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TO: ALL PRINCIPAL INVESTIGATORS/NURSES/DATA MANAGERS

FROM: NICOLE COPELAND
PROTOCOL SECTION

DATE: JUNE 13, 2016

RE: GOG-0264 – REVISION 4

Protocol Title: A RANDOMIZED PHASE II TRIAL OF PACLITAXEL AND CARBOPLATIN VS. BLEOMYCIN, ETOPOSIDE, AND CISPLATIN FOR NEWLY DIAGNOSED ADVANCED STAGE AND RECURRENT CHEMONAIVE SEX CORD-STROMAL TUMORS OF THE OVARY

NCI Version Date 12/19/2014

Study Chair: Jubilee Brown, MD; (713) 792-1380 ; E-mail: jbbrown@mdanderson.org

IRB Recommendations

(X) No review required
( ) Expedited review; however, site IRB requirements take precedence
( ) Full board review recommended because there have been changes to the eligibility and/or informed consent

Please direct questions about the recommended level of IRB review and/or re-consenting patients to your local IRB. The local IRB will make this determination. If your local IRB does not agree with the GOG's recommended level of review, please document the IRB's decision and the rationale for the decision in your study files.

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SUMMARY OF CHANGES

For Protocol Revision #4 to:

NCI Protocol #: GOG-0264
Local Protocol #: GOG-0264

NCI Version Date: December 19, 2014
Protocol Date: December 19, 2014

#	Section	Page(s)	Change
1.	Title Page	1-2	NCI version date has been updated. Includes Revisions #1-4. Lead Organization has been added. Revised footer has been added.
	ICD		NCI version date has been update on the Informed Consent

PROTOCOL GOG-0264

A RANDOMIZED PHASE II TRIAL OF PACLITAXEL AND CARBOPLATIN VS. BLEOMYCIN, ETOPOSIDE, AND CISPLATIN FOR NEWLY DIAGNOSED ADVANCED STAGE AND RECURRENT CHEMONAIVE SEX CORD-STROMAL TUMORS OF THE OVARY

NCI Version: December 19, 2014

Includes Revision 1-4

POINTS:
PER CAPITA -10
MEMBERSHIP-3
TRANSLATIONAL RESEARCH POINTS-1
Lead Organization: NRG/NRG Oncology

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OPEN TO PATIENT ENTRY FEBRUARY 8, 2010
REVISED NOVEMBER 22, 2010
REVISED OCTOBER 24, 2011
REVISED JUNE 13, 2016

SCHEMA

Patients diagnosed with histologically confirmed ovarian stromal tumor
Newly diagnosed, Stage IIA – IVB disease and must be entered within eight weeks from surgery
OR biopsy-proven recurrent disease with no prior chemotherapy

↓

Randomization (1:1)

↙ ↘

Arm I	Arm II
Treatment: • Paclitaxel 175 mg/m2 IV over 3 hours • Carboplatin AUC = 6 IV over 1 hour • Every 3 weeks x 6 cycles (=18weeks)	Treatment: • Bleomycin 20 units/m2 IV Push day 1 (MAX 30 units/cycle; Total lifetime cumulative dose should not exceed 120 units) • Etoposide** 75 mg/m2 IV Day 1,2,3,4,5 • Cisplatin 20 mg/m2 IV Day 1,2,3,4,5 • Every 3 weeks x 4 cycles (=12 weeks)
CT/MRI Scan: prior to the fourth cycle, and after the end of treatment: approximately 2 weeks after the sixth cycle of therapy	CT/MRI Scan: prior to the fourth cycles, and after the end of treatment: approximately 7 weeks after fourth cycle of therapy.

* Pulmonary Function Test (Carbon monoxide diffusion capacity) prior to Bleomycin and at day 1 of 3rd & 4th cycle

** Patients who have received prior radiation therapy will receive etoposide 60 mg/m^2 on Days 1-4 only (omit Day 5 etoposide dose, give cisplatin alone).

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1.0 OBJECTIVES

1.1 Primary Objective:

1.11 To assess the activity of paclitaxel and carboplatin with respect to progression free survival (using bleomycin, etoposide, and cisplatin (BEP) as a reference) for newly diagnosed advanced or recurrent chemonaive ovarian sex cord-stromal tumors.

1.2 Secondary Objectives:

1.21 To estimate the toxicity of paclitaxel and carboplatin, and bleomycin, etoposide, and cisplatin in this patient population.

1.22 To estimate overall survival for paclitaxel and carboplatin relative to that of BEP.

1.23 To evaluate response rate in the subset of patients with measurable disease.

1.3 Translational Research Objective:

1.31 To collect fixed and/or frozen tumor tissue for future translational research studies.

1.4 Exploratory Objectives

1.41 To explore the utility of inhibin A and inhibin B as prognostic and predictive biomarkers for ovarian sex cord-stromal tumors and to examine changes in these markers with treatment.

2.0 BACKGROUND AND RATIONALE

2.1 Background

Sex cord-stromal tumors (SCSTs) of the ovary are rare neoplasms, which account for less than 5% of all ovarian malignancies.[1] This group of ovarian stromal tumors include the granulosa cell tumor, granulosa cell–theca cell tumor, Sertoli-Leydig cell tumor (androblastoma), steroid (lipid) cell tumor, gynandroblastoma, unclassified sex cord-stromal tumor, and sex cord tumor with annular tubules. SCSTs tend to have an indolent course, compared to epithelial ovarian cancer, and can secrete hormones (i.e. granulosa cell tumors - estrogen; combined Sertoli-Leydig cell tumor - androgens).

Since SCSTs are uncommon, clinical trials exploring optimal chemotherapy treatments are limited. Most published studies have combined histologic subtypes of SCSTs, so the recommendations for treating specific tumors have been based on limited data. Most data have been gathered from patients with adult granulosa cell tumors, but treatment has often been generalized to other tumor types. Additionally, many of these tumors are clinically indolent, so long-term follow-up is required to accurately interpret outcomes data.

Surgery remains the cornerstone of initial treatment for SCSTs. Post-operative cytotoxic chemotherapy has often been given in attempt to improve cure rate. Over the past three decades, the recommended chemotherapy regimen has changed from VAC (vincristine, Adriamycin, and cyclophosphamide) to BEP (bleomycin, etoposide, and cisplatin). Since the 1980s, platinum-based chemotherapy has been the most widely used postoperative treatment.[2-5]

Studies in 1986 and 1990 investigated combinations of cisplatin, vinblastine, and bleomycin for treating advanced and metastatic granulosa cell tumors of the ovary.[6,7] In 1996, Gershenson *et al*. reported a high response rate to bleomycin, etoposide, and cisplatin (BEP) in patients with poor-prognosis SCSTs of the ovary.[8] Etoposide was substituted for vinblastine based on an earlier study in which patients with testicular germ cell tumors demonstrated reduced toxicity and equivalent efficacy.[9] The Gynecologic Oncology Group (GOG 115) subsequently evaluated BEP in the treatment of incompletely resected stage II-IV or recurrent SCSTs of the ovary.[10] The investigators found that 14 of the 38 patients who underwent second-look laparotomy had no evidence of disease, and that the six complete responders had a 24.4-month median duration of response. Based on the results of this trial, surgery followed by BEP has become a commonly utilized treatment option for patients with advanced SCSTs of the ovary.

Unfortunately, BEP is associated with high toxicity and significant risk of disease recurrence. GOG 115 showed that only one of seven patients with advanced disease experienced a durable remission and that nearly half of the patients with recurrent disease experienced progression. Likewise, despite this study's high response rate, Gershenson *et al.* noted similar limitations in durable remission.[8] Both trials also revealed significant bleomycin-related toxicity, including two cases of pulmonary toxicity and two additional deaths from bleomycin-related pulmonary fibrosis.[8,10] In addition to the cytopenias, renal dysfunction and neuropathy associated with BEP, etoposide can result in the subsequent development of secondary malignancies.

