text may include the word "worsened" or "exacerbated."

10.4412 Conditions which were recorded as "intermittent" at the study start which occur during the study must be reported if they are more frequent or of greater severity.

10.4413 The severity of each adverse event must be assessed using the NCI Common Terminology Criteria for Adverse Events, v3.0 (CTCAE).

10.5 Automated CDUS reporting**(08/27/07)**

For studies using commercial agents, the GOG Statistical and Data Center (SDC) routinely reports adverse events electronically to the CTEP Clinical Data Update System (CDUS Version 3.0). The SDC submits this data quarterly. The AEs reported through AdEERS will also be included with the quarterly CDUS data submissions.

As of 10/1/2011, this study will cease using CTCAE v3 and switch to CTCAE v4 for the purposes of reporting through AdEERS and/or CDUS. The GOG Statistical and Data Center will internally convert the adverse event terms and grades reported through AdEERS for this study from April 1, 2011 onward from version 4 to version 3. Additionally, the Statistical and Data Center will map all CTCAE v3 data reported for this study on GOG case report forms to CTCAE v4 defined terms and grades for CDUS reporting purposes. This will allow use of a consistently defined set of criteria for reporting adverse events throughout the study with minimal impact on the participating sites. **(08/27/12)**

10.6 GOG DATA MANAGEMENT FORMS (09/30/05) (08/27/07) (03/10/08)(03/30/09)

The following forms must be completed and submitted to the GOG Statistical and Data Center (SDC) in accordance with the schedule below. All forms except: Pathology report, Quality of Life forms and Quality of Life coversheet must be submitted via the SDC Electronic Data Entry System (SEDES) which is available through the GOG website (www.gogstats.org). Quality of life questionnaires are to be completed on Scantron forms and submitted by mail. Pathology material (path report and slides) should be submitted together via mail.

Form	Due within		Copies*	Comments
	Weeks	Event		
Form R and OSOM	2	Registration	1	Complete online ***
Specimen Consent Application	1	Registration	NA	Complete online
Form DR	4	Registration	1	Complete online
Pathology report Representative slides of the Primary tumor and advanced stage	6 6	Registration	2 *****	SDC via postal mail **Note: All pathology materials must be submitted together**
Form D2R-cycle 1 Subsequent cycles	2 2	Completion of each cycle of therapy	1 1	Complete online *** ****
Form T	2	Beginning of each subsequent cycle	1	Complete online *** ****
DCA	2	Completion of each cycle of Rx after cycle 1	1	Complete online
ConMed	2	Completion of each cycle	1	Complete online
FACT-OTOI/GOG/NTX and coversheet	2	Date Completed **	1	Submit Scantron, See Appendix VII **
Form Q0	2	Completion of study treatment	1	Complete online ***
Form Q	2	Disease progression, death and post-treatment follow-up	1	Quarterly for 2 years, semi-annually for 3 years, yearly thereafter
Form SP-FP01-0212 for formalin-fixed and paraffin-embedded (FFPE) primary tumor tissue (FP01)†	8	Registration	1	Submit via SEDES *f* Ship block or unstained slides for translational research with a copy of the SP Form for FP01 to the GOG Tissue Bank in Columbus Ohio†
Form SP-SB01-0212 for pre-cycle 1 serum (SB01) ‡	12	Registration	1	Submit via SEDES *f* Ship frozen serum with a copy of the SP Form for SB01 and SB02 to the GOG Tissue Bank in ColumbusOhio‡
Form SP-SB02-0212 for pre-cycle 2 serum (SB02) ‡	12	Registration	1	

Form SP-WB01-0212 for whole blood (WB01) to be shipped at ambient temperature the day the blood is collected‡‡	4 new patients 26 current patients	Registration Amendment Activation or Last Q-Form		Submit via SEDES.*f* Ship the whole blood with a copy of the SP Form for WB01 to the GOG Tissue Bank in ColumbusOhio‡‡

* The number of required copies including the original form which must be sent to the Statistical and Data Center (SDC), if it is not completed online.

** QOL is evaluated prior to registration, prior to cycles 3, 5, 7, end of treatment and one year after completing study treatment for Regimen I or II. QOL is evaluated prior to registration and then 2, 4, 6, 12 and 24 months following registration for Regimen III. Use only the Scantron form with the header "GOG Protocol 0212" provided by mail. Additional forms can be provided by the SDC upon request. Cover sheet must be submitted together with the Scantron form. If assessment is not performed, a cover sheet is still required and may be submitted electronically.

*** Use the SDC Electronic Data Entry System (SEDES), available on the GOG website to view and print a copy of each form along with instructions, and to submit forms electronically.

**** On surveillance arm submit monthly D2R and T forms indicating month on treatment in the current cycle number

***** Pathology slides are required for central review by the GOG PathologyCommittee. At least one representative stained slide (or slides) demonstrating the primary tumor, histologic cell type, and grade and **one** slide to demonstrate the most advanced stage of disease. When submitting pathology material to the GOG SDC, individual slides must be labeled with GOG Patient ID and patient initials and packed in plastic slide cassettes. Tape plastic slide cassettesshut and wrap in bubble wrap or another type of padded material prior to shipping. Ship pathology slides and two copies of the official pathology report directly to the Pathology Materials Coordinator at the GOG Statistical and Data Center, Roswell Park Cancer Institute, ResearchStudiesCenter, Carlton and Elm Streets, Buffalo,New York, 14263; phone (716) 845-5702. Please include the GOG Patient ID, patient initials, and protocol number on all pages of the pathology report and black out the patient's name.

f Form SP **must be submitted online** to the GOG SDC using SEDES regardless of whether the specimen is submitted for research.

† See footnote 3 in the Quick Scan Summary in Section 7.21 of the protocol and Section VIII of Appendix II for important details for shipping FP01 to the GOG Tissue Bank and for completing the corresponding SP Form.

‡ See footnote 4 in the Quick Scan Summary in Section 7.21 of the protocol and Section VIII of Appendix II for important details for shipping the SB01 and SB02 to the GOG Tissue Bank and for completing the corresponding SP Forms.

‡‡ See footnote 5 in the Quick Scan Summary in Section 7.21 of the protocol and Section VIII of Appendix II for important details for shipping WB01 to the GOG Tissue Bank and for completing the corresponding SP Form.

This study will be monitored by the **Abbreviated** Clinical Data Update System (CDUS) Version 1.x. CDUS data will be submitted quarterly to CTEP by electronic means. **(08/27/07)**

This study utilizes the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) for defining and grading adverse events to be reported on GOG case report forms. A GOG CTCAE v3.0 Manual is available on the GOG member web site (http://www.gog.org under MANUALS) and can be mailed to the institution registering a patient to this study if requested.**(08/27/12)**

11.0 STATISTICAL CONSIDERATIONS

11.1 *Randomization*: Treatment randomization will occur after the patient has completed her front-line platinum-taxane treatment and has consented to participate in the randomized portion of this study. A randomization procedure that tends to allocate the study treatments equally within the following stratification factors will be used:

11.11 Stage of disease at diagnosis (stage III vs.stage IV).
11.12 Presence of macroscopic disease following initial debulking surgery (yes vs. no).
11.13 Prior taxane treatment (induction regimen included docetaxel or paclitaxel only).
11.14 Route of prior platinum treatment (intraperitoneal vs. intravenous).

11.2 *Efficacy and toxicity measures*: The principle parameters employed to evaluate therapeutic effect of treatment are:

11.21 Primary efficacy endpoint: Overall survival.
11.22 Secondary efficacy endpoint: Progression free survival (PFS).
11.23 Safety Endpoints: The frequency and severity of adverse effects (Common Terminology Criteria Adverse Events -version 3.0).
11.24 Quality of life endpoints: FACT-O TOI and FACT/GOG-NTX

11.3 *Accrual, accrual rate, study duration and determination of sample size.* **(03/10/08)** Based on a previous GOG frontline treatment trial (GOG-0182) which involved patients with newly diagnosed stage III or IV epithelial ovarian cancer, the GOG institutions enroll about 1150 patients annually. It is estimated that 70% of these patients will receive a platinum and taxane based front-line therapy and hence be eligible for the current study. However, it is anticipated that about 40% of these potentially eligible patients will either progress, die, refuse maintenance therapy or experience grade 2 or more neurotoxicity from front-line treatment. Finally, studies which compare no treatment to treatment often experience some difficulty enrolling patients. Therefore, approximately 130 patients could be enrolled annually onto this maintenance study. The planned total accrual is 1100 eligible patients and therefore the estimated duration of the accrual phase is 8.5 (7 years as of Jan1, 2007) years. At least two-yearsof post-accrual follow-up is anticipated to permit maturity of survival.

Data from GOG-0182 provides an estimated median overall survival of 36 months following successful completion of carboplatin and paclitaxel frontline therapy in patients diagnosed with stage III or IV ovarian or peritoneal cancer. The sample size calculation for this study is based on a logrank test comparing the overall survival for those randomized to surveillance with those randomized to each of the taxane maintenance regimens. The type I error will be limited to 0.025 (one-tail test) for each these two comparisons accounting for interim and final analyses. The study design provides a 90% chance of correctly classifying each of the taxane maintenance regimens as active if they truly reduce the death rate 25%. This effect size is comparable to increasing the median duration of overall survival time 12 months.

11.4 *Analyses of therapeutic efficacy* **(03/10/08)(08/27/12)**

This study is a three-arm randomized phase III trial with four scheduled interim analyses. The interim analyses will focus on overall survival to determine whether continuing accrual to all of the study arms is warranted. The final analysis of overall survival will focus on comparing the group of patients randomized to surveillance with each of the groups randomized to the taxane maintenance regimens.

The principle analyses of overall survival will include all enrolled patients grouped by their randomized treatment for an intent-to-treat analysis. For the purpose of treatment comparisons, survival will be assessed from the date of randomization to the date of death and death due to any cause will be considered a failure event. The null hypothesis will be assessed with an unstratified logrank test.

*Interim analyses***(08/27/12)**

The following table summarizes the decision boundaries that will be employed for interim analyses. The timing of the interim analyses is based on the number of deaths observed among those patients randomized to the surveillance group. The decision boundaries for each interim analysis are described in terms of Z-scores in each row of the table. The boundaries based on the hazard ratio (HR) scale are approximate and are provided only as a reference. These boundaries are based on the procedure proposed by Pampallona and Tsiatis (1994) using boundary shape parameters (0, 0). These shape parameters provide error spending functions that resemble the type proposed by O'Brien-Fleming. These particular decision boundaries limit the overall type I error to 2.5% and type II error to 10% for each experimental treatment.

Interim Analysis	Approximate Information time	Number of deaths in Ref. arm	Rejection Boundary for H_0		Rejection Boundary for H_1 Non-Binding	
			Z-scale	HR-scale	Z-scale	HR-scale
1	0.35	109	3.3661	0.6181	-0.3715	1.0545
2	0.50	155	2.8163	0.7141	0.4108	0.9521
3	0.65	200	2.4700	0.7718	0.9932	0.9011
4	0.80	244	2.2260	0.8102	1.4658	0.8706
Final	1.00	301	1.9910	0.8450	1.9910	0.8450

Specifically, the first interim analysis will occur with there are at least 109 deaths among those randomized to the reference arm (Surveillance). Currently, this is expected to occur about Dec-2012. At that time, the hazard of death for each of the experimental regimens (paclitaxel and CT2103) will be compared to the reference arm with a logrank procedure. If the p-value for an unstratified logrank test of the null hypothesis (ie, no difference in hazards) is smaller than the p-value corresponding to a z-score equal to 3.3661 ($p < 0.0004$) then that experimental regimen can be deemed superior to surveillance and consideration will be given to no longer randomizing new patients to the surveillance arm. In other words, this procedure would require that the observed (experimental:reference) hazard ratio for at least one of the experimental regimens to be somewhat less than 0.6181 before consideration is given to drop the surveillance arm from the study.

The first interim analysis will also include an assessment for futility. In this case, the p-value for the unstratified logrank test will be compared to the p-value corresponding to a z-score equal to -0.3715 ($p > 0.6449$). In this case, the experimental agent can be deemed unlikely to be superior to surveillance and consideration will be given to no longer randomizing new patients to that corresponding experimental regimen. This test is similar to requiring that the observed hazard of death for each experimental arm to be no more that 5.45% higher that the surveillance arm in order to be continued in the study.

Each of the subsequent interim analyses will follow similar procedures described above but use the corresponding decision boundaries specified in the table.

The result of the interim analyses will be reviewed by the Data Monitoring Committee (DMC). The DMC convenes face-to-face meetings twice each year (January and July). Within eight weeks prior to these meetings, the study data is locked and a status report is prepared. If the required number of events for an interim analysis is satisfied, then the interim analysis is also prepared and submitted to the DMC members for their consideration. If the required number of events is projected to occur between meetings, then the DMC may opt to schedule a conference call to review the interim analysis prior to it next face-to-face meeting.However, the decision to convene a conference call to review interim analysis is made without any specific knowledge of the results.

The DMC may recommend study termination. The actual decision to terminate accrual to any particular regimen will include consideration of toxicities, treatment compliance, progression-free survival and results from external studies. In addition to the DMC, the GOG Data Safety and Monitoring Board (DSMB) reviews results from ongoing GOG studies. The DSMB reviews accumulating summaries of toxicities and all serious adverse event (SAE) reports. This committee also performs detailed reviews of deaths in which study treatment may have been a contributing cause. The DSMB reports to the DMC and may recommend study amendments to the DMC pertaining to patient safety.

Final analyses **(08/27/12)**
The primary focus of the final analysis will be a pair-wise comparison of overall survival between those randomized to surveillance and each of the taxane maintenance regimens.

The final analyses can be broken into three distinct components:

First, the surveillance group will be compared to each of the taxane maintenance regimens selected for complete accrual following interim analyses. This analysis will occur when there are at least 301 deaths reported among those patients randomized to surveillance (If taxane maintenance therapy truly reduces the death rate 25%, then expected number of deaths in the surveillance group and an active taxane maintenance group will be 301 and 265, respectively. Therefore the expected total number of deaths for each pair-wise comparison will be 566) The one-sided significance level for this unstratified logrank test is 0.023, provided the four interim analyses are conducted as planned.

This number of events provides approximately a 90% chance of detecting a true 25% reduction in the death rate. This effect size is comparable to changing the expected proportion surviving at least 36 months from 50% to 59.5%.

A second component of the final analysis will focus on the consistency of the estimated treatment effect. The consistency of the treatment effect will be assessed across patient groups defined by FIGO stage, histologic cell type, tumor grade, race, age, type of induction treatment, and indication of macroscopic residual disease following the initial debulking surgery. These analyses are primarily exploratory.

A third component of the final analysis will occur if both of the taxane maintenance regimens are deemed superior to the surveillance group as a result of the analyses of overall survival. In this case, the taxane maintenanceregimenswill be compared to each other on the basis of overall survival. The type I error for this comparison will be set to 0.05 for a 2-tail test.

11.5 *Quality of Life Analyses and Toxicities*

The principal parameters employed to assess the quality of life (QOL) and symptoms are:

11.51 A general ovarian cancer QOL score as it is assessed by the self-administered FACT-O (Basen-Engquist, et al, 2001; Cain, et al, 1998; Cella, et al, 1993).

11.52 A neuropathy score as it is assessed self-administered with the FACT-GOG/NTX (Calhoun, et al, 200; Cella, et al, 2003; Moore, et al, 2003).

The FACT-O TOI and FACT-GOG/NTX will be completed by the patient just prior to: randomization, course 3 (2 months), course 5 (4 months), course 7 (6 months), upon completion of study treatment (12 months) and finally one year after completing study treatment (24 months).

Construct and content

The general QOL will be assessed with the Functional Assessment of Cancer Therapy scale developed for ovarian cancer (FACT-O TOI). This tool produces a general QOL score and is composed of subscale scores for: physical well being (7 items), functional well being (7 items) and the Ovarian Cancer subscale (12 items). The FACT-GOG/NTX consists of 11 items, although only the 4-item subscale will be used for the principle analysis.

Hypotheses and analyses

The principal QOL question is: Are the general QOL scores as assessed with the FACT-O TOI or the neuropathy symptoms as assessed by the FACT-GOG/NTX independent of the randomized treatment? The planned test for independence of the FACT-O TOI (FACT-GOG/NTX) scores and treatment will be an analysis of covariance. The primary analyses will compare the self-reported scores for the randomized treatment groups reported 6 months after entering the study. This time point is considered appropriate since the effects of treatment, if there are any, will be apparent by this time. Also, it is anticipated that relatively few patients will have withdrawn from the study treatment or crossed-over within the first 6 months due to either disease progression or other serious adverse events. The pretreatment FACT-O TOI (FACT-GOG/NTX) score and age will be considered potential confounders. A more informative model may be possible that accounts for several repeating measurements within individual patients. However, it is recognized that several modeling assumptions regarding the pattern of missing data or the functional effect of time may be required that cannot be anticipated. Therefore, the repeating FACT-O TOI scores will be analyzed with a mixed model in an exploratory fashion. There is one additional complexity to consider in the analysis of repeating FACT-GOG/NTX scores. The distribution of these scores is noticeably truncated on the left and the scores tend to clump at zero; particularly for the pretreatment values. To analyze these data, a mixed-effects mixed-distribution model will be considered.[89] This model contains two components. The first component consists of a logistic model to estimate the odds of reporting a nonzero value and the second component models the possibly truncated distribution of the nonzero scores. Random effects are used to account for the correlation of repeating measures within an individual. The model also allows for a correlation of the random effects from the two components of the model.