In view of the limited activity and significant toxicity associated with BEP, the identification of other regimens with equivalent or improved activity and tolerability would be beneficial. Attempts to eliminate bleomycin from the BEP treatment regimen and administer etoposide and cisplatin (EP) have previously been unsuccessful in patients with nonseminomatous testicular germ cell tumors, resulting in decreased toxicity but loss of therapeutic activity.[11,12] For this reason, EP alone has been thought to constitute inadequate therapy in this group of malignancies, and EP has not been pursued as a potential treatment regimen for sex cord-stromal tumors of the ovary.

As first described in two case reports, taxanes have shown activity in patients with granulosa cell tumors.[13,14] This observation led many to treat patients with newly diagnosed or recurrent SCSTs with taxanes, alone or in combination with platinum and other agents. In a retrospective analysis of patients with newly diagnosed or recurrent SCSTs of the ovary, activity was seen with taxanes, especially when combined with a platinum agent.[15] Eleven patients received paclitaxel and a platinum agent, as adjuvant treatment. For the nine patients treated in the first-line adjuvant setting, median progression-free survival was not reached at 51 months. Of two patients treated for measurable disease in the first-line setting, one had a complete response. The clinical

response rate for 30 patients treated with a taxane +/- platinum for recurrent, measurable disease was 42%. The presence of platinum correlated with response in this setting. Although the effectiveness of single-agent taxanes versus platinum-containing regimens could not be compared, these promising results provide the basis for further investigation of paclitaxel and carboplatin in patients with ovarian sex cord-stromal tumors.

To date, no randomized controlled trial has compared BEP with paclitaxel and carboplatin in this patient population. The above studies suggest the utility of paclitaxel and carboplatin in this patient group, but it is still considered experimental without stronger evidence. This protocol is designed to determine the utility of paclitaxel and carboplatin using BEP as a reference for patients with newly diagnosed advanced and chemonaive recurrent ovarian sex cord-stromal tumors.

Table 1 below summarizes the available data for BEP in this patient population. Due to the limited historical data that is available and the lack of consistency of results across studies, it is not feasible to do a single-arm trial of paclitaxel and carboplatin combination chemotherapy and compare the results with historical control data.

Table 1: Results from Past Studies in this Patient Population

Study	N	Population	Treatment	PFS (mo) Median (95% CI)	Survival (mo) Median (95% CI)
GOG 0115[10]	16	Stage II, III, IV	B: 20 units/m2 on d 1 E: 75 mg/m2 IV on d 1-5 P: 20 mg/m2 on d 1-15 q 3 weeks x 4 courses	66 (13, NE)	NE (47, NE)
Gershenson (1996)[8]	9	Ia, IIc, IIIc, or recurrent	B: 10-15 mg on d 1-3 E: 100 mg/m2 IV on d 1-3 P: 100 mg/m2 on d 1 q 4 weeks	14 (NA)	28 (NA)
Brown (2005)[16]	11	Newly diagnosed (Retrospective review of cases)	BEP	46 (NA)	97 (NA)
Pautier (2008)[17]	20	advanced ovarian granulosa cell tumors: initial metastatic (n=5) or recurrent (n=15)	B: 30 mg on d1, 8, 15 E: 100 mg/m2 IV on d 1-5 P: 20 mg/m2 on d 1-5 q 3 weeks, for 4 courses	25 (NA)	46 (NA)
NE: not estimable NA: not available					

Of note, inhibin A and inhibin B may be helpful immunohistochemical stains to aid in the pathologic diagnosis and clinical response of sex cord-stromal ovarian tumors.[18-21] In a panel of 29 stromal ovarian tumors, all were found to be positive for inhibin A, and 59% were found to be positive for inhibin B.[22] Inhibin B may be particularly helpful in identifying recurrent disease.[23] Therefore, serum levels of inhibin A and B will be collected during this study to explore their use as prognostic and predictive

biomarkers for ovarian sex cord-stromal tumors and to examine changes in these markers in response to treatment.

2.2 Proposed Study

The proposed study will randomize newly diagnosed patients with advanced stage SCSTs and chemonaive patients with recurrent SCSTs to either carboplatin/paclitaxel OR BEP. The proposed hypothesis states that carboplatin/paclitaxel will be equally effective and less toxic than BEP**.**

A non-inferiority hypothesis is used for the primary objective. If a hazard ratio of 1.1 can be excluded (based on an upper 85% confidence limit), carboplatin/ paclitaxel will be considered not inferior to BEP.

2.3 Translational Research

The translational research component of this study will establish a bank of fixed and/or frozen tissue. As study accrual will take place over several years, the specific translational research endpoints will be deferred until after the specimen collection is complete. Future innovations in technology and biomarker development will guide the translational research studies to be done on this valuable tissue collection.

2.4 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 cancer population treated by participating institutions.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

3.11 Patients diagnosed with histologically confirmed ovarian stromal tumor [granulosa cell tumor, granulosa cell–theca cell tumor, Sertoli-Leydig cell tumor (androblastoma), steroid (lipid) cell tumor, gynandroblastoma, unclassified sex cord-stromal tumor, sex cord tumor with annular tubules].

3.12 Patients must have newly diagnosed, Stage IIA – IV disease and must be entered within eight weeks from surgery; they may have either measurable residual disease by RECIST criteria, or they may have no measurable residual disease; OR, they must have biopsy-proven recurrent disease of any stage and have never received cytotoxic chemotherapy.

3.13 Patients must have a GOG performance Grade of 0, 1, or 2.

3.14 Patients of childbearing potential must have a negative serum pregnancy test and must agree to practice an effective means of birth control.

3.15 Patients in the measureable disease cohort must have at least one "target lesion" to be used to assess response on this protocol as defined by RECIST 1.1 (Section 8.0). Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

3.16 Patients who have met the pre-entry requirements specified in Section 7.0. Patients must have adequate:

3.161 Bone marrow function: Absolute neutrophil count (ANC) greater than or equal to 1,500/mcl, equivalent to CTCAE grade 1. Platelets greater than or equal to 100,000/mcl.

3.162 Renal function: Creatinine no greater than the institutional upper limits of normal. **(11/22/2010)**

3.163 Hepatic function: Bilirubin less than or equal to 1.5 x ULN (CTCAE grade 1), SGOT (AST) less than or equal to 3.0 x ULN (CTCAE grade 1) and alkaline phosphatase less than or equal to 2.5 x ULN (CTCAE grade 1).

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

3.165 Hearing function: No signs of clinically significant hearing loss.

3.17 Patients must have signed an approved informed consent and authorization permitting release of personal health information.

3.18 Patients must have pulmonary function sufficient to receive bleomycin, with normal lung expansion, absence of crackles on auscultation, and normal carbon monoxide diffusion (DLCO), defined as greater than 80% predicted.

3.19 Patients with a history of hypersensitivity reactions to prior chemotherapy administered for previous cancer diagnoses are eligible to participate in the study, unless the hypersensitivity reaction consisted of anaphylaxis not amenable to desensitization.

3.110 Recovery from effects of recent surgery, radiotherapy, or chemotherapy.

3.1101 Patients must be entered within 8 weeks after surgery performed for either 1) initial diagnosis, staging, and/or cytoreduction, or 2) (if done) management of recurrent disease in a chemonaive patient.

3.1102 Any hormonal therapy directed at the malignant tumor must be discontinued at least one week prior to registration. Continuation of hormone replacement therapy is permitted.

3.111 Patients must be ≥ 18 years of age.

3.2 Ineligible Patients

3.21 Patients who have received any prior cytotoxic chemotherapy or biologics for sex cord-stromal tumors (SCSTs).

3.22 Patients with apparent Stage I disease who have not undergone a staging procedure.

3.23 Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer, are excluded if there is any evidence of other malignancy being present within the last five years.

3.24 Woman who are pregnant or breastfeeding.

3.25 Patients with medical history or conditions not otherwise previously specified which in the opinion of the investigator should exclude participation in this study. The investigator can consult the Study Chair or Study Co-Chairs for uncertainty in this regard.

4.0 STUDY MODALITIES

4.1 Paclitaxel (NSC #673089)

4.11 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.

Paclitaxel is supplied as a sterile solution concentrate, 6 mg/ml in 5 ml vials (30 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. It is also available in 100 and 300 mg vials.

4.12 Solution Preparation: Paclitaxel, at the appropriate dose, will be diluted in 500-1000 ml of 0.9% Sodium Chloride injection, USP or 5% Dextrose injection, USP (D5W) (500 ml is adequate if paclitaxel is a single agent). Paclitaxel must be prepared in glass or polyolefin containers due to leaching of diethylhexlphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized.

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

4.13 Storage: The intact vials can be stored in a temperature range between 2-25 C (36-77°F).

4.14 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.

4.15 Supplier: Commercially available

4.16 Administration: 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) that are used to infuse parenteral Nitroglycerin. Nothing else is to be infused through the line where paclitaxel is being administered. (See Section 5.221)

4.17 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, injection-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, alkaline phosphatase and triglycerides, hepatic failure, hepatic necrosis
Other: Alopecia, fatigue, arthralgia, myalgia, light-headedness, myopathy, headaches
Other, Vision: Sensation of flashing lights, blurred vision, scintillating scotomata

*See FDA- approved package insert for a comprehensive list of adverse events associated with paclitaxel.

4.2 Carboplatin (Paraplatin®, NSC # 241240)

4.21 Formulation: Carboplatin is supplied as a sterile lyophilized powder available in single-dose vials containing 50 mg, 150 mg and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

4.22 Solution Preparation: Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP, according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 ml
150 mg	15 ml
450 mg	45 ml

These dilutions all produce a carboplatin concentration of 10 mg/ml.

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

4.23 Storage: Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

4.24 Stability: When prepared as directed, carboplatin solutions are stable for eight hours at room temperature. Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded eight hours after dilution.

4.25 Supplier: Commercially available

4.26 Administration: See Appendix III for current Carboplatin dose calculation instructions **(11/22/2010)**

4.27 Adverse effects:
Hematologic: Myelosuppression
Gastrointestinal: Nausea, vomiting, diarrhea, abdominal pain, constipation
Neurologic: Peripheral neuropathy, ototoxicity, visual disturbances, change in taste, central nervous system symptoms
Renal: Abnormal renal function test results including serum creatinine, blood urea nitrogen, and creatinine clearance
Hepatic: Abnormal liver function tests including bilirubin, SGOT, and alkaline phosphatase
Electrolyte Changes: Abnormally decreased serum electrolyte values reported for sodium, potassium, calcium, and magnesium.
Allergic Reactions: Rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension.
Injection Site Reactions: Redness, swelling, pain; necrosis associated with extravasation has been reported.
Other: Pain, asthenia, alopecia. Cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in 6% or less of the patients. Cardiovascular events (cardiac failure, embolism, cerebrovascular accidents) were fatal in less than 1% of patients and did not appear to be related to chemotherapy. Cancer-associated hemolytic-uremic syndrome has been reported rarely. Malaise, anorexia, and hypertension have been reported as part of post-marketing surveillance.

*See FDA-approved package insert for a comprehensive list of adverse events associated with carboplatin.

4.3 Bleomycin (Blenoxane7 - NSC #125066)

4.31 Formulation: Bleomycin is available as a dry powder supplied in 15 unit vials.

4.32 Preparation: Dissolve the contents of a Blenoxane vial in 1 to 5 ml of sterile water for injection, USP, sodium chloride for injection, USP, 5% dextrose injection, USP, or bacteriostatic water for injection, USP. (Note: 1 unit = 1 mg)

4.33 Storage: The sterile powder is stable under refrigeration (2N-8NC) and should not be used after the expiration date is reached. Blenoxane is stable for 24 hours at room temperature in sodium chloride or 5% dextrose solution. Blenoxane is

stable for 24 hours in 5% dextrose containing heparin 100 units per ml or 1000 units per ml.

4.34 Adverse effects: Fever, chills, pulmonary fibrosis, stomatitis, weight loss, anorexia, renal and hepatic toxicity, erythema, rash, vesiculation, striae, hyperpigmentation, skin tenderness, hyperkeratosis, nail changes and pruritus. Rare: Myocardial infarction, CVA, thrombotic microangiopathy (HUS) or cerebral arteritis.

4.35 Supplier: Commercially available

4.36 Administration: See section 5.231

*See FDA-approved package insert for a comprehensive list of adverse events associated with carboplatin.

4.4 VP-16 (Etoposide, VePesid7 - NSC #141540)

4.41 Formulation: VP-16 injection is available in 100 mg (5 ml) sterile, multiple-dose vials. The pH of the clear, yellow solution is 3 to 4. Each ml contains 20 mg etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80/tween 80, 650 mg polyethylene glycol 300 and 30.5% (v/v) alcohol.

4.42 Preparation: The computed dose should be diluted in 500 mL NS or D5W and administered over 1-2 hours IV.

4.43 Storage: Unopened vials of VP-16 are stable for 24 months at room temperature. Vials diluted as recommended to a concentration of 0.2 or 0.4 mg/ml are stable for 96 and 48 hours, respectively, at room temperature under normal room fluorescent light in both glass and plastic containers.

4.44 Adverse effects: Leukopenia, thrombocytopenia, alopecia, nausea, vomiting, headache, fever, hypotension, anorexia, and allergic reactions.

4.45 Supplier: Commercially available.

4.46 Administration: See Section 5.232

*See FDA-approved package insert for a comprehensive list of adverse events associated with carboplatin.

4.5 Cisplatin (Platinol - NSC #119875)

4.51 Formulation: Cisplatin is available as a dry powder supplied in 10 mg and 50 mg vials and in aqueous solution in 50 mg and 100 mg vials with 100 mg mannitol and 90 mg sodium chloride.

4.52 Preparation: The 10 mg and 50 mg vials should be reconstituted with 10 ml or 50 ml with sterile water for injection, USP respectively. Each ml of the

resulting solution will contain 1 mg of Platinol. Reconstitution as recommended results in a clear colorless solution.

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

4.53 Storage: Unopened vials of dry powder are stable for the lot life indicated on the package when stored at room temperature. The aqueous solution should be stored at room temperature and protected from light. The reconstituted solution is stable for 20 hours at room temperature.

NOTE: Once reconstituted, the solution should be kept at room temperature. If the reconstituted solution is refrigerated, a precipitate will form.

4.54 Administration: See Section 5.233

4.55 Adverse effects: Leukopenia, thrombocytopenia, anemia nausea, vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy, electrolyte imbalance, hypocalcemia, hypomagnesemia, aminoglycoside, ototoxicity, ocular toxicity and allergic reactions. Infrequent: Cardiac abnormalities, anorexia, elevated SGOT, rash and alopecia.

NOTE: Aminoglycoside antibiotics given before, with, or after cisplatin may potentiate renal toxicity and should be avoided whenever possible.