Multiplicity of Outcomes

Due to the multiplicity of statistical tests, the overall type I error can become large if each hypothesis is tested at the 5% level. The treatment comparisons with regard to FACT-O TOI and the FACT-GOG/NTX will be considered separately. For each treatment comparison the significance level will be set to 0.025 (0.05/2) for a two-tail test. The analysis will begin with a global test with two degrees of freedom assessing the hypothesis that the true mean scores for each treatment group are equivalent. If this null hypothesis is rejected then the treatment groups will be compared in a pair wise fashion.

Missing information

Patient death, noncompliance, missed appointments, and patient illiteracy, can cause missing information. One or more of the QOL or adverse effects assessments may be missing for an individual on any occasion. Missing information is troublesome; particularly in studies involving repeated patient assessments. While analytical methods are available to accommodate some types of 'missingness', it is prudent to implement procedures to minimize missing data. To this end, a calendar of events which lists the required forms and the dates that these forms are to due will be available to the patient's health care provider as soon as the patient has been registered onto this study. Also, the clinic staff will be able to use the GOG web-based forms tracking system to obtain reminders of the upcoming assessments.

At semi-annual group meetings the data managers and nurses will be given presentations, which describe the goals of this study and stress the importance of

obtaining complete assessments. The semi-annual statistical report will provide a summary of QOL assessment compliance for this study while it is actively accruing patients. Finally, a study contact person will be designated to answer any questions that arise throughout the study.

Patient attrition through death is assumed not to be a significant problem since 90% of these women are expected to live at least 12 months. It is expected that at least 80% will be alive and disease free six months following randomization.

A Spanish and English version of the FACT-O is available. Women who are unable to read or have difficulty reading will not be required to participate in the QOL part of this study. Also, any women, who do not wish to participate in the QOL portion of this study, can refuse and still be eligible for the therapeutic portion.

Scoring

Within an individual assessment one or more items may not be answered. A subscale score will be computed as long as more than 50% of subscale items have been answered. A subscale score S_i with N_i items will be calculated as:

$$S_i = N_i * \frac{\sum_{j=1} (\delta_{ij} * s_{ij})}{\sum_{j=1} \delta_{ij}}$$

Where δ_{ij} is equal to 1 when the jth item has a valid response, otherwise it is equal to 0 and s_{ij} is the response score of the jth item. The total FACT-O TOI score is the sum of the subscale scores.

Statistical Power Considerations

The GOG has completed a trial in which 187 patients were treated with cisplatin and paclitaxel for 6 cycles every 21 days. These women reported their self-assessed FACT-O prior to initiating treatment and then 6 months later (Wenzel et al, ASCO, 2004). Prior to initiating study treatment, the mean and standard deviation of the FACT-O TOI scores were 74.1 and 14.1, respectively. Six months later there was a 10% attrition of patients and the mean and standard deviation of the FACT-O TOI of those recorded were 81.5 and 13.5, respectively. The correlation between pretreatment and post-treatment measurements was 0.43. Assuming there is no more than 13% attrition of patients the proposed sample size (approximately 448 patients per treatment group) provides at least 83% power to detect a 3-unit difference in the true mean FACT-O TOI scores reported at six months. This power calculation is based on the least favorable configuration of the true means.

11.6 Safety analyses **(09/30/05)**

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE v3.0) will be used to classify toxicities observed during treatment. The severity of each toxicity will be assessed according to the NCI CTCAE v3.0 grading system. Each toxicity reported will also be coded with their corresponding MeDRA codes. Patients will be tabulated according to their maximum severity for each organ system or preferred term.

Safety endpoints will be summarized with descriptive statistics for the patients in the safety analysis dataset. The safety analysis dataset will include all randomized patients who receive any of their assigned study treatment and these patients will be grouped by their assigned treatment. Patients who do not receive any of their assigned study treatment will not be included in these analyses.

11.7 Translational research

Overview of the study design
The translational research objectives of this study are to assess whether one or more biologic markers of angiogenesis are associated with either progression-free or overall survival and to develop a potentially prognostic index and possibly a predictive index.

The biomarkers to be evaluated in this study include: CD-31, TSP-1, CD105, vascular endothelial growth factor (VEGF) expression in the primary tumor tissue, and VEGF, basic fibroblastic growth factor (bFGF), angiogenin and soluble endothelial protein C receptor (sEPCR) concentrations in serum. Additionally, levels of VEGF, bFGF, angiogenin, EGF, EAN-78, GRO, IFN-(, IGF-1, IL-6, Leptin, MCP-1, PDGF-BB, PIGF, RANTES, TGF-∃1, TIMP-1, TIMP-2, Thrombopoietin, and VEGF-D will be assessed in the paired serum specimens with an antibody array. Some of these biomarker expression levels are quantitative while others are semi-quantitative. Currently, there are 24 markers of angiogenesis proposed for an evaluation.

A prognostic index will be developed utilizing the biomarker values from samples collected prior to study treatment. If this study demonstrates that taxane therapy is superior to surveillance, then a predictive index will be developed utilizing the pre-cycle 1 biomarker level or the change in biomarker values from paired samples taken prior to starting treatment (pre-cycle 1 serum) and prior to the 2^{nd}-cycle of treatment (pre-cycle 2 serum). It is hoped that the predictive index will identify patients most likely to benefit from maintenance taxane treatment.

The overall approach for this study is to develop a prognostic (predictive) index by modeling the data in a test data set and then validating the index in an independent data set. The modeling procedures for developing a prognostic index are described in the following paragraphs. The procedures for developing a predictive index are similar.

Description of the test and validation data sets
The patients registered to this study will be allocated to either a test data set or a validation data set. Assignment to the test or validation data set will be independent of either PFS or survival outcome. For practical reasons, though, individuals entering the study early will tend to be assigned to the test data set, while those entering the study later will tend to be allocated to the validation data set.

The test data set will be considered sufficiently mature to permit developing a prognostic score from the currently proposed list of markers of angiogenesis when there are at least 250 events. This number of events will provide an event-per-variable (EPV) ratio slightly greater than 10:1, not including covariate interactions.

Screening Biomarkers
The first step toward evaluating these biomarkers is to assess the distribution of each biomarker and the correlation between pairs of biomarkers. Biomarker values that appear to be extreme outliners will be investigated to determine whether there were any anomalies in the handling or processing of the specimen, which may explain the extreme values. Also, highly correlated biomarkers will be noted since these can introduce anomalies into the modeling procedures.

In order to visually assess the univariate relationship between each biomarker value and relative death rates, the marker values will be plotted against martingale residuals from a proportional hazards model that does not include the biomarker as a covariate. The martingale residuals may be smoothed over biomarker values with either piece-wise cubic polynomials, penalized curve fitting or running-mean smoothers. These plots will be used to detect departures from linearity and to assess when a more complex model may be necessary to describe the relationship between biomarker values and log hazard ratio. Cross-validation, bootstrapping or a penalized likelihood function will be used to judge the maximum degree of complexity to be considered. If restricted cubic regression splines are used, then functions with not more than four degrees of freedom should be sufficiently flexible to model the relationship.

A plot of beta residuals can be used to assess the influence of each individual on the estimated log hazard ratio. These plots can be used to identify individuals with an unusually large influence. These individuals will be investigated to determine whether there were any anomalies in the handling or processing of the specimen that may explain the unusual values.

Multivariate model
Using the functional relationships between the univariate biomarker values and the log relative hazards developed during the biomarker screening step, a multivariate model will be constructed. Covariates will be eliminated from the model in order to identify a parsimonious model that appears to have some predicative value but is not overly complex. Cross-validation, bootstrapping or a penalized likelihood function will be used to judge parsimony.

Covariate Interactions

For the purposes of building a predictive model, only second-order covariate interactions that have a biologic rationale will be considered. That is, if a particular laboratory assay measures a receptor then modeling interactions with potential ligands will be considered. In this case, it is reasonable to expect that the prognostic value of a ligand may depend on the presence of receptors in the tumor. The evaluation of third-order or higher interactions will not be evaluated at this point but considered in exploratory analyses (see below). Biologically, a third-order interaction could exist when two different ligands compete for the same receptor and one switches on and the other switches off cell growth.

A covariate may also interact with time. That is, the effect size may depend on the follow-up time. Schoenfeld residual plots vs. time are useful for identifying these types of interactions. Fitting the Schoenfeld residuals over time with either piece-wise cubic polynomials, penalized likelihood regression or running-mean smoothers may be used to visualize departures from proportional hazards.

Missing values

It is anticipated that there will not be a significant number of missing values for any of the planned biomarkers. Nevertheless, eliminating individuals due to partially missing biomarker values is not desirable, since this may introduce bias or artificially reduce the variance. Therefore, procedures for handling missing values may be necessary. Provided no more than 5% of the values for a particular biomarker are missing, values imputed from the available values can be used. If missing values account for more than 5%, but not more than 15% of the measures for a particular biomarker, then conditional imputation, which considers the correlation between the other biomarkers will be considered. Finally, if 15% or more of the values for a particular biomarker are missing, multiple imputations can be used to characterize for the additional uncertainty in the parameter estimates due to incorporating imputed values in place of unknown values.

External validation

A prognostic score for each individual in the validation dataset will be computed using the parameter estimates obtained from the modeling of the test data set. This score will be modeled with a proportional hazards model in the validation data set. The coefficient estimated from this later model provides an unbiased measure of the value of the prognostic score. The c-index (described below) can be used to assess prediction.

Exploratory analyses

While the procedure for building a prognostic score outlined above has flexibility, it is somewhat constrained in order to avoid over-fitting the data in the training set. Over-fitting leads to poor prediction and reduces the external validity of the prognostic score. It is not possible, however, to devise a modeling strategy that consistently produces the 'best' prognostic score. Therefore, exploratory analyses will be performed using alternative model building strategies to identify better prognostic scores. One alternative modeling approach is to first reduce the dimensionality of the data with cluster analyses or principal component analysis. In order to avoid bias, it is important that subsequent data modeling procedures do not incorporate any information from the validation dataset. The prognostic score from subsequent models will be assessed relative to the prognostic score developed from the proposed strategy. The c-index computed in the validation data set will be used to compare alternative prognostic scoring procedures. The c-index is the probability that the survival times from two individuals randomly selected from the validation data set can be correctly ranked based on their prognostic scores. A c-index value of 0.5 indicates that there prognostic is useless, while a value equal to 1.0 indicates a perfect prognostic index. Occasionally, the c-index is transformed so that $D_{xy} = 2*(\text{c-index} - 0.5)$. This index ranges from 0 to 1 and it is analogous to the Somers rank correlation index for censored data.

11.8 Anticipated gender and minority inclusion

This study restricts entry to women by the nature of the site of disease. The table below lists the projected percentage of patients by racial/ethnic subgroup. Prior GOG studies in this population have not indicated that there is substantial heterogeneity of treatment effects among racial/ethnic subgroups. Therefore, this study design does not incorporate specific hypotheses concerning treatment interactions involving race or ethnicity.

0.1% American Indian, Native Alaskan
0.2% Eastern Indian
1.7% Asian, Pacific Islander
2.5% Hispanic
4.5% Black
91.0% White

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APPENDIX I

FIGO STAGE GROUPING FOR PRIMARY CARCINOMA OF THE OVARY

(1985)

These categories are based on findings at clinical examination and/or surgical exploration. The histologic characteristics are to be considered in the staging, as are results of cytologic testing as far as effusions are concerned. It is desirable that a biopsy be performed on suspicious areas outside the pelvis.

Stage I — Growth limited to the ovaries.

Stage IA — Growth limited to one ovary; no ascites.
No tumor on the external surface; capsule intact.

Stage IB — Growth limited to both ovaries; no ascites.
No tumor on the external surfaces; capsules intact.

Stage IC* — Tumor either Stage IA or IB but with tumor on the surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.

Stage II — Growth involving one or both ovaries with pelvic extension.

Stage IIA — Extension and/or metastases to the uterus and/or tubes.

Stage IIB — Extension to other pelvic tissues.

Stage IIC* — Tumor either Stage IIA or IIB but with tumor on the surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.

Stage III — Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastasis equals Stage III. Tumor is limited to the true pelvis but with histologically verified malignant extensions to small bowel or omentum.

Stage IIIA — Tumor grossly limited to the true pelvis with negative nodes but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces.

Stage IIIB — Tumor of one or both ovaries with histologically confirmed implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter. Nodes negative.

Stage IIIC — Abdominal implants >2 cm in diameter and/or positive retroperitoneal or inguinal nodes.

Stage IV — Growth involving one or both ovaries with distant metastasis. If pleural effusion is present there must be positive cytologic test results to allot a case to Stage IV. Parenchymal liver metastasis equals Stage IV.

* In order to evaluate the impact on prognosis of the different criteria for allotting cases to Stage IC or IIC, it would be of value to know if rupture of the capsule was (1) spontaneous or (2) caused by the surgeon and if the source of malignant cells detected was (1) peritoneal washings or (2) ascites.

APPENDIX II

Specimen Procedures for GOG-0212

I. Quick Scan Summary of the Specimen Requirements for GOG-0212. †

Refer to Section 7.21 of the Protocol for a copy of the Quick Scan Summary Table.

II. Obtaining a GOG Bank ID for Any GOG Protocol

Only one GOG Bank ID (# # # # - # # - G # # #) is assigned per patient, and all specimens and accompanying paperwork for each patient must be labeled with this coded and confidential tracking number. A GOG Bank ID can be obtained from the GOG Tissue Bank during regular business hours (Monday - Friday from 8:30 AM - 5:00 PM Eastern Time) by phone (866-464-2262/866-GOG-BANC) or FAX (614-722-2897).

Obtain the GOG patient study ID for any GOG protocol with specimen requirements other than GOG-0136 (specimen banking protocol) before contacting the GOG Tissue Bank to obtain the GOG Bank ID.

The staff at the participating GOG institution is required to keep accurate records of the GOG Bank ID assigned for each patient enrolled on this protocol. Check your records to ensure that only one GOG Bank ID is requested for each patient, and that this GOG Bank ID is used to label the specimens and complete the specimen transmittal form (Form SP). If confirmation of the assigned GOG Bank ID is desired, ask the GOG Tissue Bank to send you a confirmatory fax or e-mail for your records.

III. Requesting Single-Chamber Specimen Kits for GOG-0212

A. Ordering Single-Chamber Specimen Kits for GOG-0212

1. Single-Chamber Specimen Kits can be ordered for each patient enrolled on GOG-0212 from the GOG Tissue Bank during regular business hours (Monday - Friday from 8:30 AM - 5:00 PM Eastern Time) by phoning 866-464-2262 (866-GOG-BANC) and specifically requesting Specimen Procurement and Shipping Kits for GOG-0212. Provide the GOG Tissue Bank staff with the appropriate shipping information, including a contact name, so that the materials are delivered to the appropriate individual. Also, try to plan ahead so that the kits can be shipped by ground transportation whenever possible. GOG Institutions are encouraged to batch ship the two serum specimens per patient to reduce work load and costs as long as the staff has access to approved ultra-cold storage such as an ultra-cold freezer <-70^{o}C to store the serum onsite before. If this is the case, please request one kit per patient and use the one Single-Chamber Specimen Kit to ship up to two serum specimens. If your institution does not have access to approved ultra-cold storage for the frozen serum, you will not be able to batch the pre-cycle 1 and pre-cycle 2 serum specimens in one Single-Chamber Specimen Kit but instead will need to ship the pre-cycle 1 or the pre-cycle 2 serum in separate Single-Chamber Kits on the day the serum is prepared, **These kits must only be used for the serum specimen submissions.** Please submit the formalin-fixed primary tumor specimen in your own container**.** For shipping information, please see Section VII.
2. After you obtain IRB approval for this protocol, your first set of Single-Chamber Specimen Kits for GOG-0212 can be ordered; replacement kits can be ordered as needed based on the number of patients your institution is putting on the protocol. Always try to have replacements available.

B. Materials Provided in the Single-Chamber Specimen Kits for GOG-0212

Each Specimen Kit for GOG-0212 consists of a single-chamber shipping container suitable for shipping two frozen serum specimens. In addition, two 15-ml screw-cap polypropylene conical tubes for mixing the two serum specimens, four sets of five 1.8 ml screw-cap cryogenic vials (cryotubes) for the serum aliquots, and plastic zip-lock bags will be included in the single-chamber kit. Finally, a secondary shipping envelope with absorbent material, a dry ice label (UN1845), an Exempt Human Specimen Sticker, and a Federal Express form (pre-billed to the GOG Tissue Bank) will also be included.

C. Unused Materials or Unused Single-Chamber Specimen Kits for GOG-0212

Unused materials or unused Single-Chamber Specimen Kits for GOG-0212 need to be returned to the GOG Tissue Bank. Contact the GOG Tissue Bank if you have any question about the return of unused material.

IV. Submitting a Primary Tumor Specimen for GOG-0212

A. Requirement and Purpose

Archival FFPE primary tumor (block or 20 unstained slides) will only be required from women on GOG-0212 who give permission for their tumor tissue if available from a previous surgery for submission and use for this research study.

Patients may participate in this treatment protocol even if they don't give permission for their left over tumor tissue to be used for this research study. **If tumor can not be submitted for GOG-0212, please indicate the reason in item 5 on the SP Form such as patient refused, not enough tumor for research, or referring site won't release tumor.**

To satisfy this requirement, the site can submit a block (1st choice) or 20 unstained sections (2nd choice) to the GOG Tissue Bank as described in Section VIII. If you will be submitting slides, please submit at least **20** unstained 5 micrometer sections on positively charged slides suitable for standard immunohistochemistry assays.

The type of tumor tissue (primary) and specimen (block or slides) must be specified on the specimen transmittal form (Form SP) for each tumor specimen.