Severe renal toxicity can be largely avoided by induction of a diuretic before, during and after treatment.

Mild renal dysfunction is a common complication (10%) of chronic therapy and may require discontinuation of therapy if BUN > 30 mg/dl or creatinine > 2.0 mg/dl develop.

Mild or severe electrolyte abnormalities may occur (5%) as acute or chronic complications, especially hypokalemia or hypomagnesemia. Monitoring of electrolytes and electrolyte replacement will usually correct these abnormalities. Rarely, severe hypomagnesemia and hypocalcemia may require replacement therapy and discontinuation of treatment with cisplatin.

Allergic reactions are rare. If accompanied by respiratory symptoms, allergic reactions require discontinuation of treatment. Patch or skin tests are recommended for patients with suspected allergy to cisplatin. An emergency set for the treatment of allergic reactions should be available in the treatment area.

Local necrosis and thrombophlebitis can be avoided by careful administration.

Neurotoxicity may be related to cumulative dose and severe toxicity can be largely avoided by careful monitoring for evidence of paresthesias and timely discontinuation of treatment. Ataxia has been described.

Ototoxicity may occur.

NOTE: Eighth (VIII) nerve toxicity resulting in hearing loss and (less commonly) vestibular symptoms is a well documented complication of cisplatin treatment and is usually related to total cumulative dose.

4.56 Supplier: Commercially available

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It is advised that patients placed on cisplatin, whether as a single agent therapy or combination, be questioned concerning hearing loss. Patients with a history of hearing loss should be considered for pre-treatment audiometry with follow-up audiometry as clinically indicated. It is recommended that patients be queried concerning hearing loss before each cycle of cisplatin.

*See FDA-approved package insert for a comprehensive list of adverse events associated with carboplatin.

4.6 Pathology

4.61 Malignant tumors of the ovarian stroma are: granulosa cell tumor, granulosa-theca cell tumor, Sertoli-Leydig cell tumor (androblastoma), steroid (lipid) cell tumor, unclassified sex cord stromal tumor, sex cord tumor with annular tubules, and gynandroblastoma.

4.62 The following definitions are those of the World Health Organization: (from Tavassoli FA, Devilee P (eds), World Health Organization Classification of Tumours, Pathology and Genetics of Tumours of the Breast and Female Genital Organs, IARC Press, Lyon, 2003):

Ovarian stromal tumors (sex cord stromal tumors) contain granulosa cells, theca cells, collagen producing stromal cells, Sertoli cells, Leydig cells, and cells resembling their embryonic precursors, singly or in various combinations. Specific nomenclature reflects the cellular constituents of the tumors i.e.:

Granulosa cell tumors (granulosa-theca cell tumors) are tumors containing granulosa cells, theca cells, and stromal cells resembling fibroblasts singly or in various combinations. The tumor contains more than a small component of granulosa cells.

Sertoli-Leydig cell tumors (androblastomas) are tumors containing Sertoli and Leydig cells of varying degrees of maturity; indifferent gonadal cells of embryonal appearance are present in certain cases.

Gynandroblastoma is a very rare tumor in which collections of granulosa cells with typical Call-Exner bodies coexist with hollow tubules lined by Sertoli cells.

Unclassified sex cord stromal tumors are those in which sex cord and/or stromal elements are present although they cannot be specifically identified as either ovarian or testicular in type.

Sex cord tumor with annular tubules is a rare tumor in the unclassified category which is commonly multifocal and of microscopic size. It is seen disproportionately often in patients with the Peutz-Jeghers syndrome, and is characterized by simple and complex ring-shaped solid tubules containing cells of Sertoli or granulosa type, by the presence of hyaline bodies, and by a tendency to calcify in a manner similar to that of the gonadoblastoma.

4.63 All metastatic implants submitted by the surgeon will be submitted for histologic examination if disease is found histologically (if a staging biopsy was not performed, or if the biopsies did not show tumor, slides do not have to be submitted from the staging procedure). If implants are identified, a representative slide confirming the disease as malignant shall be submitted for review.

4.64 Primary tumors should be sampled at a minimum rate of one section per two centimeters of greatest diameter of tumor. All slides containing tumor on these cases should be submitted to the GOG. Form F (Pathology Form) and three copies of the dictated pathology report must be submitted with the required slides.

4.65 If the uterus is removed, representative sections of endometrium must be submitted. If the uterus is not removed, endometrial sampling is required and sections must be submitted for pathology review.*

4.66 Peritoneal fluid from the primary surgery must be sent for cytology as an aspirate or washing. Three copies of the dictated cytology report and a representative slide (or representative photomicrograph) of positive specimens must be submitted. If no tumor is found in the cytology specimen only the cytology report should be submitted.

* Section 4.65 is not required if the uterus was previously removed for reasons not related to the current illness.

Please see sections 7.2 and 10.2 for additional instructions and requirements.

5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

Sites must submit, all IRB approvals (initial and continuing) on NCI sponsored adult Cooperative Group phase I, II & III prevention and treatment studies to the CTSU Regulatory Office, at the Coalition of Cancer Cooperative Groups in Philadelphia. A CTSU IRB/Regulatory Approval Transmittal Sheet should be submitted along with the CTSU IRB Certification Form or its equivalent. (CTSU forms can be downloaded at https://www.ctsu.org/public/rss2_page.aspx). IRB submissions can be faxed or e mailed (preferred methods) or mailed to: **(11/22/2010)**

Email, Mail or Fax to:
Cancer Trials Support Unit (CTSU)
ATTN: Coalition of Cancer Cooperative Groups (CCCG)
Suite1100
1818 Market Street
Philadelphia, PA 19103
FAX: 1-215-569-0206
CTSURegulatory@ctsu.coccg.org

5.1 Patient Registration

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

5.11 Patient must have signed an approved informed consent and authorization permitting release of personal health information. Current FDA, NCI and institutional regulations concerning informed consent will be followed.

5.12 All eligibility requirements indicated in section 3.0 must be satisfied.

5.13 The Fast Fact Sheet data for this protocol must be gathered and the pretreatment testing as required in Section 7.0.

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

5.141 Instructions for web-based registration and randomization can be found by going to the GOG Web Menu page, selecting "Start/finish a patient registration," and then selecting "Directions" found on the left side of the page. Assistance is available from the Statistical and Data center by phone if necessary (1-800-523-2917).

5.142 Alternatively, when necessary, patient registration can take place by phoning the GOG Statistical and Data Center 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 Patients will be randomized in a 1:1 ratio to one of the two treatment arms below. The randomization will be stratified by the presence or absence of measurable disease.

5.22 **Arm I: Paclitaxel and Carboplatin**

If randomized to this arm, patients will receive the following:

5.221 Paclitaxel (175 mg/m^2) IV by 3-hour infusion on day 1 every 21 days for 6 cycles (=18 weeks), unless progression or adverse effects prohibit further therapy.

5.222 Carboplatin (AUC of 6) IV by one hour infusion on day 1 every 21 days for 6 cycles (=18weeks), unless progression or adverse effects prohibit further therapy.

5.23 **Arm II: Bleomycin, Etoposide, and Cisplatin (BEP)**

If randomized to this arm, patients will receive the following:

5.231 Bleomycin (20 units/m^2; max dose is 30 units) is to be given on day 1 as IV push every three weeks for four cycles (=12 weeks). The total cumulative bleomycin dose shall not exceed 120 units.

Bleomycin will be discontinued permanently if the carbon monoxide diffusion capacity has decreased more than 20% from baseline, or at any time if the patient develops rales or lack of expansion on physical examination of chest (see section 6.56).