Unstained sections of primary tumor tissue will first be shipped to the GOG Tissue Bank in Columbus Ohio and then distributed in batches to Dr. Robert Burger at Fox Chase Cancer Center and Dr. Bradley Monk and Robert Burger at the University of California Irvine Medical Center to examine the tumor expression of CD-31, thrombospodin-1 (TSP-1), CD-105 (endoglin), and vascular endothelial growth factor (VEGF) as described in the Laboratory Procedures for GOG-0212 (Appendix III).

B. Time Point

The primary tumor tissue must be collected during primary cytoreductive surgery.

C. Format for Labeling the Specimen

Label the archival primary tumor with the GOG protocol number (GOG-0212), the GOG Bank ID (####-##-G###), the specimen code (FP01 for formalin-fixed and paraffin-embedded primary tumor tissue), and the collection date (mm/dd/yyyy). This specimen may be labeled with the pathology accession number and block identifier, but must not be labeled with personal identifiers.

D. Instructions for Preparing the Primary Tumor Tissue

1. **Obtain a Primary Tumor Specimen.** Obtain a piece of formalin-fixed and paraffin-embedded primary tumor specimen, a representative paraffin-block or 20 unstained sections, 5 μm in thickness, captured on charged slides suitable for a standard immunohistochemistry assay, from the Pathology Department at your institution or a referring site.
2. **Complete the Form SP**. Complete a GOG Specimen Form (Form SP) as specified in Section VII. Submit a copy of Form SP with the specimen when it is shipped to the GOG Tissue Bank, and retain a copy in your files.
   * Please remember to specify the type of specimen (fixed tissue) in item 8, item shipped (block or slides) in item 9 and type of tissue (primary tumor) in item 22 on the SP Form.
3. **Ship the Tumor Specimen.** Ship the archival primary tumor specimen to the GOG Tissue Bank **in your own shipping container** using the U.S. Postal Service at your expense as described in Section VIII.

V. Preparing Serum for GOG-0212

A. Requirements

Two serum specimens will only be required from women on GOG-0212 who give permission for some of their blood to be submitted to the GOG Tissue Bank for this research study.

Each serum specimen will need to be prepared from 10 ml of blood drawn into a **plain red-top Vacutainer® tube** at two time points as described in Section V-G, and shipped to the GOG Tissue Bank as described in Section VIII.

Patients may participate in this treatment protocol even if they don't give permission for their serum to be used for this research study. **If this is the case indicate that "patient refused" as the reason in item 5 on the SP Form. If the serial serum can not be submitted for GOG-0212, please indicate the reason in item 5 on the SP Form, such as patient refused, tried but not able to draw blood, or Non-US site logistically infeasible.**

B. Time Points

1. **Pre-Cycle 1 Serum**. The first serum time point will be prior to starting cycle 1 of therapy for patients randomly allocated to Regimen I or II, or within 1 week of study enrollment for patients randomly allocated to Regimen III.
2. **Pre-Cycle 2 Serum**. The second serum time point will be prior to starting cycle 2 of therapy for patients randomly allocated to Regimen I or II, or 4-6 weeks after study enrollment for patients randomly allocated to Regimen III.

C. Purpose

Serum specimens will first be shipped to the GOG Tissue Bank in Columbus Ohio and then Dr. Robert Burger at Fox Chase Cancer Center, Dr. Bradley Monk at the University Of California at Irvine Medical Center, Dr. Doris Benbrook at the University of Oklahoma Health Sciences Center, and Drs. Debbie Stearns-Kurosawa and Shinichiro Kurosawa at at the Oklahoma Medical Research Foundation to quantify the circulating levels of specific angiogenic markers as described in Appendix III.

In case it is necessary to adjust for the contribution of platelet-derived VEGF in the serum specimens, an accompanying platelet count will need to be collected at each time-point from each patient. The level of VEGF in serum can then be expressed in pg/ml as well as pg/10^6 platelets to adjust for the contribution from the platelets. Serum VEGF expressed in pg/ml and pg/10^6 platelets will then be compared with tissue-derived VEGF (results from the immunohistochemistry assays).

D. Format for Labeling the Specimen

Label the serum specimens with the GOG protocol number (GOG-0212), the GOG Bank ID (####-##-G###), the specimen code (SB01 for the pre-cycle 1 serum and SB02 for pre-cycle 2 serum), and the collection date (mm/dd/yyyy).

E. Equipment and Supplies Needed for Preparing the Serum Specimen

In addition to the materials provided in each of the Single-Chamber Specimen Kits for GOG-0212, you will need gloves, red top Vacutainer® tube(s), tube rack, a permanent marker, a syringe with a 16-18 gauge needle (or a transfer pipette), dry ice, a centrifuge, a refrigerator or a bucket with wet ice, and access to appropriate freezing/storage space to collect each serum specimen.

F. Guidelines and Recommendations for Preparing the Serum Specimens

Ideally, the serum will be processed within 2 hrs from the time the blood is drawn to freezing when possible and must be frozen within 4 hrs of the blood draw. The faster the serum can be processed from blood draw to freezing the better. Serum processed within 1-2 hrs is the highest quality; serum processed within 2-4 hrs is a lower quality. Serum processed more than 4 hrs after drawing the blood is the poorest-quality serum for testing. Tracking the serum processing time is also critical in assessing specimen quality and suitability for testing.

Ideally, the serum will be frozen in an ultra-cold freezer ($\leq$ -70^{o}C), in liquid nitrogen (liquid or vapor phase), or by direct exposure with excess dry ice. If ultra-cold freezing conditions are not available at your site, a non-cycling -20^{o}C freezer can be used; however, the amount of time the serum is kept in this type of freezer should be kept to a minimum because this temperature is not cold enough to achieve a frozen solid state (water-based liquids will be frozen solid at $\leq$ -56^{o}C). A non-cycling freezer is a freezer that will build up frost and requires defrosting by hand. Serum kept in a non-cycling -20^{o}C freezer should be surrounded with excess dry ice to allow the serum to achieve and then maintain a frozen solid state. Storage of serum in a frost-free -20^{o}C freezer will repeatedly damage the specimen each time the freezer cycles (that is, as the freezer thaws and then refreezes). Serum frozen under ultra-cold conditions represents the highest quality specimen suitable for all types of laboratory testing. Serum frozen in a non-cycling -20^{o}C provides a lower -quality specimen suitable for restricted types of laboratory testing. Serum frozen in a frost-free -20^{o}C freezer provides the lowest-quality serum which has limited usefulness

for research purposes. Tracking the freezing conditions for each serum specimen is of critical importance to assess specimen quality and suitability for testing.

G. Instructions for Preparing Each Serum Specimen

1. **Label Cryotubes**. Label the screw-cap cryotubes for each time point with the GOG protocol number, the GOG Bank ID, the Specimen Code and the collection date.
   * ***For GOG-0212, label ten 1.8 ml screw-cap cryotubes for each time point, and use the specimen code SB01 for pre-cycle 1 serum and SB02 for pre-cycle 2 serum.***
2. **Draw Blood**. Draw 10 ml of blood into a red top Vacutainer® tube.
3. **Allow Blood to Clot**. Allow the blood to clot upright at room temperature for 30 minutes.
   * *If the blood cannot be centrifuged immediately (next step), store the clotted blood at 4^oC or in a bucket with excess wet ice for no longer than 3 hrs from the time of the blood draw. The faster the blood can be centrifuged after the 30 min clotting step, the better.*
4. **Centrifuge Blood**. Centrifuge the blood to separate the serum (clear straw-colored liquid) from the fibrin clot and the blood cells.
   * ***The optimal centrifugation conditions are ~3,500 x g at 4^oC for 10 min. The minimal centrifugation conditions are ~1000 x g at room temperature for 15 minutes. The longer centrifugation time compensates for the slower speed. Avoid centrifugations without refrigeration longer than 15 min because excess heat may build up in the unit and damage the serum.***
5. **Mix and Aliquot Serum**. Remove the caps from the blood tube, the 15 ml conical tube and the cryotubes. After drawing the serum into a sterile syringe with a 16-18 gauge needle (or into a transfer pipette), transfer the serum into the 15 ml conical tube. To allow for thorough mixing of the serum, recap the 15 ml conical tube, invert the tube gently several times, and then remove the cap. Dispense (aliquot) the serum evenly into as many of the labeled screw-cap cryotubes as possible. Cap the cryogenic vials securely.
   * ***Fill each cryotube with a minimum of 0.25 ml (cc) to a maximum of 1.7 ml (cc) of serum. It is better to separate the serum into more cryotubes with a smaller volume than into fewer cryotubes with a larger volume.***
6. **Freeze Serum**. Freeze the serum in the cryotubes immediately in an upright position, when possible, using an appropriate type of freezing/storage space as described in Section V-F.
7. **Complete the Form SP.** Complete a GOG Specimen Form (Form SP) as specified in Section VII. Include a copy of Form SP with the specimen when it is shipped to the GOG Tissue Bank, and retain a copy in your files.
   * ***Specify the type of storage condition prior to shipment (ultra-cold freezer/liquid nitrogen [N_2]/dry ice) in item 12, type of blood collection tube (red-top) in item 16, that a platelet count is required in item 17, the platelet count in item 18 and the date of the platelet count in item 19 on Form SP for each serum specimen. Items 17-19 can be completed after the fact as an amendment when the data is available.***
8. **Ship Serum to the GOG Tissue Bank**. Ship the frozen serum with excess dry ice to the GOG Tissue Bank in the Single-Chamber Specimen Kit provided by the GOG Tissue Bank as described in Section VIII.
   * ***A maximum of 20 cryotubes can be packaged into each Single-Chamber Specimen Kit.***

H. Instructions for Obtaining the Platelet Count to Accompany Each Serum Specimen

1. **Dislodge Anticoagulant**. Gently tap a lavender (purple) top Vacutainer® tube to dislodge the EDTA anticoagulant from the stopper and walls of the tube.
2. **Draw Blood**. Draw blood into the Vacutainer® tube with EDTA until the vacuum is exhausted.
3. **Mix Blood With EDTA**. Mix the blood and anticoagulant by gently inverting the tube 5-10 times.
4. **Determine Platelet Count**. Send the blood tube to your clinical laboratory to determine the platelet count.
5. **Enter Platelet Information on Form SP**. Enter the platelet count in item 18 and the date the platelet count was determined in item 19 on Form SP. If the value is not available before the frozen serum is shipped to the GOG Tissue Bank, Form SP can be amended and re-submitted online, or corrected by hand and an amended copy of the form faxed to the GOG Statistical and Data Center at 716-845-8393.
   * ***Thank you for your cooperation in providing this valuable piece of data.***

VI. Preparing Whole Blood for GOG-0212

A. Requirements

An amendment has been approved to collect a whole blood specimen from new patients on GOG-0212 as well as women who have already been enrolled on GOG-0212 regardless of randomization and treatment. Blood must

only be collected from women who give permission for their blood to be submitted to the GOG Tissue Bank for future research.

Women already enrolled on GOG-0212 will need to be re-consented for this collection. If the patient does not give permission, select "No" in the online Specimen Consent Application for the question "Did your patient give permission for her blood to be collected for submission and use for this research study" and enter "patient refusal" as the reason the specimen was not collected/submitted in item 5 on the SP Form for this whole blood specimen.

If the patient gives permission, 10 ml blood will need to be drawn into a purple-top Vacutainer® tubes with the anti-coagulant EDTA at one time point. The whole blood will need to be collected as described in Section VI-D and shipped to the GOG Tissue Bank as described in Section VIII.

Patients may participate in this treatment protocol even if they don't give permission for their blood to be used for future research or if the submitting institution is a Non-US site and submission of blood is logistically infeasible. **If blood can not be submitted for GOG-0212, please indicate the reason in item 5 on the SP Form, such as patient refused, tried but not able to draw blood, or Non-US site logistically infeasible.**

B. Time Point

Whole blood will need to be collected prior to or after starting treatment on this phase III trial or at any time during follow up. Although the collection time point is flexible, we encourage sites to try and collect the blood as soon as possible to remove this requirement from your patient's form schedule. For new patients, please try to collect this blood specimen within 4 weeks of registration. For women already enrolled on GOG-0212 that will require re-consenting, please collect this blood specimen at the patient's next visit which can be before, during or after treatment, or at any time during follow up. If you need to get an extension for submitting the whole blood specimen, please contact Kathleen Darcy via email at darcy@gogstats.org or ask for one the Translational Research Scientists at 716-845-5702.

This whole blood specimen **MUST be** drawn into a standard purple-top Vacutainer® tube with the EDTA anti-coagulant and **shipped at ambient temperature the day the blood is drawn** via Federal Express **in your own shipping container for next morning delivery to** the GOG Tissue Bank on a Monday through Friday schedule for Tuesday through Saturday delivery as described in Section VIII for immediate processing. **Do not collect blood the day before a holiday** as staff will not be available at the Bank to receive or process the blood. **Please make other arrangements to collect this blood specimen on a different day.**

C. Purpose

The purpose of this whole blood specimen is to bank DNA from whole blood for research, specifically to evaluate the association between single nucleotide polymorphisms (SNPs) and measures of clinical outcome including overall survival, progression-free survival and adverse events. Whole genome SNP-association studies and evaluation of individual SNPs will be performed by Dr. Michael Birrer at MGH Cancer Center and/or investigators approved by the GOG Committee on Experimental Medicine based on available funding and expertise.

D. Instructions for Collecting One 10 ml Tube of Whole Blood for DNA Extraction and SNP Analysis

1. **Label the Purple-Top Vacutainer® Tube.** Label the 10-ml Purple-Top Vacutainer® tube with EDTA for this protocol with the GOG protocol number (GOG-0212), GOG Bank ID Number (####-##-G###), the Specimen Code (WB01 for whole blood), and the collection date (mm/dd/yyyy).
2. **Draw Blood**. Draw 10 ml of blood into a standard 10-ml Purple-Top Vacutainer® tube with EDTA until the vacuum is exhausted**.**
3. **Mix Blood with the EDTA**. Mix the blood with the anticoagulant (EDTA) by gently inverting the tube 5-10 times.
4. **Store the Blood at Room Temperature.** Store the blood at room temperature until the specimen can be shipped to the GOG Tissue Bank.
   **** Please recall that the blood specimens drawn for GOG-0212 must be shipped the day the blood is drawn to insure that high quality DNA can be extracted from the specimen.***
5. **Complete the Form SP**. Complete the GOG Specimen Form (Form SP) online using SEDES as specified in Section VII. Submit a copy of Form SP with the specimen when it is shipped to the GOG Tissue Bank, and retain a copy in your files.
   **** Please remember to indicate the Specimen Type is "Whole blood" in item 8, the Items Shipped is "Tube/Vial" in item 9, the quantity shipped is "1" in Item 10, the "Storage Type" is "Room***

Temperature" in Item 12, the "Type of blood collection tube" is "EDTA" in item 16, and "Platelet count required" is "No" in item 17 on Form SP for this whole blood specimen.

6. **Ship the Blood.** Ship the blood for a given GOG-0212 patient the day the blood is drawn to the GOG Tissue Bank as described in Section VIII.
   * ***Please note that the blood specimen must be shipped the day the blood is drawn for delivery the next morning as this specimen must undergo immediate processing upon receipt to extract high quality DNA.***

VII. Submitting Form SP for GOG-0212

A. Summary of the Form SP Requirements for Each UC0701 Patient

One Form SP must be completed and electronically submitted to the GOG Statistical and Data Center (SDC) ***for each specimen*** required for the protocol regardless of the specimen submission status using the SDC Electronic Data Entry System (SEDES). Specific instructions for completing Form SP are available via SEDES by scrolling down to the SP Forms for GOG-0212.

B. Instructions for Submitting Form SP Online

Form SP must be submitted to the GOG SDC online using SEDES which is available on the GOG Web Menu under *Registration/Data Entry*. To access Form SP for online submission, log onto the GOG Web Menu and use SEDES to electronically enter Form SP data. Any questions about access or problems should be directed to the User Support Department at the GOG Statistical and Data Center at support@gogstats.org or by phoning 716-845-7767. Retain a printout of the completed form for your records and include a copy of the completed form when the specimen is shipped to the GOG Tissue Bank. It is not necessary to send a completed Form SP to the GOG Tissue Bank when the specimens are not submitted.

VIII. Shipping Specimens for GOG-0212

A. All specimens will be shipped to the GOG Tissue Bank at the following address:

GOG Tissue Bank – Protocol GOG-0212
Nationwide Children's Hospital
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: (614) 722-2865
Fax: (614) 722-2897
E-mail: gogbank@nationwidechildrens.org

B. Primary Tumor Specimen

The primary tumor specimen (FP01) must be shipped to the GOG Tissue Bank within 8 weeks of study enrollment. To satisfy this specimen requirement, a paraffin block or 20 unstained sections of representative primary tumor tissue must be shipped to the GOG Tissue Bank **using your own shipping container** at the address provided using the US Postal Mail at your own expense. If shipping slides, please pack slides in a plastic slide cassette labeled with the GOG protocol code, Bank ID, specimen code and collection date. Tape the slide cassette shut and wrap in bubble wrap in bubble wrap or another type of padded material before shipment.

C. Pre-Cycle 1 and Pre-Cycle 2 Serum Specimens

The pre-cycle 1 serum specimen (SB01) and the pre-cycle 2 serum specimen (SB02) must be shipped to the GOG Tissue Bank using the Single-Chamber Specimen Kits provided by the GOG Tissue Bank for this protocol. Please follow the instructions provided below for packing up to 20 cryotubes of frozen serum in a Single-Chamber Specimen Kit.