5.232 Etoposide (VP-16) (75 mg/m^2) IV over 60 minutes daily times five days, every three weeks for four cycles (= 12 weeks).
*Patients who have received prior pelvic radiation therapy will receive etoposide on days 1-4 only.

5.233 Cisplatin (20 mg/m2) IV over 30 minutes IV daily times five days, every three weeks for four cycles (=12 weeks).

5.24 Methods of Protocol Administration

5.241 Biometric Considerations for Dose Calculation

5.2411 Maximum body surface area used for dose calculations of paclitaxel, etoposide, and cisplatin will be 2.0 m^2 as per the GOG Chemotherapy Procedures Manual.

5.2412 Maximum body surface area used for dose calculations of bleomycin will be 1.5 m^2 because the maximum dose allowable is 30 units.

5.2413 Weight Change: If a patient's weight changes by ≥ 10% during the course of the study, the doses of paclitaxel, carboplatin, bleomycin, etoposide, and cisplatin will be recalculated.

5.2414 Rounding Dose: Doses of paclitaxel and carboplatin, may be rounded to the nearest 5 mg. Doses of bleomycin, etoposide and cisplatin may be rounded to nearest 1mg.

5.242 Dosing of Carboplatin

See Appendix III for current Carboplatin dose calculation instructions. **(11/22/2010)**

Note: Carboplatin dose will be recalculated if patient has weight change ≥ 10% from baseline. (10/24/2011)

5.243 Sequence and timing of drug administration

5.2431 Arm I: Paclitaxel will be infused over 3 hours. Due to the risk of immediate hypersensitivity reaction, paclitaxel should be infused prior to carboplatin. Carboplatin will be administered as a 60 minute infusion following paclitaxel.

5.2432 Arm II: First, bleomycin given as an IV push (day 1 only). Second, etoposide given over 60 minutes (day1-5). Third, cisplatin given over 30 minutes (day1-5).

Refer to Appendix IV for General Chemotherapy Guidelines. (10/24/2011)

5.244 Premedications

5.2441 Paclitaxel:

For all courses where paclitaxel is to be administered, it is recommended that a preparative regimen be employed one hour prior to the treatment regimen on that day, to reduce the risk associated with hypersensitivity reactions to these drugs.

This regimen should include a standard dose of dexamethasone (either IV or PO), an anti-histamine H1 (diphenhydramine 25-50mg IVP or orally, or an equivalent dose of an alternate H_1 blocker such as loratadine or fexofenadine), and a standard

dose of antihistamine H2 IVP (such as cimetidine, ranitidine, or famotidine).

5.245 Concomitant anti-neoplastic therapy

Prior to documented disease progression, the following therapeutic modalities will be considered protocol violations:

- Reassessment or cytoreductive surgery
- Anti-neoplastic therapy not otherwise specified in the current protocol, including cytotoxic, biologic, hormonal, or radiation therapy, regardless of indication (treatment of measurable disease or consolidation therapy).
- Hormone replacement therapy is NOT a protocol violation.

5.246 Antiemetic Regimens

It is anticipated that nausea and vomiting may be a significant side effect of each regimen (BEP and carboplatin/paclitaxel). The following representative antiemetic regimens are suggested:

• Ondansetron 8-32 mg IV 30 minutes prior to administration of chemotherapy and dexamethasone 10-20 mg PO/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 mg IV 30 minutes prior to chemotherapy.

• Aprepitant (Emend) – To treat delayed nausea/vomit for patients on either treatment arms, consider the addition of Aprepitant 120mg PO day 1 and Aprepitant 80mg PO day 2 and 3, along with dexamethasone 12mg PO day 2 and day 3.

6.0 TREATMENT MODIFICATIONS

In order to maximize dose intensity on this study, there will be no dose reductions unless treatment is delayed for more than two weeks, or if patients experience febrile neutropenia, sepsis, or thrombocytopenia as described below. Any patient who is delayed must be evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met. Treatment delays are to be kept to a minimum and every effort should be made to maintain the intended schedule. No treatment delays are permitted for other than documented toxicity. No dose escalation is planned for this study.

6.1 General Guidelines for Hematologic Toxicity:

6.11 Treatment modifications will be based on the absolute neutrophil count (ANC) rather than the total white count (WBC).

6.12 Treatment modifications will be employed in a sequential manner using cycle delay, dose reduction, and addition of myeloid growth factors, as directed.

6.13 Subsequent cycles of therapy will not begin until the ANC is $\geq$ 1,500cells/mm^3 and the platelet count is $\geq$ 100,000 cells/mm^3. Therapy will be delayed on a week-by-week basis until these values are achieved. Patients who fail to recover adequate counts within a three-week delay will be removed from study only after one of the Study Chairs has been contacted. Follow-up on the patient will continue as described in Section 7.0.

Exceptions:

- Patients who received G-CSF prior to the current cycle may begin with ANC $\geq$ 1000 cells/mm3, if clinically appropriate, to allow for transient reductions in ANC after discontinuation of G-CSF.

- Patients who are delayed more than 7 days may begin with ANC $\geq$ 1000 cells/mm3, if clinically appropriate; as they will receive G-CSF with subsequent therapy

6.14 Use of Hematopoietic Cytokines and Protective Agents

The use of hematopoietic cytokines and protective reagents are restricted as noted:

6.141 In general, patients will NOT receive prophylactic filgrastim (G-CSF), PEG-filgrastim (Neulasta), or sargramostim (GM-CSF) unless they experience treatment delays or recurrent neutropenic complications after treatment modifications as specified. In particular, hematopoietic growth factors should not be used to avoid initial chemotherapy dose modifications as stipulated in the protocol. However, patients may also receive growth factors for management of neutropenic complications in accordance with clinical treatment guidelines. If required, it is recommended that growth factors be initiated the day after the last dose

of chemotherapy and typically continuing for a minimum of 10 days or until the ANC is sustained above >1000/mm3. Growth factors should be discontinued if the ANC exceeds 10,000/ mm3 and should not be used within 72 hours of a subsequent dose of chemotherapy.

6.142 Patients will NOT receive prophylactic thrombopoietic agents unless they experience recurrent Grade 4 thrombocytopenia after treatment modifications as specified below.

6.143 Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia. Treating physicians should be aware of the recent changes in prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival, and that these agents are administered only to avoid red blood cell transfusions. They do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted.
http://www.fda.gov/Medwatch/safety/2007/safety07.htm

6.144 Patients may NOT receive amifostine or other protective reagents, unless indicated in the study design.

6.15 There will be no dose modifications for paclitaxel, cisplatin or bleomycin based on hematologic toxicity.

6.2 Modifications for Hematologic Toxicity (Nadirs)

Table A: Modification Instructions for Dose-Limiting Hematologic Toxicity
(Arm1: Carboplatin/paclitaxel; Arm 2: BEP)

DLT ANC	DLT PLT	First occurrence	Second occurrence	Third occurrence
YES	NO	Arm 1: Reduce carboplatin one AUC unit Arm 2: Discontinue day #5 etoposide.*	Arm 1:Add G-CSF and maintain all current drug doses Arm 2: Add G-CSF and maintain all current drug doses.	Discontinue chemotherapy
YES	YES	Arm 1: Reduce carboplatin one AUC unit Arm 2: Discontinue day #5 etoposide.*	Arm 1: Add G-CSF and decrease carboplatin one AUC unit. Arm 2: Add G-CSF and discontinue day #4 etoposide.*	Discontinue chemotherapy
NO	YES	Arm 1: Reduce carboplatin one AUC unit Arm 2: Discontinue day #5 etoposide.*	Arm 1: Decrease carboplatin one AUC unit. Arm 2: Discontinue day #4 etoposide.*	Discontinue chemotherapy

*** For patients with prior pelvic radiation, who start on a day1-4 schedule: dose modification would be to discontinue day #4 etoposide (first occurrence) and day #3 etoposide (second occurrence).**

6.21 Initial occurrence of dose-limiting neutropenia (defined in 6.22) or dose limiting thrombocytopenia (defined in 6.23) will be handled according to Table A.