Instructions for Shipping Frozen Serum Specimens

1. **Pre-fill Kit.** Remove the foam lid from the Single-Chamber Specimen Kit provided by the GOG Tissue Bank and layer dry ice into the chamber until it is about 1/3 full.
2. **Bag Serum.** Transfer the cryotubes of frozen serum for each patient and time point into a zip-lock bag. Expel as much air as possible before sealing the bag.

3. **Transfer Specimens.** Transfer the zip-lock bags with a maximum of 20 cryotubes into a plastic biohazard secondary envelope containing absorbent material, and then put the secondary envelope into the Tyvek envelope. Expel as much air as possible before sealing both envelopes.
   * ***When possible, please try to pack the cryotubes for a single time point for two GOG-0212 patients into each Single-Chamber Specimen Kit provided by the GOG Tissue Bank.***
4. **Pack Specimens and Dry Ice.** Place the Tyvek envelope containing the frozen serum specimens into the Single-Chamber Specimen Kit and then fill the kit to the top with dry ice.
5. **Insert SP Forms.** Insert a folded copy of the SP Forms for these specimens into the Single-Chamber Specimen Kit.
6. **Seal Kit.** Place the styrofoam cover on top of the Single Chamber Specimen Kit and then seal the kit securely with filament or other durable sealing tape.
7. **Complete and Attach AirBill**. Complete the pre-printed *FedEx Express US Airbill*, insert it into the plastic pouch, and attach the pouch to the top of the kit.
8. **Attach Other Labels**. After completing the Dry Ice Label (UN1845), attach the Dry Ice Label and an Exempt Human Specimen Sticker to the side of the box.
9. **Arrange for Pick-Up**. Make arrangements for Federal Express pick-up through your usual institutional procedure or by calling 1-800-238-5355. When requesting pick-up, be sure to give the account number (1290-2562-0) on the pre-printed air-bill and stress that pick-up is at your institutional address.
10. **Ship Specimens.** Ship the frozen serum specimens and the SP Forms to the GOG Tissue Bank at the address provided above via Federal Express Priority Overnight delivery using the GOG Tissue Bank's Federal Express Account Number (1290-2562-0). Please ship specimens Monday through Thursday for a Tuesday through Friday delivery.

D. Submission of Whole Blood for GOG-0212.

A whole blood specimen will be required for all patients who give permission for their blood to be submitted for future research.

Shipping Blood According to International Air Transportation Association (IATA) Standards.

Although the GOG Tissue Bank will not provide a specimen kit for shipping this whole blood specimens to the GOG Tissue Bank for GOG-0212, your institution will still be required to comply with IATA standards (www.iata.org).

To ship whole blood specimens to the GOG Tissue Bank at ambient temperature you will need the following: (1) sturdy shipping container (e.g., a FedEx Box or another type of cardboard or Styrofoam box), (2) biohazard bag with absorbent material, (3) puncture and pressure resistant envelope (e.g. Tyvek envelope), (4) Exempt Human Specimen Sticker, and (5) blank *FedEx Express US Airbill*.

If you do not have these materials available at your Institution, you may order them from any supplier.

Biohazard bag and absorbent material can be ordered from Saf-T-Pak (Phone: 800-814-7484; Website: www.saftpak.com).

- STP-710 Disposable 2-Part Secondary Pressure Vessel, Medium (i.e., secondary shipping envelope)
- STP-151 100 mL Absorbent Strip – 6 inches (i.e., absorbent material)

Cardboard FedEx shipping boxes are available from FedEx at no charge. If you do not have a FedEx pick-up and supply center at your Institution, you can request that your Driver bring extra boxes to you at your next pick-up. FedEx Customer Service can be reached at 800-Go-FedEx (800-463-3339).

If your Institution has a small number of patients on GOG trials or has limited funding to purchase supplies, please consider "cost sharing" with other GOG institutions or your parent institution.

Instructions for Shipping Whole Blood Specimens For DNA Extraction and SNP Analysis Using Your Own Shipping Container

***Special reminder*:** The whole blood specimens for this protocol must be shipped to the GOG Tissue Bank at ambient (room) temperature the day the blood is drawn. These blood specimens must be drawn in a 10-ml purple-top Vacutainer® tube with the anti-coagulant EDTA and can be shipped on a Monday through Friday schedule for Tuesday through Saturday morning delivery. Bank staff will be available for immediate processing of the blood specimens upon receipt. Bank staff do not work holidays and will not be available to process the blood so d**o not**

collect blood for GOG-0212 the day before a holiday. Please make other arrangements to collect this blood specimen on a different day. **Please note that you can place up to 4 different blood specimens in one biohazard bag.**

1. **Place the Whole Blood Tube(s) into a Biohazard Bag with Absorbent Material.** Place the whole blood specimen labeled with the protocol code, Bank ID, specimen code (WB01) and collection data into a biohazard bag with an absorbent strip. Expel as much air as possible before sealing the bag.
2. **Place the Blood Tube(s) into a Tyvek Envelope.** Next place the blood wrapped in padding into a Tyvek envelope. Expel as much air as possible before sealing the envelope.
3. **Place the Tyvek Envelope into a Sturdy Cardboard Box and include Bubble Wrap or Other Padding as Needed.** Place the Tyvek envelope containing up to 4 whole blood specimens into a sturdy cardboard box like the smallest cardboard FedEx box. If you are using a larger cardboard box, you can batch ship blood in more than one Tyvek envelope each containing up to 4 tubes of blood. Include bubble wrap or other padding as needed to secure the Tyvek envelope(s) inside the box.
4. **Place the SP Form(s) into the Cardboard Box.** Insert a print out of the SP Form(s) for the whole blood specimen(s) into the cardboard box.
5. **Tape the Cardboard Box.** Seal the cardboard box with filament or other durable sealing tape.
6. **Complete and Attach the *Airbill.*** Complete a *FedEx Express US Airbill* with the following information. In section 3 enter: GOG Tissue Bank / Protocol GOG-0212, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus Ohio 43205. Phone: (614) 722-2865. In section 4a, check "*FedEx Priority Overnight"*. In section 5, check "*FedEx Box*" or "*Other*". If blood is collected on a Friday, please ship "*FedEx Priority Overnight*" for Saturday delivery by checking "*Saturday Delivery"* in section 6. Saturday delivery is **only available** for the shipment of whole blood. In section 7, check Bill to: "Recipient" and enter the GOG Tissue Bank's Federal Express account number: 1290-2562-0.
7. **Complete and Attach Other Labels.** Attach the Exempt Human Specimen Sticker to the side of the cardboard box.
8. **Arrange for Federal Express Pick-Up.** Make arrangements for Federal Express pick-up through your usual institution procedure or by calling 1-800-238-5355. When requesting a pick-up, be sure to give the GOG Tissue Bank Federal Express account number (1290-2562-0) and stress that pick-up is at your institutional address.
10. **Ship the Specimens to the GOG Tissue Bank.** Ship the whole blood specimen(s) and the SP Form(s) at ambient temperature to the GOG Tissue Bank at the address provided above on a Monday through Friday schedule for a Tuesday through Saturday morning delivery.

IX. Banking Specimens for GOG-0212

The GOG Tissue Bank staff will be responsible for all of the general activities associated with receiving, banking and distributing the clinical specimens submitted for GOG-0212. The Bank staff will also be responsible for preparing and distributing two single-chamber Specimen Kits with the materials specified in Section III for this protocol. The cost of shipping the GOG-0212 specimens from the GOG participating institutions to the GOG Tissue Bank will be billed to the GOG Tissue Bank Federal Express account.

Upon receipt of any shipments containing specimens for GOG-0212, the GOG Tissue Bank staff will immediately assess the type, quantity, and condition of the clinical specimens received; complete the appropriate fields in the GOG Specimen Form; enter the specimens into their database system; and store the specimens under the appropriate conditions. The GOG Tissue Bank staff will complete the bottom part of Form SP for each specimen and submit the data to the GOG Statistical and Data Center electronically within 3 business days of receiving any clinical specimens for this protocol. A copy of the completed Form SP for each specimen will be retained in the files kept at the GOG Tissue Bank. In addition, the GOG Tissue Bank will work with the GOG Statistical and Data Center to reconcile specimen identifiers, information, condition, and quality as needed.

A. Primary Tumor Specimen

The formalin-fixed and paraffin-embedded primary tumor tissue will be received as a block or 20 unstained sections. Staff at the GOG Tissue Bank will make sure that each block or section is labeled with the GOG protocol number (GOG-0212), GOG Bank ID, the appropriate specimen code (FP01) and the collection date.

1. **Block**. If the primary tumor is received as a paraffin block, each block will be stored under vacuum and protected from light. Just before distribution for laboratory testing, 20 unstained sections will be prepared and captured on charged slides that are labeled with the identifiers indicated above. The slides will then be wax-dipped, stored under vacuum, and protected from light prior to distribution.

2. **Unstained Sections**. When the primary tumor is received as unstained sections, the slides will need to be wax-dipped, stored under vacuum, and protected from light.

B. Pre-Cycle 1 and Pre-Cycle 2 Serum

Frozen serum will be stored at the Bank in an ultra-cold freezer ($\leq -70^{o}C$) or in a liquid nitrogen storage tank. Staff at the GOG Tissue Bank will make sure that each serum specimen is labeled with the GOG protocol number (GOG-0212), GOG Bank ID, the appropriate specimen code (SB01 or SB02), and the collection date.

C. Whole Blood

Each whole blood specimen will need to be processed immediately upon receipt to extract DNA, assess the DNA concentration and quality, and then to store the DNA in an ultra-cold freezer in aliquots labeled with the GOG protocol code, Bank ID, specimen code (WB01-DNA) and collection date. Ideally the blood will be received in a liquid state in a purple-top Vacutainer® tube with EDTA. Staff at the GOG Tissue Bank will need to document the date of DNA extraction using the format mm/dd/yyyy, DNA concentration in [brackets] and 260/280 ratio in (parenthesis) in item 30 on Form SP and to note comments regarding specimen condition in item 31 on Form SP.

X. Distributing Specimens for Laboratory Testing for GOG-0212

Chairs of the GOG Committee for Experimental Medicine and the GOG Tissue Utilization Subcommittee will coordinate to make decisions regarding when specimens will be distributed to approved-investigators for approved laboratory testing. The GOG Statistical and Data Center and the GOG Tissue Bank will work together to coordinate the physical distribution of the specific specimens for select patients to the approved investigators for laboratory testing. Specimen selection will be based on information regarding specimen procurement and condition as well as patient eligibility, evaluation criteria, statistical considerations, and relevant clinical information.

For each shipment, the GOG Tissue Bank staff will e-mail the investigator and the GOG Statistical and Data Center an electronic file that includes an inventory of all specimens included in the shipment with the specimen specific identifiers as well as quantity and condition of the specimens being shipped. The GOG Statistical and Data Center will email the investigator an electronic file containing the specimen identifiers with relevant information regarding specimen condition, suitability for testing, eligibility/evaluability for a given component of the research study, and fields for the laboratory data if appropriate. The investigator will need to use the specimen identifiers in the electronic

file from the GOG Statistical and Data Center to avoid having to enter these identifiers thus reducing redundant data entry and minimizing the chance for errors when connecting the laboratory testing data to the clinical information for the GOG participating institutions.

A. Primary Tumor Tissue

When appropriate, the GOG Tissue Bank staff will be responsible for shipping a specified number of unstained sections of primary tumor tissue from select GOG-0212 patients to the approved investigators given below.

- To determine the tumor expression of the angiogenic markers (CD-31, TSP-1, CD-105, and VEGF), ten unstained sections will be distributed to Drs. Bradley Monk and Robert Burger (see Appendix III). Requests for distribution of additional sections will need to be submitted to both the GOG Statistical and Data Center and the GOG Tissue Bank.

B. Pre-Cycle 1 and Pre-Cycle 2 Serum

When appropriate, the GOG Tissue Bank staff will be responsible for shipping an appropriate number of pre-cycle 1 and pre-cycle 2 serum aliquots from select GOG-0212 patients to the approved investigators given below.

- To quantify the concentrations of angiogenic markers (angiogenin and VEGF), two aliquots of pre-cycle 1 and pre-cycle 2 serum will be distributed to Drs. Bradley Monk and Robert Burger (see Appendix III). Requests for distribution of additional aliquots will need to be submitted to both the GOG Statistical and Data Center and the GOG Tissue Bank.

- To quantify the concentrations of angiogenic markers (VEGF, bFGF, EGF, EAN-78, GRO, IFN-γ, IGF-1, IL-6, LEPTIN, MCP-1, PDGF-BB, PIGF, RANTES, TGF-β1, TIMP-1, TIMP-2, Thrombopoietin, and VEGF-D), three aliquots of pre-cycle 1 and pre-cycle 2 serum will be distributed to Dr. Doris Benbrook (see Appendix III). Requests for distribution of additional aliquots will need to be submitted to both the GOG Statistical and Data Center and the GOG Tissue Bank.

- To quantify the concentration of sEPCR, one aliquot of pre-cycle 1 and pre-cycle 2 serum will be distributed to Drs. Shinichiro Kurosawa and DJ Stearns-Kurosawa (see Appendix III). Requests for distribution of additional aliquots will need to be submitted to both the GOG Statistical and Data Center and the GOG Tissue Bank.

C. DNA from Whole Blood

When appropriate, the GOG Tissue Bank staff will be responsible for shipping an appropriate quantity of DNA with corresponding Q/C data to Dr. Michael Birrer at MGH Cancer Center and/or a CEM-approved investigator for whole genome SNP-associations studies and/or evaluation of individual SNPs.

The investigators performing the laboratory testing on the GOG-0212 specimens will not be given access to any personal identifiers. The investigators will be responsible for the direct supervision and oversight of the laboratory testing performed on the specimens from patients participating in GOG-0212 (see Appendix III). The individuals at the respective laboratories will be responsible for keeping accurate records of all laboratory testing performed on the GOG-0212 specimens, ensuring that the laboratory testing results are linked to the appropriate specimen-specific identifiers and transferring relevant laboratory data to the GOG Statistical and Data Center. The study chair will coordinate with the study co-chairs, scientific collaborators and the GOG Statistical and Data Center to analyze, report, and publish the study results.

XI. Distributing Specimens for Future Research

All of the residual FFPE tumor tissue, serum specimens and DNA still remaining after completion of GOG-0212 will be banked in the GOG Tissue Bank and made available as needed for approved cancer or non-cancer research projects based on GOG Tissue Bank - Specimen Distribution Policies if the following condition is satisfied: Each study patient in question must have provided permission for the use of her specimens for cancer and/or non-cancer research. These responses (choices) will be documented on the informed consent document that the patient signs for the protocol and

electronically when the staff at the treating GOG institution enters the patient's choices online using the Specimen Consent Application available on the GOG website.

The Specimen Consent Application also captures the patient's decision regarding (1) the use of her clinical information collected by the GOG as part of her participation in this trial for future research that uses her specimens, (2) the use of her specimens to be used for future research to study changes in genetic material (those passed on in families or that are not passed on in families but are either natural changes or influenced by environment and lifestyle), and (3) for someone at your institution such as a doctor or nurse to contact her in the future to ask her to take part in more research.

The specimens will be used for research purposes only until they are used up or until the patient changes her mind. The staff at the GOG treating institutions will use the Specimen Consent Application to amend the patient's choice(s) regarding the future use of her specimens if the patient changes her mind. This application shares information with the GOG Statistical and Data Center and the GOG Tissue Bank and has management, reporting, confirmation and validation features. If the patient does not give permission for the use of her specimens for future cancer or non-cancer research, the GOG Tissue Bank will be instructed to destroy (incinerate) any remaining specimens to insure that the patient's wishes are honored.

Chairs of the GOG Committee for Experimental Medicine and the GOG Tissue Utilization Subcommittee will coordinate to make decisions regarding when specimens will be distributed to approved investigators for approved laboratory testing. The GOG Statistical and Data Center and the GOG Tissue Bank will work together to coordinate the physical distribution of the specific specimens for select patients to the approved investigators for laboratory testing. Specimen selection will be based on information regarding specimen procurement and condition as well as patient eligibility, evaluation criteria, statistical considerations, and relevant clinical information. The GOG Statistical and Data Center will email the investigator an electronic file containing the specimen identifiers with relevant information regarding specimen condition, suitability for testing, eligibility/evaluability for a given component of the research study, and fields for the laboratory data if appropriate. For each shipment, the GOG Tissue Bank staff will e-mail the investigator and the GOG Statistical and Data Center an electronic file that includes an inventory of all specimens included in the shipment with the specimen specific identifiers as well as quantity and condition of the specimens being shipped.

The investigators performing approved research on any GOG-0212 specimens will not be given access to any personal identifiers. The investigators will be responsible for the direct supervision and oversight of the laboratory testing performed on these specimens. The individuals at the respective laboratories will be responsible for keeping accurate records of all laboratory testing performed in the GOG specimens, ensuring that the laboratory testing results are linked to the appropriate specimen-specific identifiers and transferring relevant laboratory data to the GOG Statistical and Data Center for analysis. The approved principal investigator (PI) will coordinate with co-PIs, scientific collaborators and the GOG Statistical and Data Center to analyze, report, and publish the research results. Any presentation or publication will comply with the GOG Publications Policy and acknowledge the National Cancer Institute grants to the GOG Administrative Office (CA 27469), the GOG Tissue Bank (CA 11479) and the GOG Statistical and Data Center (CA 37517).

APPENDIX III

Laboratory Procedures for GOG-0212

I. Quick Scan Summary of the Laboratory Testing for GOG-0212.

Assays	Specimens	Results	Testing Laboratories
Immunohisto-chemistry (IHC) Assays	Archival Primary Tumor Tissue (FP01)	Expression of CD-31, thrombospodin-1 (TSP-1), CD-105 (endoglin), and vascular endothelial growth factor (VEGF).	Dr. Robert Burger at Fox Chase Cancer Center and Dr. Bradley Monk at the University of California at Irvine Medical Center
Enzyme-Linked Immunosorbent Assays (ELISA)	Serial serum specimens: pre-cycle 1 (SB01), pre-cycle 2 (SB02)	Concentrations of angiogenin and VEGF	Dr. Robert Burger at Fox Chase Cancer Center and Dr. Bradley Monk at the University of California at Irvine Medical Center
		Concentrations of VEGF, bFGF, and sEPCR	The Laboratories of Dr. Doris Benbrook at the University of Oklahoma Health Sciences Center, and Drs. Debbie Stearns-Kurosawa and Shinichiro Kurosawa at the Oklahoma Medical Research Foundation.[2, 3]
Angiogenesis Antibody Array Assay	Serial serum specimens: pre-cycle 1 (SB01), pre-cycle 2 (SB02)	Level of EGF, EAN-78, GRO, IFN-γ, IGF-1, IL-6, LEPTIN, MCP-1, PDGF-BB, PIGF, RANTES, TGF-β1, TIMP-1, TIMP-2, Thrombopoietin, VEGF and VEGF-D	The Laboratory of Dr. Doris Benbrook at the University of Oklahoma Health Sciences Center.[2]
Single Nucleotide Polymorphism Analysis	DNA extracted from whole blood	Whole genome SNP association studies and/or individual SNP analyses.	The Laboratory of Dr. Michael Birrer at the MGH Cancer Center and/or CEM-approved investigator(s)

II. Immunohistochemistry Assays for GOG-0212

A. Markers of Angiogenesis:

Immunohistochemistry assays will be performed in the Laboratory of Dr. Brad Monk at the University of California Irvine Medical Center and in the Laboratory of Dr. and Bob Burger at Fox Chase Cancer Center in Elkins Park, PA to examine the expression of angiogenic markers including CD-31, TSP-1, CD-105 and VEGF in sections of primary tumor (FP01) from patients participating in GOG-0212.

1. Immunohistochemistry Procedures:

Appropriate 5 μm thick unstained serial sections will be deparaffinized, incubated in 3% hydrogen peroxide in distilled water for 10 min, and rinsed in tap water followed by distilled water. Immunohistochemical assays will be carried out using the commercially available primary antibodies indicated in the following table, an automated immunostainers (Ventana, Tucson AZ; BioGenex, San Ramon, CA) and highly sensitive avidin-biotin detection kits (BioGenex). Antigen retrieval methods will include pronase digestion for CD-31 and VEGF. Non-specific binding sites will be blocked with goat serum for 10 minutes at room temperature. Sections will be incubated for 30-60 minutes with the appropriate primary antibody solution at room temperature, rinsed three times for 5 minutes each in phosphate-buffered saline (PBS), and exposed to biotinylated goat anti-mouse antibodies for 30 minutes at room temperature. After rinsing with PBS (five times), the sections will be exposed to a streptavidin-horseradish peroxidase conjugate for another 30 minutes at room temperature, and, after thorough rinsing with PBS, incubated with 3,3'-diaminobenzidine for exactly 5 minutes at room temperature. The sections will be then rinsed in PBS, counterstained with filtered hematoxylin for 1 minute, rinsed for 10 minutes with tap water, dehydrated in ascending alcohol series, cleared in xylene, and cover-slipped with Permount. Titrations have been performed for all antibody reagents to ensure minimal background staining and optimal antigen detection. Negative antibody controls for background staining in all immunostaining experiments will utilize mouse IgG as the primary antibody.

Biomarker	Type of Primary Antibody	Source	Clone #
CD-31	anti-CD-31 mouse antibody	Dako	JC/70A
TSP-1	anti-TSP-1 mouse antibody	Immunotech Inc.	p12
CD-105	anti-CD-105 mouse antibody	Calbiochem	14-124
VEGF	anti-VEGF mouse antibody	Dako	SN6h

2. Specimen and Assay Controls:

The positive controls for TSP-1 and VEGF immunostaining will be formalin-fixed and paraffin-embedded MCF7-WT human breast carcinoma cell line which expresses high levels of TSP-1 and VEGF and the doxorubicin-resistant derivative MCF7-40F which expresses low TSP-1 and VEGF. Formalin-fixed and paraffin-embedded invasive breast carcinomas that do not express VEGF will be used as a negative control for the VEGF immunohistochemistry assay. Angiogenesis controls with intermediate vessel counts will be run in parallel with each series of slides to ensure appropriate CD-31 and CD-105 staining. An invasive breast carcinoma specimen with high micro-vascular staining will be used for the positive control tissue, and the non-

staining areas in the same tumor tissue will be used for the negative control tissue for these markers. CD-31 and CD-105 will be evaluated in endothelial cells. Although TSP-1 and VEGF are both secreted proteins, this study will focus on evaluating the immunohistochemical expression of TSP-1 and VEGF within tumor cells and endothelial cells.

3. Data Acquisition and Evaluation Procedures:

a. Semi-Quantitative Method

After the individual immunohistochemistry assays are completed, the reviewers, who will be blinded to histopathologic and clinical data as well as the specimen identity, will independently examine each slide using light microscopy. The individual tissue sections will be scored for intensity and percent of specific staining for CD-31, TSP-1, CD-105 and VEGF within endothelial cells and/or tumor cells. The intensity of staining will be scored as follows: 1+ when less than 5% of the appropriate cells display staining, 2+ when greater than 5% of the appropriate cells exhibit light brown (mild) staining, 3+ when greater than 5% of the appropriate cells display moderate brown staining, 4+ when greater then 5% of the appropriate cells exhibit dark brown staining equal to the intensity observed in the positive control tissue, 5+ when greater than 5% of the appropriate cells exhibit a staining intensity that is greater than observed in the positive control tissue. Immunohistochemistry scores will be assigned on the basis of multiplying the percent of positive cells by the intensity of staining [IHC score = % positive cells x (intensity)]. When possible, a minimum of 1000 cells will be assessed for CD-31, TSP-1, CD-105 and VEGF staining, respectively.

The results for each biomarker will be evaluated as a percent of positively stained cells (continuous data from 0-100%), the intensity of the staining expressed as a categorical variable from 1+ to 5+, and then an aggregate IHC score from 0 through 500. In addition, a modified angiogenic index (AI) has been developed to integrate scores for CD-31 and TSP-1 into a single value. Values ranging from 1 to -4 will be assigned to the histologic score intervals [IHC score described above] listed for each marker (see the following table). These values will be summed for the two markers to determine the mAI, with a mAI of +2 representing the most favorable score and a mAI of -8 reflecting the least favorable score.

mAI Score	TSP-1 IHC Score	CD-31 IHC Score
1	30+	0-30
0	25-30	30-70
-1	20-25	70-85
-2	15-20	85-100
-3	10-15	100-123
-4	0-10	123+

b. Quantitative Method

Image analysis (IA) using the CAS 200 system (Becton Dickinson, San Jose, CA) will be performed to quantify the staining intensity of the CD-31, TSP-1, CD-105 or VEGF marker-positive cell populations. Quantitative cellular and nuclear antigen protocols will be utilized. Technologists, who are blinded to clinical data and cell line identifiers, will carry out IA. All measurements obtained on the CAS 200 IA

system will be derived from calibrated conversion of pixel information. For IA of CD-31, TSP-1, CD-105 or VEGF, the instrument threshold will be set using a series of positive and negative slides to the value at which the best discrimination between cell membrane, cytosol and nuclei is observed. Antibody threshold will be set to read zero pixels for isotype-matched irrelevant monoclonal antibody. At least 10 fields of positive areas will be analyzed for each specimen. Values will be converted to the product of positive area and positive stain expressed as optical density (O.D.) units using CAS 200 software. Antigen preservation will be evaluated in most cases with positive control slides and vimentin staining (dilution 1:200, Dako, Carpenteria, CA). Under these experimental conditions, IHC scores, IA results and the amounts of target protein expressed as the number of molecules per cell in human breast cancer specimens were closely correlate ($r > 0.9$).

4. Data Transfer:

Dr. Monk or his representative will forward the various types of immunohistochemistry results for CD-31, TSP-1, CD-105 or VEGF along with the appropriate specimen identifiers (GOG Protocol Number, Bank ID, Specimen Code and Collection Date) for each slide to the GOG Statistical and Data Center. The tissue biomarker level and the corresponding specimen tracking information for each slide will then be entered into the GOG Ingres relational database. The blinded anonymous laboratory data with the specimen identifiers (the GOG Bank ID Number, Specimen Code and Collection date) will then be merged with the clinical data for these cases. The appropriate statistical analysis will then be performed at the GOG Statistical and Data Center. The study chairs will coordinate with the GOG Statistical and Data Center to prepare the reports and manuscript(s) for this study.

5. References:

Brewer, CA; Setterdahl, JJ; Li, MJ; Johnston, JM; Mann, JL; McAsey, ME**.** Endoglin expression as a measure of microvessel density in cervical cancer.Obstetrics and Gynecol, 2000; *96*:224-8.

Khoury H, Kyshtoobayeva A, Mechetner E, Burger R, Monk B, Fruehauf J. Thrombospondin-1 may regulate angiogenesis in cervical carcinoma. The Annual AFMR meeting December 1998.

Figge J, Bakst G, Weisheit D, Solis O, and Ross JS. Image analysis quantitation of immunoreactive retinoblastoma protein in human thyroid neoplasms with a streptavidin-biotin-peroxidase staining technique. Am J Pathol 1991; *139*: 1213-1219.

Peters WA, Liu PY, Barrett RJ, Stock RJ, Monk BJ, Berrek JS, Souhami L, Grigsby P, Gordon B, Alberts DS. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000; *18(8)*: 1606-1613.

Wied GL, Bartels PH, Bibbo M, Dytch HE. Image analysis in quantitative cytopathology and histopathology. Hum Pathol 1989; *20*: 549-571.

III. Enzyme-Linked Immunosorbent Assays for GOG-0212

Enzyme-linked immunosorbent assays (ELISAs) will be performed under the direct supervision of to Dr. Robert Burger at Fox Chase Cancer Center, Dr. Bradley Monk at the University Of California at Irvine Medical Center, Dr. Doris Benbrook at the University of Oklahoma Health Sciences Center, and Drs. Debbie Stearns-Kurosawa and Shinichiro Kurosawa at the Oklahoma Medical Research Foundation. Drs. Bob Burger and Brad Monk will quantify the concentration of angiogenin and vascular endothelial growth factor (VEGF) in serial serum specimens from patients participating in GOG-0212 (Section A). Dr. Benbrook will quantify the levels of VEGF and basic fibroblast growth factor (bFGF) (Section A). Finally, Drs. Stearns-Kurosawa and Shinichiro Kurosawa at the University of Oklahoma Health Sciences Center will quantify the concentration of soluble endothelial protein C receptor (sEPCR) (Section B).

A. ELISA Detection Of Angiogenin, VEGF and bFGF

1. Procedures:

Validated ELISA kits (as indicated in the following table) will be used to quantify the concentration of angiogenin, VEGF and bFGF in the available paired serum specimen. The laboratory personnel will be responsible for running the paired specimens (pre-cycle 1 and pre-cycle 2 serum) from a particular patient on the same ELISA plate with appropriate standards and controls. This will ensure that the specimens for each case will be evaluated in the same assay with appropriate controls to minimize and adjust for assay variability.

Biomarker	Type ELISA Kit (R&D Systems, Inc.)	Catalog #
Angiogenin	Quantikine Human ANG Immunoassay	DAN00
VEGF	Quantikine Human VEGF Immunoassay	SVE00
bFGF	Quantikine Human bFGF Immunoassay	SSFB75

Briefly, the microtiter plates, available from R&D Systems, Inc. (Minneapolis, MN), will be pre-coated with monoclonal antibodies specific for angiogenin, VEGF or bFGF. Standards, controls and specimens will be incubated in the wells and any angiogenin, VEGF or bFGF present within these samples will bind to the immobilized antibody. Individual samples will be evaluated in duplicate at multiple dilutions and thawed just prior to the assay. A standard curve will be generated for each assay using six (6) two-fold dilutions of control protein (recombinant human angiogenin, VEGF or bFGF). Control and standards will be included on each ELISA plate. Unbound substances will be washed away and an enzyme-linked antibody specific for angiogenin, VEGF or bFGF will then be incubated in the wells. After washing away unbound antibody, the color reagent or the substrate and amplifier solutions will be added to the wells. A stop solution will then be added to terminate the color development process.

2. Data Acquisition and Evaluation Procedures:

The intensity of color development is directly proportional to the amount of angiogenin, VEGF or bFGF bound in the first step and will be measured using an automatic microplate reader at 450 nm and 540 nm. Individual samples will be evaluated in duplicate and thawed just prior to the assay. A standard curve will be evaluated on the individual plates run for each assay using six (6) two-fold dilutions of control protein (recombinant human angiogenin, VEGF or bFGF). Background staining at 540 nm will be subtracted from the absorbance at 450 nm and then duplicate readings will be averaged for each standard, assay

control and sample. The concentration of angiogenin, VEGF or bFGF in each sample will be interpolated from the respective standard curve. In addition, repeat measurements will be obtained on different aliquots of a subset of serum samples to determine inter-assay reliability within a laboratory (angiogenin and bFGF) and between laboratories (VEGF). For example, VEGF concentrations will be quantified in all of the paired serum specimens in Dr. Burger's Laboratory whereas Dr. Benbrook's Laboratory will perform replicate testing in a subset of 15% of the available paired serum specimens defined by the GOG Statistical and Data Center. Known concentrations of purified recombinant protein will be spiked into a few of the serum specimens to confirm the linearity and recovery of these assays. These different determinations will allow the intra-assay and inter-assay precision, sensitivity as well as specificity of each of these validated assays to be documented for this study.

3. Data Transfer:

Drs. Burger, Monk and Benbrook will be responsible for forwarding the interpolated ELISA results for angiogenin, VEGF and/or bFGF along with the appropriate specimen identifiers (GOG Protocol Number, Bank ID, Specimen Code and Collection Date) for each specimen evaluated in each ELISA run and the controls to the GOG Statistical and Data Center. The biomarker level with the corresponding specimen tracking information will then be entered into the GOG Ingres relational database. The blinded laboratory data with the specimen identifiers will then be merged with the clinical data for these cases. The appropriate statistical analysis will then be performed at the GOG Statistical and Data Center. The study chairs will coordinate with the GOG Statistical and Data Center to prepare the reports and manuscript(s) for this study.

B. ELISA Detection Of sEPCR

1. Procedure:

sEPCR levels will be quantified using a commercially available ELISA kit (Asserachrom ® sEPCR, Diagnostica Stago, Asnières, France). All samples will be run in duplicate using a total of 10 µl serum per well. Specificity of the test will be ensured by the use of two monoclonal antibodies. The sample containing sEPCR will be added to a plastic microwell pre-coated with a first monoclonal antibody directed against sEPCR. Antigen in the paired serum specimens will be immobilized by one of its epitope and revealed by a second monoclonal antibody directed against another epitope of the sEPCR and coupled with horseradish peroxidase (HRP). Colour development will be visualized using the chromogen tetramethylbenzidine (TMB).

2. Data Acquisition and Evaluation Procedure:

The bound HRP will catalyze the oxidation of the TMB which has an absorbance maximum at 450 nm. The intensity of color development will be directly proportional to the amount of sEPCR bound in the first step and measured using an automatic microplate reader at 450 nm. The assay measures ranges from 50 – 1000 ng/ml sEPCR with intra- and inter-assay variation of <8%. Controls will include reference specimens from healthy adult female populations with concentrations in excess of 300 ng/ml. In a healthy adult population, sEPCR levels have a bimodal distribution. About 75-80% of individuals are in the low sEPCR group (<200 ng/ml). About 20-25% of individuals are in the high sEPCR group

(≥200 ng/ml). Individuals in the high sEPCR group are considered to have higher thrombin activity, which causes the high sEPCR levels.

3. Data Transfer:

Dr. Stearns-Kurosawa will forward the interpolated ELISA results for sEPCR along with the appropriate specimen identifiers (GOG Protocol Number, Bank ID, Specimen Code and Collection Date) for each specimen evaluated in each ELISA run and the controls to the GOG Statistical and Data Center. The biomarker level with the corresponding specimen tracking information will then be entered into the GOG Ingres relational database. The blinded laboratory data with the specimen identifiers will then be merged with the clinical data for these cases. The appropriate exploratory statistical analysis will then be performed at the GOG Statistical and Data Center. The study chairs will coordinate with the GOG Statistical and Data Center to prepare the reports and manuscript(s) for this study.

4. References

1. Kurosawa, S., Stearns-Kurosawa, D. J., Hidari, N., and Esmon, C. T. Identification of functional endothelial protein C receptor in human plasma. J. Clin. Invest., *100:* 411-418, 1997.

2. Kurosawa, S., Stearns-Kurosawa, D. J., Carson, C. W., D'Angelo, A., Della, V. P., and Esmon, C. T. Plasma levels of endothelial cell protein C receptor are elevated in patients with sepsis and systemic lupus erythematosus: lack of correlation with thrombomodulin suggests involvement of different pathological processes. Blood, *91:* 725-727, 1998.

IV. Angiogenesis Antibody Array Assay for GOG-0212

A. The Ray Bio Human Angiogenesis Array

The Angiogenesis Antibody Array will be used to simultaneous assess the level of angiogenin, bFGF, VEGF, EGF, EAN-78, GRO, IFN-γ, IGF-1, IL-6, Leptin, MCP-1, PDGF-BB, PIGF, RANTES, TGF-β1, TIMP-1, TIMP-2, thrombopoietin and VEGF-D in the pre-cycle 1 and pre-cycle 2 serum specimens from patients participating in GOG-0212. This testing will be performed in the Laboratory of Dr. Doris Benbrook at the University of Oklahoma Health Sciences Center. The exact luminex platform to be used will be re-evaluated based on available data at the time the testing is to be initiated.