6.22 Dose-Limiting Neutropenia (DLT-ANC) is defined by the occurrence of febrile neutropenia or prolonged Grade 4 neutropenia persisting ≥ 7 days. There will be no modifications for uncomplicated Grade 4 neutropenia lasting less than 7 days. Febrile neutropenia is defined within the CTCAE as fever **with or without** clinically or microbiologically documented infection with ANC less than 1,000 /mm^3 and fever greater than or equal to 38.5°C.

6.23 Dose-limiting thrombocytopenia (DLT-PLT) is defined by any occurrence of Grade 4 thrombocytopenia (<25,000/mm^3) or bleeding associated with

Grade 3 thrombocytopenia (25,000 to <50,000/mm3). There will be no modifications for uncomplicated Grade 3 thrombocytopenia.

6.3 Modifications for Delayed Hematologic Recovery

Table B: Modifications for Delayed Hematologic Recovery (NOT DLT)		
Category	Delay (days)	Modification
Delay-ANC	1-7:	No change
	8-21	Arm1: Add G-CSF with next cycle Arm2: Discontinue day #5 etoposide* and add G-CSF with next cycle
	>21	Arm1: Discontinue chemotherapy Arm2: Discontinue chemotherapy
Delay-PLT	1-7:	No change
	8-21:	Arm1: Decrease carboplatin one AUC unit Arm2: Discontinue day #5 etoposide.*
	>21:	Arm1: Discontinue chemotherapy Arm2: Discontinue chemotherapy

*** For patients with prior pelvic radiation, who start on a day1-4 schedule: dose modification would be to discontinue day #4 etoposide.**

6.31 Delay on the basis of neutropenia (Delay-ANC) is defined if the ANC is less than 1,500 cells/mm3 (CTCAE Grade 3 or worse) within 24 hours prior to scheduled therapy, or less than 1,000 cells/mm3, if the patient received G-CSF during the previous cycle.

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

6.33 Modifications noted above (TABLE B) are only required for management of delays in the absence of dose reductions stipulated by nadir DLT-ANC and/or DLT-PLT (as noted above).

6.4 Non-hematologic Toxicity:

Table C: Modifications for Non-hematologic Toxicity			
Drug	Regimen -2 Level	Regimen -1 Level	Regimen Starting Dose
Paclitaxel	110 mg/m2	135 mg/m2	175 mg/m2
Carboplatin	4	5	6
Bleomycin	discontinue	discontinue	20 units/m2
Etoposide	75mg/m2 day 1-3	75mg/m2 day1-4	75mg/m2 day1-5
Cisplatin	20mg/m2 day1-3	20mg/m2 day1-4	20mg/m2 day1-5

*** For patients with prior pelvic radiation, who start on a day1-4 schedule: dose modification would be to discontinue day #4 etoposide or cisplatin (-1Level) and discontinue day #3 etoposide or cisplatin (-2Level).**

6.41 Neurologic Toxicity: Patients who experience ≥ grade 2 neurotoxicity requires one dose reduction (Arm 1: paclitaxel only, Arm 2: cisplatin only). Treatment will be delayed up to three weeks until toxicity resolves to ≤ grade 1. If toxicity dose not resolve within 3 week delay, patient will discontinue the treatment (Arm 1: paclitaxel, Arm 2:cisplatin) and Study Chair will be notified. Docetaxel could be substituted for paclitaxel after 3 week delay, only after discussion with Study Chair.

6.42 GI Toxicity: There will be no dose modifications for nausea, vomiting, diarrhea or constipation. It is recommended that routine medical measures be employed to manage these symptoms. Any other Grade 4 gastrointestinal toxicity requires a one dose level reduction.

6.43 Hepatic Toxicity: Hepatic toxicity is not expected as a direct complication of chemotherapy in this untreated patient population using the prescribed dose and schedule for each regimen. However, the development of Grade 3 (or greater) elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin requires reduction of one dose level in paclitaxel (arm 1) and delay in subsequent therapy for a maximum of three weeks until recovered to Grade 1.

6.44 Renal Toxicity: For Arm 1, renal toxicity (associated with reduction in GFR) is not expected as a direct complication of chemotherapy in this untreated patient population using the prescribed dose and schedule of each regimen. As such, there are no specific dose modifications for renal toxicity.

However, for Arm 1, the target AUC dose of carboplatin must be recalculated each cycle in any patient who develops renal insufficiency, defined by serum creatinine greater than 1.5 x institutional upper limit normal (ULN), CTCAE Grade ≥ 2.

See Appendix III for current carboplatin dosing instructions. **(11/22/2010)**

For Arm 2, patients who experience any serum creatinine rise above 2.0 mg/dl will require discontinuation of bleomycin (excreted by kidneys) and one dose reduction in cisplatin and etoposide. Treatment will be delayed up to three weeks until toxicity resolves to ≤ grade 1. If toxicity dose not resolve within 3

week delay, patient will discontinue the treatment and Study Chair will be notified.

To avoid renal toxicity, standard hydration with cisplatin should be administered.

6.45 Cardiac Toxicity: Asymptomatic bradycardia is not an indication for discontinuation of therapy or for routine monitoring. If any other arrhythmia is documented, monitoring may be required. A paclitaxel infusion may be discontinued for a cardiac arrhythmia that shows evidence of AV nodal block (e.g. Mobitz type l or 2 or total heart block). Any arrhythmia that is felt to necessitate discontinuation of paclitaxel should be discussed with the Study Chair. **(11/22/2010)**

6.46 Pulmonary Toxicity: Decline in pulmonary function as evidenced by decreased lung expansion, crackles on ausculation, decrease in oxygen saturation (O2 sat <90% on room air) or decrease in pulmonary diffusion capacity of carbon monoxide (DLCO) to 20% of its baseline value requires discontinuation of the bleomycin from the BEP regimen (Arm 1). Etoposide and cisplatin can be continued for the duration of the planned treatment course.

6.47 Potential modifications for other non-hematologic toxicities with an impact on organ function of Grade 2 (or greater) require discussion with one of the study co-chairs except where noted below in Section 6.471.

6.471 Special Modifications Study Treatment

6.4711 For any CTCAE Grade 3 non-hematologic adverse event (except controllable nausea/emesis) considered to be at least possibly related to study treatment, protocol directed treatment should be held until symptoms resolve to <= CTCAE Grade 1. If a CTCAE Grade 3 adverse event persists for > three weeks or recurs after resumption of therapy, the patient may be taken off protocol directed treatment after consulting with the Study Chair.

6.4712 For any CTCAE Grade 4 non-hematologic adverse event (except controllable nausea/emesis), the patient may be taken off protocol directed treatment therapy after consulting with the Study Chair.

6.48 Management of Hypersensitivity Reactions and Supportive Care

6.481 Hypersensitivity Reactions: When hypersensitivity reactions occur to paclitaxel or its vehicle (Cremophor), they present almost universally during the first few minutes of infusion. Continued treatment may be considered if the reaction if not life-threatening; however, patients must be cautioned of potential recurrences of the reaction. Should the patient decide to continue with treatment it is preferable that this be done on the same day of the occurrence. Additional doses of dexamethasone and cimetidine may be administered.