1. Procedures:

The manufacturer, RayBio provides the buffers and antibodies with each set of RayBio arrays. The array membranes will be incubated with the blocking buffer at room temperature for 30 minutes. One hundred microliters of serum will be diluted in 900 microliters of blocking buffer and incubated on the membrane for 1 hour at room temperature. The membranes will be washed 3 times with 2 mls of Wash Buffer I for 5 minutes each time with shaking, followed by 2 washes with Wash Buffer II at room temperature with shaking. Biotin-conjugated antibodies to each of the 20 captured proteins and the control protein will be diluted in 1 ml and incubated on the membrane for 1 hour at room temperature. The washing steps will be repeated. The bound biotinylated antibody will be detected by incubated the membranes with horseradish peroxidase (HRP)-

conjugated streptavidin at room temperature for 1 hour. Then, the membranes will be incubated with the detection buffer for 1 minute. The membrane will be partially dried and wrapped in Saranwrap and exposed to a PhosporImager screen.

2. Specimen and Assay Controls:

Controls will include serum from a normal individual that is collected and batched. Both unspiked serum, and serum spiked with angiogenin, bFGF or VEGF at the median level observed in preliminary studies will be used.

3. Data Acquisition and Evaluation Procedures:

Each of the antibodies spotted on the array is present in duplicate. The intensity of the spots will be measured and compared with the unspiked and spiked controls and between the pre-cycle 1 and pre-cycle 2 serum specimens from patients randomized to the three regimens. A phosphorimager will be used to visualize the signal and spots will be quantified with ImageQuant Software (Molecular Dynamics). Electronic files of the images and quantifications will be saved. The detection range reported by RayBio is much greater than by ELISA. For example, the detection range for IL-2 is from 25 to 250,000 pg/ml. As determined by densitometry, the variation between two spots ranged from 0 to 10% in duplicated experiments. In contrast, the variation reported by ELISA can be 20%. The expense of the arrays precludes performing standard curves for each factor. Standard curves will only be performed using purified or recombinant forms of angiogenin, bFGF and VEGF as well as a subset of angiogenic markers of that show distinct differences in expression between time points or patient groups that vary by outcome. Repeat measurements will be obtained using a second aliquot of a subset of 15% of the available paired serum specimens defined by the GOG Statistical and Data Center to determine inter-assay reliability. Determinations of angiogenin, bFGF and VEGF concentrations in the paired serum specimens evaluated using this antibody array will be directly compared with that obtained using each of the validated ELISA kits, respectively. In addition, inter-assay variation will also be compared. It is hoped that this type of comparison will provide relevant information regarding the relative clinical utility of this new technique compared with a conventional ELISA.

RayBioTM Human Angiogenesis Antibody Array I and 1.1 Map

	A	B	C	D	E	F	G	H
1	POS	POS	NEG	NEG	Angiogenin	EGF	EAN-78	b FGF
2	POS	POS	NEG	NEG	Angiogenin	EGF	EAN-78	b FGF
3	GRO	IFN-γ	IGF-I	IL-6	IL-8	LEPTIN	MCP-1	PDGF-BB
4	GRO	IFN-γ	IGF-I	IL-6	IL-8	LEPTIN	MCP-1	PDGF-BB
5	PlGF	RANTES	TGF-β1	TIMP-1	TIMP-2	Thrombopoietin	VEGF	VEGF-D
6	PlGF	RANTES	TGF-β1	TIMP-1	TIMP-2	Thrombopoietin	VEGF	VEGF-D
7	BLANK	BLANK	BLANK	BLANK	BLANK	BLANK	BLANK	POS
8	BLANK	BLANK	BLANK	BLANK	BLANK	BLANK	BLANK	POS

4. Data Transfer:

Dr. Benbrook will forward the results from the antibody arrays along with the appropriate specimen identifiers (GOG Protocol Number, Bank ID, Specimen Code and Collection Date) for each specimen evaluated and the controls to the GOG Statistical and Data Center.

The biomarker level with the corresponding specimen tracking information will then be entered into the GOG Ingres relational database. The blinded laboratory data with the specimen identifiers will then be merged with the clinical data for these cases. Appropriate statistical analysis will be performed at the GOG Statistical and Data Center. The study chairs will coordinate with the GOG Statistical and Data Center to prepare the reports and manuscript(s) for this study.

5. References:

Huang, R.P. Detection of multiple protein in an antibody-based protein microarray system. J. Immunol. Methods, 2001; *255*:1-13.

Huang, R.P. Simultaneous detection of multiple proteins with an array-based enzyme-linked immunosorbent assay (ELISA) and enhanced chemiluminescence (ECI). Clin. Chem. Lab Medicine, 2001; *39*: 209-214.

Wang, C.C., Huan, R.-P., Sommer, M., Lisoukov, H., Huang, R. Lin, Y., and Burke, J. Array-based multiplexed screening and quantitation of human cytokines and chemokines. Journal of Proteome Research, 2002; *1*: 337-343.

V. Single Nucleotide Polymorphism (SNP) Analysis for GOG-0212

Whole genome SNP-association studies and/or individual SNP analyses will be performed using the best available platforms and procedures at the time the testing is to be initiated. For example, studies to examine common polymorphisms in the excision repair cross-complementation group 1 (ERCC1) gene, involved in nucleotide excision repair (NER) of platinum-induced damage, and the breast cancer 1 (BRCA1) or BRCA2 genes, important determinants of response to platinum drugs and taxanes, would be conducted using Sequenom's MALDI-TOF platform and the procedure described below.

1. Procedure:

The *ERCC1* codon 118, *ERCC1 C8092A, BRCA1* P871L (EX12+1485C>T, RS799917) and *BRCA2* N372H (Ex10+321A>C, RS144848) polymorphisms will be genotyped using Sequenom's MALDI-TOF platform (iPLEXTMGOLD Assay). Briefly, PCR amplification will be performed using SNP-specific primers followed by a base extension reaction using iPLEX chemistry. Five ng of DNA will be added to each PCR reaction mixture in a 384-well plate. The PCR conditions will be controlled to be 94°C for 15 minutes, followed by denaturation at 94°C for 20 seconds, annealing at 56°C for 30 seconds, extension at 72°C for 1 minute for 45 cycles, and final incubation at 72°C for 3 minutes. The PCR products will then treated with SAP (shrimp alkaline phosphatase, Sequenom) for 20 minutes at 37°C and then 5 minutes at 85°C to remove excess dNTP. A random set of 10% of the cases will be tested in duplicate to assess the reliability of the results. Previously genotyped control standards will be included on each 384-well plate.

2. Specimen and Assay Controls:

Previously genotyped control standards will be included on each 384-well plate as controls.

3. Data Acquisition and Evaluation Procedures:

Distributions will be provided by genotype for each polymorphism under evaluation. A random set of 10% of the cases will be tested in duplicate to assess the reliability of the results. Results will be compared with data at http://snp500cancer.nci.nih.gov.

4. Data Transfer:

Dr. Birrer or the CEM approved investigator will forward the results from the whole genome SNP associations studies and/or the individual SNP analyses with the appropriate specimen identifiers (GOG Protocol Number, Bank ID, Specimen Code and Collection Date) for each specimen evaluated and the controls to the GOG Statistical and Data Center. The genotyping data with the corresponding specimen tracking information will then be entered into the GOG Ingres relational database. The blinded laboratory data with the specimen identifiers will then be merged with the clinical data for these cases. Appropriate statistical analysis will be performed at the GOG Statistical and Data Center. The study chairs will coordinate with the GOG Statistical and Data Center to prepare the reports and manuscript(s) for this study.

INFORMATION ON THE COLLECTION AND USE OF SPECIMENS FOR RESEARCH

You are being asked to allow samples of your bodily materials (tissue, cells, blood, urine or other material) to be collected and used in research. Such bodily materials are referred to as specimens. Specimens can be used to help doctors and scientists learn more about caring for and treating people with cancer and other diseases. The use of specimens in scientific research can also help doctors and scientists understand why some people develop cancer and others don't, and why some people have cancers that respond or don't respond well to current therapies, for example.

The research that may be done with your specimens is not designed specifically to help you, but it may help others with cancer or other diseases in the future. Reports about research done with your specimens will not be given to you or your doctor, or be put in your health record. The research will not have an effect on your care.

If you agree to participate in one of the studies conducted by the Gynecologic Oncology Group (GOG), your specimens will be collected and used for the research described for that particular study. We will also ask you to decide whether your specimens, if still available after completion of that research study, can be used for future research. You will be asked whether your specimens can be used for cancer research, or for research for health problems other than cancer. You can still participate in a GOG study even if you do not allow your specimens to be used for future research, unless the main purpose of the study is to collect and save (bank) specimens for future research. If this is the case, the informed consent document for the study will clearly state this fact. You will always have the right to change your mind about the use of your specimens for future research. This issue will be discussed in more detail in one of the paragraphs provided below.

When research is performed on specimens connected with clinical information about the person, including the person's disease and how the person responds to treatment for example, doctors and scientists can specifically study how to prevent, detect, treat and cure cancer and other diseases, or how to predict response to therapy, toxicities, recurrence and overall survival. This is why we will ask your permission to use the clinical information that the GOG will collect about you as part of your study participation for future research that will use your specimens. Records of your clinical information will be stored at the GOG Statistical and Data Center in Buffalo, New York and at your treating institution. The GOG will utilize all possible methods to protect your privacy and confidentiality. Research investigators that may study your specimens will never be given your name, address, phone number, Social Security number or any other personal information. In addition, your specimens will never be labeled with your name or other type of personal identifier. Your clinical specimen will be labeled with a unique series of letters and numbers. The GOG uses the unique series of letters and numbers as confidential codes to keep track of the clinical specimens, and sends research investigators specimens labeled only with these codes.

Your clinical specimens will be used for research purposes and will not be sold. However, the research done with your clinical specimens may help to develop new products and therapies in the future, or may be used to establish a cell line that could be patented and licensed. In any event, there will be no direct financial benefit to you.

If you agree to allow your specimens to be used for future research, there is a chance that your specimens may be used to study genetic changes or differences that are passed on in families and may include such things as DNA analysis to identify a change or difference in your DNA that could contribute to the development of cancer or enable you to respond to a particular therapy for example. Even if your specimens are used for genetic research, they will not be labeled with your name or other personal identifier, and the results will not be put in your health records.

The choice to let us collect your specimens for research is up to you. No matter what you decide to do, it will not affect your care.

If you agree now that your clinical specimens can be collected and used for research, you can change your mind at any time. At that time, please contact the staff at your treating institution, typically your doctor or nurse, and tell them that you have changed your mind about allowing your specimens to be used for research. The staff at your treating institution will update the GOG regarding your wishes about using your specimens for the current research study, for future cancer research and/or for future research for health problems other than cancer. If necessary, the GOG will destroy (incinerate) all of your specimens to make sure that they will no longer be used for research.

When a patient participates in a clinical research study, there is a risk that information from the person's health records may be released. The staff at your treating institution and at the GOG will protect your records so that your information is kept private and confidential. The chance that your information will be given to someone in error is very small.

There may also be risks associated with the collection of a particular type of specimen. The exact type of specimen to be collected and any associated risks will depend on the study you participate in and this information will be described in the informed consent document for the research study. For example, collection of a blood specimen may result in slight discomfort, bleeding, or bruising at the site of the blood draw. Carefully read the Consent Document that accompanies this pamphlet for a description of the research study, the requirements, the types of medical and laboratory tests to be carried out and the potential benefits and risks associated with the study.

Please see the next section for some frequently asked questions regarding the collection and use of specimens for research. A short glossary is also provided at the end of this pamphlet. An expanded cancer dictionary is provided on online at http://cancer.gov/dictionary/.

FREQUENTLY ASKED QUESTIONS

1. Where do specimens come from and how are they used?

Specimens such as tissue, cells, blood, urine, saliva, and mucus, come from people (human subjects), like you, who give permission (consent) to have bodily material collected, saved and used for research. These specimens are collected by a trained member of the clinical staff like a doctor or nurse and are used for approved research. People who are trained to handle clinical specimens and also know how to protect the donor's rights make sure that the highest standards are followed. Your clinical specimens are sent to the GOG Tissue Bank for storage. Staff in the GOG Tissue Bank will then send the clinical specimens to doctors and scientists for research that has received the appropriate approval. Your doctors and nurses do not work for the GOG Tissue Bank, but they have agreed to help collect specimens from their patients who provide consent. Staffs at clinics and hospitals across the country collect clinical specimens from their patients in the same way. In this way, the research is not specific to one person but general to people across the country.

2. What kinds of laboratory testing will be used on specimens?

Researchers are interested in determining how normal cells become cancer cells, how the body reacts to cancer cells, how cancer spreads in the body, and how cancer cells respond to treatment, for example. Clinical specimens play a very important role in this research and your bodily material can be used to study DNA (genetic material), RNA, proteins, and other components of the human body to understand the role they play in cancer and other diseases. There are many laboratory tests that a researcher can use on clinical specimens including an immunoassay (to measure the amount of one protein in a tissue, cells or bodily liquid like serum, plasma or urine), in situ hybridization (to measure the amount of one piece of DNA or RNA in a tissue or cells), flow cytometry (to measure the amount of DNA, RNA or a protein in cells), microarrays (to measure the amount of thousands of pieces of RNA in a tissue or cells), proteomics (to measure the amount and size of thousands of proteins or pieces of proteins in tissue, cells or bodily liquid like serum, plasma or urine), or genetic testing (to look for a change called a mutation in a gene like BRCA1 or BRCA2 in your DNA).

3. Will I find out the results of the research using my specimens?

No, you will not receive the results of research done with your clinical specimens. When the research study is completed, the results and conclusions of the study will be published so that the entire scientific community can benefit from the research. The results from research will not affect your treatment or care right now, but they may help people like you in the future.

4. How could my health records be used in ways that might be harmful to me?

Health records could be used against patients and their families to deny insurance or employment to people with certain illnesses like AIDS or cancer. Information found in health records regarding genetic diseases passed down in families may also be used against you or your family members. Research results will not be added to your health record to prevent these types of events.

5. Who do I contact if I have questions?

You may want to contact the staff at your clinic or hospital like your doctor or nurse with any questions. The medical staff will do their best to answer your question(s) or direct you to someone who can. For additional information you can call the National Cancer Institute's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) or visit a website that provides accurate and carefully reviewed information like: http://www.cancer.gov, http://seer.cancer.gov, http://cancertrials.nci.nih.gov, http://cancernet.nci.nih.gov, http://bioethics.gov. Be aware that there are sites on the web that provide information that is misleading or inaccurate (contains mistakes or errors). Let your health care professional know if you have any questions.

GLOSSARY

Biopsy - removal of a piece of tissue from the body, which is then examined under a microscope to check for cancer cells.

BRCA1 and BRCA2 -two genes that are often changed (mutated) in families with a high risk of developing breast and ovarian cancer. When a person inherits an altered or mutated copy of BRCA1, that individual has an increased chance of developing breast, ovarian or prostate cancer.

Cancer - is a term for diseases in which abnormal cells divide without control. Cancer cells can invade nearby tissues and spread through the blood and lymphatics to other parts of the body.

Cell - the basic unit of any living organism that can reproduce itself exactly. Humans are made from millions of cells that are adapted to carry out particular functions.

Clinical information - includes medical history, diagnosis, treatment, and outcome.

Clinical trial or protocol - Research studies that involve patients. Each study is designed to find better ways to prevent, detect, diagnose, or treat cancer and other diseases, and to answer scientific questions. A clinical trial is a specific type of research activity that involves administration of a test intervention (a drug, surgical procedure, diagnostic test or medical device or example) to humans in order to evaluate the intervention.

DNA (deoxyribonucleic acid) - the substance of heredity; a large molecule that carries the genetic information present in each cell. The other type of nucleic acid found in the body is RNA, which is transcribed from DNA and translated into proteins.

Flow cytometry - a laboratory test to determine the amount of DNA, a piece of DNA or RNA, or a particular protein present in cells.

GOG Tissue Bank - the organization funded by the National Cancer Institute to collect, process, store and distribute clinical specimens from people participating in studies (clinical trials or protocols) conducted by the Gynecologic Oncology Group.

Gynecology - the branch of medicine dealing with diseases and health of the female reproductive organs.

Gynecologic cancer - cancer of the ovaries, cervix, uterine, endometrium, vulva, and vagina for example.

Gynecology Oncology Group (GOG) - the cooperative clinical trials group focused on the prevention and treatment of gynecologic cancers. The GOG is a national organization dedicated to clinical research in the field of gynecologic cancer. The purpose of the GOG is to improve the treatment of gynecologic cancer through research encompassing surgery, radiation therapy, chemotherapy, pathology, immunology, and/or gynecologic nursing as well as translational or experimental research in clinical specimens.

Human subjects - a person who participates in a research study.

Immunoassay - a laboratory test to measure the amount of a specific protein in a thin slice (section) of tissue, cells or liquid like serum, plasma or urine. **In situ hybridization** - a laboratory test to measure the amount of a piece of DNA or RNA in thin slice (section) of tissue or cells.

Microarrays - a laboratory test to measure the amount of thousands of pieces of RNA in a tissue or cells to determine an RNA expression pattern or profile in the specimen.