A suggested procedure would be to administer the drug first with 1 mL of the original IV solution diluted in 100 ml over one hour, then 10 mL in 100 ml over one hour, and finally, the original solution at the original speed. No additional dose adjustments should be made for other hypersensitive reactions. Subsequent courses of treatment may be preceded by 24 hours of premedications (dexamethasone 20 mg orally every 6 hours and cimetidine 300 mg orally every 8 hours) prior to administering intravenous premedications and incremental administration of the offending chemotherapeutic drug, as suggested above.

If oral premedication and desensitization results in a hypersensitivity reaction, intravenous premedications for 24 hours prior to the administration of chemotherapy may be given followed by incremental administration of the offending chemotherapeutic drug, as suggested above.

Docetaxel could be substituted for paclitaxel for significant hypersensitivity reactions, only after discussion with Study Chair.

If the patients fails intravenous desensitization or substitution to docetaxel, then the patient should come off study.

6.482 Supportive care: In addition to other aspects of supportive care, particular attention should be paid for adequate control of nausea and vomiting, including use of HT3 receptor antagonists as required. The patient should be transfused as needed without interruption of therapy. Platelet transfusions may also be required in rare instances. See Section 5.244 and 5.246 for additional information.

7.0 STUDY PARAMETERS **(11/22/2010)**

7.1 The following observations and tests are to be performed and recorded on the appropriate form(s):

Observations and Tests	Pre-treatment	During Treatment		Post-Treatment
	Prior to initial study treatment	Weekly During Treatment	Prior to Each Cycle	Following Cycle 6 Arm 1 or Cycle 4 Arm II; Then Every 3 months x 2 years; Then every 6 months x 3 years, then annually thereafter
History & Physical Exam, Pelvic Examination, Performance Status	1		2	X
EKG **(11/22/2010)**	1			
Biopsy for recurrent disease **(10/24/2011)**	3,11			
Serum pregnancy test	4		X	
Toxicity Assessment	5		X	X
Radiographic Tumor measurement	1		7	7
CBC with Differential, Platelet Count	5	X	6	
Creatinine, Serum Magnesium, Bilirubin, SGOT, Alk. Phosphatase, β-hCG	5		X,6	
Urinalysis	5			
Inhibin A, Inhibin B	10		8	8
Chest imaging (X-ray or CT scan of chest)	1			
Pulmonary diffusion capacity for carbon monoxide (DLCO)	1		9	

1. Must be obtained within 28 days prior to initiating protocol therapy.
2. Directed history and physical examination and evaluation of performance status should be done prior to each cycle of treatment. Pelvic examination may be deferred prior to each cycle, and instead be performed according to the schedule for Radiographic Tumor measurement, as noted in Footnote 7 below.
3. Required only in the setting of recurrent disease; not required for patients with newly diagnosed disease.
4. Should be done if the patient is of child-bearing potential. A serum sample must be obtained within 72 hours prior to initiating protocol therapy. For subsequent cycles, serum or urine tests are acceptable.
5. Must be obtained with 14 days prior to initiating protocol therapy.
6. Must be obtained within 4 days of re-treatment with protocol therapy.
7. Follow-Up Radiographic Assessment of Disease. In the absence of disease progression by criteria in Section 8.3, imaging using the same modality and encompassing the same field as in the initial pre-treatment evaluation should be repeated with the following schedule:
    a) After cycle 3 (before cycle 4).
    b) 2 weeks after cycle 6 in the carboplatin/paclitaxel arm or 7 weeks after completion of cycle 4 in the BEP arm, then every 3 months for 2 years and then every 6 months thereafter.
8. Obtain on all patients initially and prior to each cycle of therapy. Obtain every 3 months for two years if elevated at time of treatment discontinuation.
9. Should be obtained just prior to day one of cycle #3 and cycle #4 of bleomycin for patients on the bleomycin-containing arm only (Arm II).
10. Should be obtained after surgery but not longer than 28 days before the initiation of treatment.
11. Should be obtained within 8 weeks prior to study entry.

7.2 Stained Pathology Slide Requirements For Central Review To Confirm Eligibility

Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility for the protocol. At least one representative H&E stained slide (or slides) demonstrating primary site, histologic cell type, and grade, and **one** H&E stained slide showing the most advanced stage of disease will be required. If the most advanced stage of disease is not documented by histology, the method of stage documentation needs to be stated (e.g. CT, MRI, etc.). If this protocol allows patients with recurrent or persistent disease, slides from recurrence and/or persistent disease will be required only if recurrence/persistent disease is confirmed by histology or cytology.

When submitting pathology material to the GOG Statistical and Data Center individual slides must be labeled with GOG Patient ID, patient initials and the surgical / pathology accession number (e.g., S08-2355) and block identifier (e.g., A6). Do not label the slides with disease site (e.g., right ovary) or procedure date. Pack the labeled slides into plastic slide cassette(s). Tape plastic slide cassettes shut and wrap in bubble wrap or another type of padded material prior to shipping. 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. Ship pathology slides, three copies of both the Pathology Form F (if required for the protocol) and the official pathology report in your own shipping containing using postal mail at your own expense directly to the **Pathology Materials Coordinator at the GOG Statistical and Data Center, Roswell Park Cancer Institute, Research Studies Center, Carlton and Elm Streets, Buffalo, New York, 14263**; phone (716) 845-5702. The GOG Upload Application in SEDES is an alternative method for submitting pathology reports and Form F to the GOG Statistical and Data Center. Please see sections 4.6 and 10.2 for additional instructions and requirements.

7.3 Research Specimen Requirements

Twenty-five serial sections on charged slides or a block will be obtained from the primary tumor tissue or from biopsy of recurrent disease, when available. If there is insufficient tissue to meet these requirements, this does NOT exclude the patient from participating. Any tissue that can be submitted, up to the amount listed below, should be submitted.

Specimen Requirement (Specimen Code)	**Collection Time Point**	**Ship Specimen To The GOG Tissue Bank**
Twenty-five (25) serial sections on charged slides suitable for immuno-histochemistry OR a block from the primary tumor tissue (FP01) or biopsy of recurrence	Archived	Within six (6) weeks following enrollment. Ship in a suitable container at room temperature (see Appendix II)

8.0 EVALUATION CRITERIA

8.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

8.11 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment on study.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

8.12 *Disease Parameters*

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions,

leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

8.13 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin

lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. PET-CT scans are not always done with oral and IV contrast. In addition, the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed. For these reasons, the GOG will not allow PET-CT use for RECIST 1.1 response criteria.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Inhibin A and inhibin B: Although these levels are being measured in this protocol, inhibin results will not be used to assess response or progression, or to make treatment decisions.

8.14 Response Criteria

8.141 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

8.142 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If CA125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of CA125 level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

8.143 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

8.15 Duration of Response

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

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

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

8.16 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

8.17 Survival

Survival is defined as the duration of time from start of treatment to time of death or the date of last contact.

9.0 DURATION OF STUDY

9.11 As specified in sections 5.0 and 6.0, depending on the arm to which they are randomized, patients will receive 6 cycles of paclitaxel and carboplatin, or 4 cycles of bleomycin, etoposide, and cisplatin, unless disease progression or adverse effects prohibit further treatment. The patient can refuse the study treatment at any time.

9.12 Patients will be followed (with completion of all required case report forms) until disease progression or study withdrawal. In addition, following disease progression, patients will be monitored for delayed toxicity and survival for a period of 10 years with Q forms submitted to the GOG Statistical and Data Center, unless consent is withdrawn.

10.0 STUDY MONITORING AND REPORTING PROCEDURES

10.1 ADVERSE EVENT REPORTING FOR A COMMERCIAL AGENT

10.11 Definition of Adverse Events (AE) **(11/22/2010)**

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.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

The CTCAE Manual version 4.0 is also available on the GOG member web site (http://www.gog.org under MANUALS).