National Cancer Institute (NCI) -a component of the National Institutes of Health (NIH), one of the eight agencies that compose the Public Health Service (PHS) in the Department of Health and Human Services (DHHS). The NCI is the Federal Government's principal agency for cancer research and training. That NCI coordinates the National Cancer Programs which conducts and supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention and treatment of cancer, rehabilitation from cancer, and the continuing care of cancer patients and the families of cancer patients.

Plasma - the liquid part of blood after adding an anticoagulant and removing the blood cells.

Proteins - substances composed of amino acids that are essential to body structure and proper functioning.

Proteomics - a laboratory test to simultaneously measure thousands of proteins/fragments in a tissue, cells or liquid like serum or urine to determine the protein expression pattern (profile) in the specimen.

Research - a systematic investigation designed to develop or contribute to general knowledge, to discover new information, revise conventional wisdom, and develop new treatments.

RNA (ribonucleic acid) - one of the two nucleic acids found in all cells. In the cell, RNA transfers genetic information from DNA to proteins. RNA is transcribed off DNA and then translated to produce protein.

Saliva - the watery fluid secreted by glands in the mouth.

Serum - the liquid part of blood after coagulation and removal of the fibrin clot and blood cells.

Specimen - a small part or sample of any substance or material obtained for testing. A human specimen specifically represents a bodily material such as tissue, cells, blood, serum, plasma or urine collected for testing.

Tissue - a collection of cells specialized to perform a specific function.

Urine - the liquid waste secreted by the kidney.

APPENDIX V

General Information

About the Collection, Banking and Use of Gynecologic Oncology Group (GOG) Specimens for Research

Your staff and Institutional Review Board (IRB) are being presented with this pamphlet because the Gynecologic Oncology Group (GOG) has a protocol with specimen requirements under review for activation at your institution. As part of the participation in the GOG protocol, patients at your institution will be asked to allow samples from their body (tissue, cells, blood, urine or other material) to be collected and used in research. Such bodily materials are referred to as specimens. Specimens can be used to help doctors and scientists learn more about caring for and treating people with cancer and other diseases. The use of specimens in scientific research can also help doctors and scientists understand why some people develop cancer and others don't, and why some people have cancers that respond or don't respond well to current therapies, for example.

The research that may be done with these types of specimens is not designed specifically to help your patient, but it may help others with cancer or other diseases in the future. Reports about experimental research done with your patient's specimens will not be given to your institution to put in your patient's health record. The research will not have an effect on your patient's care.

If your patient agrees to participate in one of the studies conducted by the GOG, her specimens will be collected and used for the research described for that particular study. We will also ask your patient to decide whether her specimen(s), if still available after completion of that research study, can be used for future research. Your patient will be asked whether her specimens can be used for cancer research or for research for health problems other than cancer. Your patient can still participate in a GOG study even if she does not allow her specimens to be used for future research. It should be noted that the GOG does have a few studies that are designated as banking protocols. Banking protocols are different that other GOG studies in that the purpose of the banking protocol is to collect and bank specimens for future research. Patients participate in a banking protocol are required to provide initial consent for their specimens to be available for future research, but these patients can change their mind at any time and the GOG will honor their wishes. This topic is covered in greater detail below.

When research is performed on specimens connected with clinical information (not personal identifiers) about the person, including details about the person's disease and how the person responds to treatment for example, doctors and scientists can specifically study how to prevent, detect, treat and cure cancer and other diseases, or how to predict response to therapy, toxicities, recurrence and overall survival. This is why we will ask your patient to provide permission to use clinical information that the GOG will collect as part of her study participation for future research involving her specimen(s). The GOG will honor your patient's specific consent choices for future research and will utilize all possible methods to protect her privacy and confidentiality. For example, the research investigators that study your patient's specimens will never be given her name, address, phone number, Social Security number or any other personal information. In addition, your patient's specimens will never be labeled with her name or other type of personal identifier. Your patient's specimen will be labeled with a unique series of letters and numbers. The GOG uses the unique series of letters and numbers as confidential codes to keep track of the individual specimens, and sends research investigators specimens labeled only with these codes.

Your patient's specimens will be used for research purposes and will not be sold. However, the research done with your patient's specimens may help to develop new products and therapies in the future, or may be used to establish a cell line that could be patented and licensed. In any event, there will be no direct financial benefit to your patient.

If your patient agrees to allow her specimens to be used for future research, there is a chance that her specimens may be used for experimental genetic testing to study genetic changes or differences that are passed on in families and may include such things as DNA analysis to identify a change or difference in her DNA that could contribute to the development of cancer or enable her to respond to a particular

therapy for example. Even if your patient's specimens are used for experimental genetic research, they will not be labeled with her name or other personal identifier, and the results will not be put in her health records.

The choice to let your patient's specimens to be collected, banked and used for research is up to her. No matter what your patient decides to do, it will not affect her care.

If your patient agrees now that her specimens can be collected, banked and used for research, your patient can change her mind at any time. At that time, the patient should be instructed to contact the staff at your treating institution, typically your doctor or nurse, and tell them that she has changed her mind about allowing her specimens to be used for research. The staff at your treating institution will update the GOG regarding your patient's wishes about participating in the current research study, future cancer research and/or for future research for health problems other than cancer. If necessary, the GOG will destroy (incinerate) all of your patient's specimens to make sure that they will no longer be used for research.

When a patient participates in a clinical research study, there is a risk that information from the person's health records may be released. The staff at your treating institution and at the GOG will protect your patient's records so that her information is kept private and confidential. The chance that the patient's information will be given to someone in error is very small.

There may also be risks associated with the collection of a particular type of specimen. The exact type of specimen to be collected and any associated risks will depend on the study your patient is asked to participate in and this information will be described in the informed consent document for the research study. For example, collection of a blood specimen may result in slight discomfort, bleeding, or bruising at the site of the blood draw. The patient will be instructed to carefully read the Consent Document for the protocol and an informational pamphlet drafted specifically for the patient about the collection and use of specimens for research. The consent document will contain a description of the research study, the requirements, the types of medical and laboratory tests to be carried out and the potential benefits and risks associated with the study along with the language specifically required by your Institutional Review Board.

If your staff or IRB has questions that are not addressed in this pamphlet, please contact one of the Translational Research Scientists at the GOG Statistical and Data Center. Kathleen Darcy can be reached at 716-845-7768 or darcy@gogstats.org, and Zoe Miner can be reached at 716-845-1528 or zminer@gogstats.org.
Please see the next section for some frequently asked questions regarding the collection, banking and use of GOG specimens for research. A cancer dictionary is available on online at http://cancer.gov/dictionary/ that provides a description of most of the medical and research terminology included in this pamphlet.

Frequently Asked Questions

About the Collection, Banking and Use of GOG Specimens for Research

What are human specimens, where do they come from and what are they used for?
Tissue, cells, blood, urine, saliva, and mucus are common human specimens that can be obtained from people who give permission (consent) to have their bodily material collected and used for research. Specimens are collected by a member of the clinical staff (like a doctor or nurse) who has been trained to handle and process specimens and who also knows how to protect the donor's privacy rights. Specimens collected from GOG patients are used in approved research that will help to find out more about cancer and other diseases.

Why is research using human specimens important?

Some of the questions that researchers using human specimens hope to answer include what causes cancer, how to prevent, detect, and treat cancer, how to predict which people will develop cancer, and how to determine which patient will respond to a specific therapy.

Many investigators are also interested in using specimens from people at a higher than normal risk for developing cancer to learn about the causes of cancer and how to prevent it. These patients may not yet have cancer but have a high risk of developing it because they have a strong family history, a certain type of pre-malignant cells, or a specific type of viral infection. Research on specimens from high-risk individuals may help determine better ways to detect cancer during its early stages.

In addition to learning about cancer, research using human specimens can also answer other health questions like finding the causes of diabetes, heart disease, and Alzheimer's disease, or better ways to detect, prevent and treat diseases. Some investigators may try to discover how a therapy works or what causes a therapy to stop working in certain people with certain diseases. Other researchers may look for genetic or epigenetic factors that cause or prevent certain people from getting a specific disease.

Where are GOG specimens stored?
Most specimens from GOG patients will be stored at the GOG Tissue Bank, a biorepository that is supported by the National Cancer Institute. The GOG Tissue Bank is located in Children's Hospital in Columbus, Ohio. The GOG Tissue Bank is authorized to collect, process, store, and distribute human specimens for approved research. Specimens are stored in an area of the hospital with restricted access using storage that is optimal for each specimen type.

Occasionally there will be a GOG protocol that will require that the specimen obtained from the patient must be directly sent to a specified laboratory for testing. This mechanism is only permitted under very specific circumstances and must be approved by the GOG Protocol Committee. A justification as to why it is necessary to ship specimens directly to the testing laboratory instead of the GOG Tissue Bank will be provided in the GOG protocol documentation.

How are GOG specimens labeled for storage and distribution?
Each GOG specimen is labeled with a unique series of letters and numbers called a person-specific Bank ID (# # # # - # # - G # # #), a protocol-specific specimen code (two letters that specify the exact specimen type and two number to specify the collection sequence or subtype), and the collection date (mm/dd/yyyy). Personal identifiers such as patient name, address, or Social Security number are not used.

Does the GOG Tissue Bank have any clinical information that can be linked to the patient?
For certain cases, the GOG Tissue Bank has access to personal identifiers like patient initials or occasionally patient name. In addition, the GOG Tissue Bank has access to information available to tumor registries such as demographics (patient age at diagnosis or study entry, race, ethnicity) and survival (whether the patient is alive or dead and date of death) as authorized by the National Cancer Institute. However, there are strict guidelines and regulations that restrict the type of information that the GOG Tissue Bank can share with research investigators. For example, the GOG Tissue Bank is prohibited from distributing personal identifiers to research investigators.

How long are GOG specimens stored at the GOG Tissue Bank?
GOG specimens submitted to the GOG Tissue Bank for research will be retained until they are completely exhausted (used up). However, if a patient changes her mind on the use of her specimens, GOG has an online application that can be accessed by the institutions that captures both the initial patient consent choice for the protocol and future research and any subsequent changes. If a patient decides she no longer wants her specimens to be used for research, the GOG Tissue Bank will destroy (incinerate) any remaining specimens from that patient to honor her wishes.

How do doctors and scientists obtain specimens from the GOG Tissue Bank for their research?
Researchers from universities, hospitals, or research institutions apply to the GOG and the GOG Tissue Bank to obtain clinical specimens for a research project. To apply, the researcher must provide a written

description of the research project with justification, rationale and experimental details about the research along with documentation that will demonstrate that the investigator is qualified to do the research including having the experience, funding, equipment, and trained staff. The formal application material is reviewed for scientific merit, clinical relevance, specimen availability, and feasibility. Approval must be obtained at several levels and can include the GOG, the GOG Statistical and Data Center, the GOG Tissue Bank, Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute, and the investigator's Institutional Review Board (IRB). The GOG Tissue Bank will only distribute specimens to investigators who have obtained proper approval for their research project.

What kinds of laboratory testing will be done on specimens from GOG patients?
GOG specimens can be used to study DNA (genetic material), RNA, proteins, and other components of the human body to understand the role(s) they play in cancer and other diseases. There are many laboratory tests that a researcher can use to examine specimens including: 1) immunoassay (to measure the amount of a protein in a tissue, cells, serum, plasma, or urine); 2) in situ hybridization (to measure the amount of one kind of DNA or RNA in a tissue or cells); 3) flow cytometry (to measure the amount of DNA, RNA or a protein in cells); 4) gene expression arrays (to simultaneously measure the amount of thousands of RNA transcripts in a tissue or cells); 5) proteomics (to simultaneously measure thousands of proteins or peptides in tissue, cells, serum, plasma, or urine); 6) genetic testing (to look for a change [mutation or polymorphism] in a gene or in DNA); or (7) genomic testing (to look for a chromosomal change, for example). A specific research project may use one or more types of laboratory tests on each specimen to get accurate and meaningful results. When an investigator applies to obtain GOG specimens for research, a detailed description of the objectives, testing methods, controls, and evaluation criteria must be provided.

Will genetic testing be done on specimens from GOG patients?
There is a chance that GOG specimens may be used to study genetic changes or differences that are passed on in families and may include such things as DNA analysis to identify a change or difference in genetic material that could contribute to the development of cancer or enable a patient to respond to a particular therapy for example. Defective genes have been shown to cause some human diseases, like cystic fibrosis and some cancers. The development and progression of certain types of breast, ovarian, prostate and colon cancer involve defective genes. Specimens from GOG patients may be used to look for defective genes that are present in human diseases including cancer. Only approved experimental genetic testing will be performed on specimens from GOG patients, and the results of this research will not be put in the patient's medical records.

Will GOG patients find out the results of research performed on their specimens?
No, GOG patients will not receive the results of experimental research carried out with their specimens. Experimental research is conducted with the specific purpose of expanding the present understanding about something that is incompletely understood. We must first understand the implications of the experimental finding before it can be shared with individuals in a meaningful manner. In addition, research often takes a long time because specimens are obtained from many people and then used for one or more types of laboratory tests. It often takes a long time to collect and interpret the laboratory data. Thus, results and conclusions may not be available for many years. It is important for GOG patients to understand that the results from research studies using their specimens will not affect their treatment or care right now, but may help people like them in the future. At the completion of GOG studies, the results are summarized in manuscripts and published in Scientific and/or Clinical Journals. If your patient requests information about the general results of the GOG study that she participated in, please provide your patient with the citation for the publication and/or a copy of the manuscript if available.

Why is information from GOG patient health records needed for research?
Investigators working within the GOG framework may need to have their laboratory data obtained from specimens collected during treatment studies analyzed with certain types of clinical information (not personal identifiers) like disease characteristics, treatment or outcome depending on the nature of the GOG study. Laboratory testing performed on specimens linked with clinical information will have the greatest potential to impact future treatment and care of patients because the laboratory results can be analyzed directly with the clinical information. Approved information from the patient's health records will

be sent to the GOG as part of participating in a GOG study. The GOG has strict policies and procedures to protect the patient's privacy and maintain confidentiality. The patient's name or other personal identifying information will never be sent to a researcher.

Will the researcher be given personal identifying information about members of the patient's family?
No.

How could patient health records be used in ways that might be harmful to the patient?
Health record information could be used to deny insurance or employment to patients and/or their family members with certain illnesses like AIDS or cancer. Information found in health records regarding genetic diseases may also be used against patients and/or their family members. Experimental research results will not be added to the patient's health record.

How is the privacy of the GOG patient submitting specimens protected?
Specimens in the GOG Tissue Bank are not labeled with the patient name, address, phone number, Social Security number or anything else that could identify the patient or her family. Instead, the GOG Tissue Bank uses a unique series of letters and numbers as confidential codes to keep track of the specimens, and distributes specimens labeled only with these codes. Investigators obtaining specimens from the GOG Tissue Bank should never claim that they have received identified specimens because GOG specimens will never be distributed labeled with personal identifiers. Even if a specimen arrives at the GOG Tissue Bank with a personal identifier, that identifier is immediately removed and replaced with a label containing the appropriate confidential code for that case.

Will research using specimens from GOG patients result in the development of a commercial product?
It is possible that research results obtained from laboratory testing of specimens from GOG patients will result in the development of beneficial treatments, devices, new drugs, or procedures, and that some of these products may be marketed and made commercially available. GOG patients will not receive any financial compensation for any commercial product developed as a result of research that used their specimens.

Whom should GOG patients contact if they have questions?
Patients are free to ask questions at any time regarding any issue. They are encouraged to first contact the doctor, nurse, or other members of the research staff at their institution with any questions. The medical staff should try to do their best to answer the patient's question(s) or should direct them to someone who can. For additional information about cancer or clinical trials, you can direct the patient to call the National Cancer Institute's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237) or visit a website that provides accurate and carefully reviewed information like: http://www.cancer.gov, http://cancertrials.nci.nih.gov, http://cancernet.nci.nih.gov, http://seer.cancer.gov, http://bioethics.gov. Please caution the patient to be aware that there are sites on the web that provide information that is misleading or inaccurate (contains mistakes or errors). Always encourage your patient to let her health care professionals know if she has any questions.

How are human specimens for research defined using acceptable IRB terminology?
There are three kinds of specimens defined based on the amount of patient information that accompanies each specimen. With "anonymous" specimens it is impossible for the individual source of the specimen to be identified. "De-identified specimens" are not labeled with personal identifiers, but are labeled with a unique patient code and there is a master list linking personal identifiers to the unique patient code found on the specimens. Investigators performing research using de-identified specimens must state that he/she will not link specimen codes or the laboratory data generated for those specimens to the patient identifiers (Code Access Agreement). "Linkable or Identified Specimens" may be labeled with personal identifiers or codes and the investigator performing research on the specimens is able to link the specimen codes to the personal identifiers.

How should GOG specimens be defined using acceptable IRB terminology?
Because GOG specimens are labeled with confidential codes and both the GOG Statistical and Data Center and the GOG Institution have the information that links the codes to the personal and health information of the participating patients, GOG specimens should be considered de-identified specimens. The GOG Statistical and Data Center will have the links for all patients participating in GOG protocols with specimen requirements. The GOG institutions will only have the links for their own patients. The GOG will not release detailed clinical information including personal identifiers to outside individuals including research investigators. All investigators wishing to perform analyses on laboratory data obtained using GOG specimen and the linked clinical data must work with the GOG Statistical and Data Center or a designee selected by the GOG who signs material transfer and confidentiality agreements with the organization. It is mandatory that investigators have IRB approval (renewed annually) from their institutions in order to receive any specimens from the GOG Tissue Bank. Depending on the scope and nature of the project, the investigator will indicate what type of specimen is needed to fulfill the objectives of the study: anonymous, de-identified, or linked. GOG investigators who perform research using linked clinical information utilize de-identified specimens and the statistical analysis of the laboratory and clinical data are performed within the GOG Statistical and Data Center or a designee as indicated above. GOG investigators who perform research using specimens with no intent to analyze the laboratory data with clinical data can be classified as one who uses anonymous specimens.

Is every Institutional Review Board (IRB) the same?
Yes in that every IRB is required to comply with Federal Regulations and assure HIPAA Compliance. However IRBs differ in that they are not mandated to utilize standardized application procedures, guidelines for specimen banking, consent language, or a time frame for reviewing an application for approval.

How does the GOG Tissue Bank operate?
The GOG Tissue Bank has been funded and managed as a direct subcontract with the GOG since 1991. As such, the GOG Committee for Experimental Medicine (CEM) and its Tissue Utilization Subcommittee (TUS) have the authority to set the policies as to how the bank is run. The membership of TUS includes pathologists, clinicians, basic or translational research scientists and data managers so that issues concerning specimen availability, collection and utility can all be addressed in an informed fashion. The TUS has been active in the administration of the bank by defining the directions and scope of bank activities, by establishing standardized procedures for specimen collection within GOG institutions, and by introducing the concept of a virtual tissue bank. Dr. Michael Cibull, as a GOG pathologist and TUS Chair, acts as the liaison between the GOG Tissue Bank and CEM. He also directs the review efforts confirming all diagnoses on tumors received at the GOG Tissue Bank with two other GOG pathologists, and assesses the tissue integrity of the specimens microscopically. This information is entered into the GOG Tissue Bank database. As Principal Investigator and Director of the Bank, Dr. Stephen Qualman is responsible for onsite quality assurance activities including proper specimen storage, processing specimens, disbursement of specimens, and maintenance of storage facilities. Dr. Cibull, Dr. Qualman, and bank employees hold periodic conference calls regarding bank operations and their administrative decisions are reflected in a written report to the TUS and CEM at GOG meetings every six months.

Specimens stored at the GOG Tissue Bank are considered to be part of the internal bank (for specimens connected with detailed clinical information linked to personal identifiers) or the external bank (specimens connected with little or no clinical information). All new protocol initiatives requesting internal bank specimens are presented in writing, first at the TUS meeting, followed by the CEM meeting, and receive subsequent approval/disapproval at the Protocol Committee. In addition, a specific set of National Cancer Institute (NCI) requirements must be followed by GOG when disbursing specimens from either the internal or external bank. These include: documentation of the investigator's detailed project and the peer-reviewed funding obtained for the project; demonstration of local IRB approval and a commitment to protect patient rights and maintain patient confidentiality; and a signed agreement limiting the investigator's use of specimens for research purposes with the proper observance of universal precautions. These expectations reflect the input of the GOG and the NCI Intergroup Banking Committee of which Drs. Cibull and Qualman were inaugural members.

How is a specimen linked to the patient information in the database?
Within the Ingres relational database used by the GOG Statistical and Data Center, the combination of the Bank ID, specimen code and collection data are housed in a Specimen Database table that also contains the GOG patient study ID (format: # # # - # # # # - # # # - X X). The GOG patient study ID, in turn, can be connected to another patient specific ID number. The clinical information for the patient is housed in other Ingres database tables. The GOG patient study ID can be connected to protocol-specific patient information while the patient specific ID number can be connected to personal identifiers (patient name, initials, birth date, social security number). Access to the personal identifiers is restricted with multiple security layers built in to prevent accidental or intentional misuse. There are certain routines that are run to ensure that only one patient specific ID exists for an individual. A person may, however, have more than one GOG patient study ID if she participates in more than one GOG protocol. A person may also have more than one specimen collected for more than one protocol. The combination of these identifiers provides a unique, confidential specimen-specific coding.

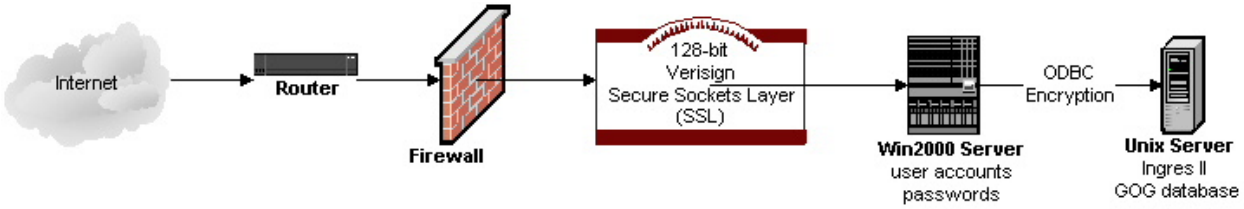
What procedures are in place to honor patient consent for GOG protocols and future research?
Web based entry is now available from the GOG Statistical & Data Center website http://www.gogstats.org/ to register and then update if needed a patient's consent choices for the collection and use of specimen(s) for a GOG research study and/or for future research. To access the Patient Consent for Specimen Collection/Research web application, click on the GOG Web Menu link. Enter your username and password at the GOG Web Menu Login page then click on the Patient Consent for Specimen Collection/Research link in the Report/Applications column. This web application allows the GOG institutions to notify the GOG Tissue Bank of the patient's consent choices for this protocol and future research so that the GOG Tissue Bank is in a position to honor the patient's wishes. Any questions about access or problems should be directed to the User Support department at the GOG Statistical and Data Center at support@gogstats.org or 716-845-7767. If you do not have a GOG Web Menu username and password, call the GOG Statistical and Data Center User Support Department at (716) 845-7767 Monday - Friday 8:30am - 5:00pm EST or go to the following link https://webreg.gogstats.org/regweb/Help /loginhelp.html fill out the form, print it, and fax it to (716) 845-8393 Attn. User Support.

The institution must use the online consent application to enter the patient's consent choices for a particular protocol with specimen requirements within 7 days of study entry and then update the application as needed to reflect the patient's expressed wishes. This web based application provides the GOG Tissue Bank with the information it needs to implement the patient's wishes, and to enables the Statistical and Data Center to monitor, verify and provide reports summarizing the activities associated with this application to the Tissue Utilization Subcommittee and the Committee for Experimental Medicine which are responsible for the governance of the Bank.

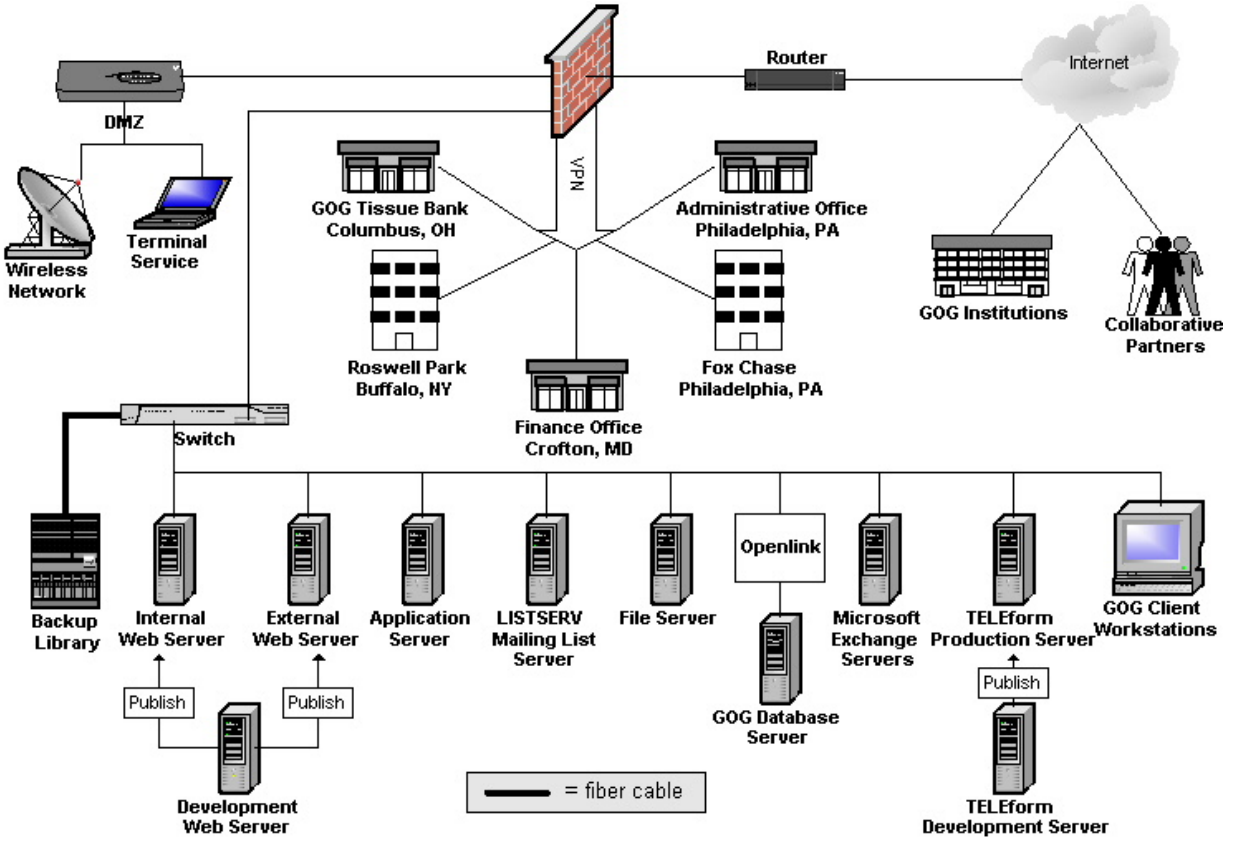
What procedure is in place to return specimens from the GOG Tissue Bank to an individual institution for diagnostic purposes?
Research material is returned from the GOG Tissue Bank to the institution only if the specimen is required for diagnostic purposes at the site. At such times, the institution should send a letter to the Translational Research Scientists in the GOG Statistical and Data Center at Roswell Park Cancer Institute, Carlton and Elm Streets, Buffalo, New York 14263 indicating that the research material for a patient with a particular GOG study ID needs to be returned for diagnostic purposes along with relevant shipping information. The Statistical and Data Center will then inform the GOG Tissue Bank as to what specimen(s) need to be returned to which institution using specified shipping information.

What procedures, equipment and staffing are in place to protect patient privacy and maintain confidentiality at the GOG Statistical and Data Center?
Patient records for GOG studies are stored in the GOG Statistical and Data Center at Roswell Park Cancer Institute in Buffalo, NY. Physical security for our offices consists of locked doors, web cameras viewed by around the clock security staff, a physical security walk-through each shift, environmental sensors, key access to the floor and individual offices, and locked file cabinets. Access to the clinical data housed at the GOG Statistical and Data Center is securely multi-layered. Internet traffic destined for the

Statistical and Data Center must first pass through a Cisco router, which contains access lists permitting only certain Internet protocols to reach the Cisco firewall. At the firewall, even greater levels of security are applied to Internet traffic. In addition, Verisign's SSL 128-bit certificate encrypts web traffic between the Statistical and Data Center and the Internet-based session where a username/password combination must be successfully passed to the web server for verification. Once the user account has been verified, access between the web server and the database server is encrypted once again using ODBC drivers. The Statistical and Data Center Internet connection is equipped with a Cisco Pix Firewall whose integrated hardware and software package delivers a full stateful protection solution and utilizes IP Security (IPSec) for virtual private networking capabilities. The logs from the Pix are monitored regularly and anomalies are quickly researched. Every user who accesses the Statistical and Data Center's web site to register patients, to key electronic data, or to generate reports is required to have an individual user account. Each account is assigned specific access level restrictions that limit the account to specific applications and the acquisition of clinical data.
Finally, all staff within the Statistical and Data Center receive annual training in areas of HIPAA Compliance and Research Involving Human Subjects, and review weekly emails reinforcing policies and procedures in protecting patient's rights, maintaining patient confidentiality and complying with HIPPA regulations.



The support of the Statistical and Data Center office, GOG organization, and regulatory compliance relies on the underlying computing network installed and managed at the Statistical and Data Center. The Statistical and Data Center network facilitates secure GOG data transmissions and electronic communications. The network connection to the Internet is provided by a connection to Global Crossing's Internet backbone. The diagram below depicts three separate zones within the Statistical and Data Center network. The first zone contains the Virtual Private Network (VPN) connections to other GOG entities and Roswell Park Cancer Institute, which require a secure connection for the transfer of data. The second zone contains a neutral zone, DMZ to prevent outside users from obtaining direct access to the servers containing secure GOG proprietary information. The third and largest zone contains the Statistical and Data Center's servers and workstations.



The Statistical and Data Center manages a cross platform server infrastructure consisting of Intel and Alpha architectures. These servers run the Windows 2000 Server, Red Hat Linux, Open VMS, or the Tru64 operating systems. The services, provided by the Statistical and Data Center's network configuration, are distributed into primary and secondary servers so that the workload is shared and the services are redundant. This ensures that the workload on any one server is not too much for the server to handle, and that a secondary server can continue processing the workload when necessary. The GOG database and its front end are run on Tru64 Unix and Linux boxes. Proprietary applications are in the process of being ported from Open VMS to Linux, with Open VMS eventually phasing out. The Statistical and Data Center's current database server is a Hewlett Packard (HP) Alpha Server DS20. The server utilizes dual 500Mhz Alpha 21264 processors for symmetric multiprocessing. The server contains 512 MB of SDIMM memory with the capacity up to 4 GB. The server is equipped with 256 bit-wide data paths, dual 64 bit PBI buses and dual ultra-wide SCSI buses. The operating system in use is HP's Tru64 Unix, which offers multiprocessing and 64-bit performance. The relational database management system employed on this server is Computer Associates' Ingres II. Ingres II is a 64-bit application that takes full advantage of the Tru64 Operating System's 64-bit performance. The Ingres II relational database management system is a highly reliable application that takes full advantage Tru64 Unix operating system installed on the database server. The installation's configuration is spread across multiple hard drives to further improve performance; the system's software, log file, checkpoint & journaling and multiple database locations are all on separate physical disks. The database server's sole purpose is to provide access to the GOG's clinical and production databases. User account access to the server is limited to the IT staff. The Statistical and Data Center's applications make use of OpenLink's ODBC drivers and Computer Associates' NetU to gain access to the databases hosted on the DS20. A second DS20E is employed for the investigation of newly released Tru64 operating system and software upgrades and/or patches from Hewlett Packard, Computer Associates' Ingres II, and OpenLink. This server serves a dual purpose in that it is also used as a development server to host databases for software development. The Statistical and Data Center utilizes Intel-based desktops and laptops running Windows 2000 as user workstations.

Electronic entry, retrieval, updating/editing, and viewing of information by staff within the GOG Organization, Statistical and Data Center, GOG Tissue Bank, GOG institutions, and GOG investigators is restricted. Specific end users are granted select privileges and access based on their role and authorized responsibilities. The Information Technology Staff in the GOG Statistical and Data Center, the Administrative Office and at Fox Chase control the assigned privileges and access, distribute user accounts, and set the layered security mechanisms.

What policies are in effect for analyzing the laboratory and clinical data associated with GOG specimens.
The GOG has a clear policy that it will not release detailed clinical information including personal identifiers to outside parties. Investigators wishing to perform translational research on specimens connected with detailed clinical information must work within the GOG framework and agree to have the laboratory data analyzed within the GOG Statistical and Data Center or by a designee selected by the GOG leadership and the GOG Statistical and Data Center. The designee is required to sign material transfer and confidentiality agreements with the GOG prior to any transfers of clinical data. Personal identifiers like patient name and social security number will always be stripped prior to data transfer. Electronic transfer of any clinical information will always utilize the secure encrypted transfer mechanisms maintained and upgraded as needed by the Information Technology staff in the Statistical and Data Center.

Who is the gatekeeper for all of the stored specimens identifiers?
The GOG Statistical and Data Center.

Who should you contact if you still have questions regarding the collection, banking and use of GOG specimens for research?
You should fell free to contact the Translational Research Scientists in the GOG Statistical and Data Center. Kathleen Darcy can be reached at 716-845-7768 or darcy@gogstats.org. Zoe Miner can be reached at 716-845-1528 or zminer@gogstats.org.

As additional questions are brought to our attention and appropriate responses are drafted, this pamphlet will be revised and be made available. Check the GOG Translational Research Web-Page for information about newly released updates and to obtain files that can be down loaded or printed.

APPENDIX VI

Instructions for Using the Web-Based Specimen Consent Application (09/30/05)

The institution must enter the online Specimen Consent choices for any patient enrolled on a GOG protocol that has specimen requirements. This can be done using the webbased Specimen Consent application and must be completed within 7 days of patient enrollment.

The web-based Specimen Consent can be found on the GOG Statistical & Data Center website at http://www.gogstats.org/. This application allows the staff at GOG participating institutions to register and later update, if needed, the patient consent choices for the use of her specimens. To access the Specimen Consent application, click on the **GOG Web Menu** link. When prompted, enter your username and password and then click on the **Report/Applications** column and select the **Specimen Consent link.**

This application will capture the patient's choices for the use of her specimens in the research specified in the protocol in addition to future cancer and non-cancer research. Based on the choices that the patient makes in the consent document, her specimens will either be available for research or they will be destroyed. Reporting, confirmation, and validation layers are built into this online application to verify that the appropriate action is taken for each patient.

Any questions about access or problems with the application should be directed to User Support at the GOG Statistical and Data Center at mailto:support@gogstats.org or 716845-7767. If you do not have a GOG Web Menu username and password, call User Support at 716-845-7767 Monday – Friday 8:30 AM – 5 PM ET or go to the following link: https://webreg.gogstats.org/gog/help/loginhelp.html. Fill out the form, print it, and fax it to 716-845-8393 Attn: User-Support.

Thank you for enabling us to honor your patient's wishes.