10.12 Reporting Expedited Adverse Events

Depending on the phase of the study, use of investigational or commercial agents, and role of the pharmaceutical sponsor, an 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 before final submission to CTEP. 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 AEs 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.

10.13 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 Any Commercial 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:

- There are no additional instructions or exceptions to AdEERS expedited reporting requirements for this protocol.

10.14 Procedures for Expedited Adverse Event Reporting: **(11/22/2010)**

10.141 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.

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. **(10/24/2011)**

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. 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.

10.15 Automated CDUS reporting

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.

10.2 DATA MANAGEMENT FORMS **(11/22/2010)**

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: the Pathology Report **must** be submitted via the SDC Electronic Data Entry System (SEDES) which is available through the GOG website (www.gogstats.org).The GOG Uploader Application in SEDES is an alternate method for submitting the pathology report to the GOG SDC.

Form	Due within		Copies*	Comments
	Weeks	Event		
Specimen Consent Application	1	Registration	N/A	Mandatory submission via SEDES
Form R (Registration Form)	2	Registration	1	Mandatory submission via SEDES
Form OHR (Recurrent Gynecologic Cancer – On Study History Form)	2	Registration	1	Mandatory submission via SEDES
Form DR (Pre-Treatment Summary Form)	2	Registration	1	Mandatory submission via SEDES
Form D2M (Solid Tumor Evaluation Form	2	Registration	1	Mandatory submission via SEDES
Primary disease: Form F (Pathology Form) Pathology Report Stained Slides Recurrent or Persistent Disease: Form F (Pathology Form) Pathology Report Stained Slides	 6 6 6 6 6 6	 Registration Registration Registration Registration Registration Registration	 2** 2** ** 2** 2** **	Submit together to SDC via postal mail or pathology report via report uploader Submit together to SDC via postal mail or pathology report via report uploader
Form D2R (Cycle Dose Drug Form)	2	Completion of each cycle of therapy	1	Mandatory submission via SEDES
Form D2M (Solid Tumor Evaluation Form)	2	Clinical response assessment	1	Mandatory submission via SEDES
Form T (Common Toxicity Reporting Form)	2	Beginning of each subsequent cycle	1	Mandatory submission via SEDES
Form Q0 (Treatment Completion Form)	2	Completion of study Rx and change in Rx	1	Mandatory submission via SEDES

Form Q (Follow-up Form)	2	Disease progression; death; normal follow-up	1	Mandatory submission via SEDESquarterly for 2 years, semi-annually for 3 more years,then annually thereafter
Form SP-FP01-0264	6	Registration	Online	SEDES
Form SP-RP01-0264	6	Registration	Online	SEDES

* The number of required copies including the original form, which must be sent to the Statistical and Data Center.

** Please see Sections 4.6 and 7.2 for additional pathology requirements and instructions.

This study will be monitored by the **Abbreviated** Clinical Data System (CDUS) Version 3.0 CDUS data will be submitted quarterly to CTEP by electronic means.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study design overview and registration

This is a randomized, two-arm, Phase II clinical trial. Patients will be randomized in a 1:1 ratio to paclitaxel and carboplatin or bleomycin, etoposide, and cisplatin (BEP). A BEP control arm is being used because historical data for progression free survival and other endpoints are limited and not consistent across studies in this patient population (see section 2.1).

The randomization will be stratified by whether the patient has measurable disease.

All patients on this study will be registered and randomized centrally at the GOG Statistical and Data Center. Prior to registration, eligibility will be reviewed via Fast Fact Sheet verification. The treatment assignment will be concealed from institutions and patients until registration with verification of eligibility. Randomization with equal probabilities to the two treatment regimens will be carried out following study registration. All reports will include a complete accounting of all patients registered to this protocol.

11.2 Data collection

The principal parameters to be collected, analyzed and reported to examine the therapeutic effect and tolerability of the treatment regimen are:

11.21 Outcome variables

11.211 Primary: progression-free survival

11.212 Secondary: tumor response rate and overall survival

11.22 Tumor characteristics: tumor size as measured by the maximum dimension of the tumor, histologic cell type, and tumor grade

11.23 Host characteristics: age at entry, performance status, race, and ethnicity

11.24 Adverse effects: frequency and severity of adverse events as assessed by the CTCAE version 4.0. **(11/22/2010)**

11.3 Accrual

A survey of GOG institutions was done in September 2006 in order to examine whether there were sufficient resources and interest in a study of first-line treatment for patients with newly diagnosed SCSTs of the ovary. Based on the results from this survey, we anticipate accrual to be approximately 15 patients per year.

11.4 Primary Objective and Hypothesis, Sample Size and Design, and Duration

Primary Objective and Hypothesis:

The primary objective of the study is to compare PFS for paclitaxel and carboplatin versus BEP in women with newly diagnosed SCSTs of the ovary. PFS is being used as the primary endpoint in the study for the following reasons. First, it avoids the

confounding effects of post-progression therapy, which impact analyses of overall survival. Second, it provides an assessment of clinical benefit by measuring tumor burden.

For the primary analyses, patients will be included in their randomized treatment group; analyses by actual treatment received will be considered exploratory.

The primary analysis of PFS will occur after 38 progressions or deaths have been observed in the control arm and will include all patients for an intent-to-treat analysis. For the purpose of treatment comparisons, PFS will be assessed from the date of randomization, and death due to any cause will be considered a failure event.

A noninferiority hypothesis will be used at the final analysis, in which if the 85% upper confidence limit (CL) excludes a noninferiority margin of 1.10, the carboplatin + paclitaxel arm will be considered noninferior to BEP.

An adaptive design will be used that will allow the study to be stopped early for superiority, i.e., if the experimental arm (paclitaxel and carboplatin) is superior to BEP or for futility, i.e., if it is deemed unlikely that the study could declare noninferiority at the end of the study.

Sample Size and Design:

The study will utilize an adaptive, two-stage design. At the end of the first stage, four results are possible based on the analysis of PFS:

(1) superiority may be declared,
(2) the study may be deemed futile,
(3) a second stage may be required and permitted due to the first stage results being insufficient to declare superiority, or
(4) the study may be deemed inconclusive and a second stage of accrual foregone due to other priorities.

We allow a relatively large overall α (type I error) of 0.15 because this is a phase II, screening design in a rare tumor population. We target a power of approximately 85% for a hazard ratio of 0.67. Twenty events are required in either arm (i.e., control or experimental, not total) for the interim analysis, and 38 events are required in the control arm for the final analysis. **(11/22/2010)**

Table 2 below shows the power and expected analysis times for the interim and final analyses. Due to the uncertainty in the expected median PFS value, these are presented for two scenarios of median PFS: 60 and 30 months,

For example given a median PFS of 60 months and a hazard ratio of 0.667, we would expect the interim analysis to occur after 7.2 years, and at the interim analysis, there would be a 3% probability of declaring the study futile, a 10% probability of declaring paclitaxel and carboplatin to be superior to BEP, and a 87% chance of the results being considered inconclusive, at which point, we could decide to continue to the second stage of the study, or forego the second stage and deem the study inconclusive. If a second stage was utilized, we would expect total accrual to take 8.5 years, and the final

analysis to occur after 11.1 years, and overall, the study would have 87% power to declare paclitaxel and carboplatin to be superior to BEP.

If the median PFS were 30 months and the hazard ratio were 0.667, we would expect the interim analysis to occur after 5.4 years. If a second stage were utilized, we would expect the final analysis to occur after 8.3 years (i.e., at the end of accrual, with no additional follow-up period required), and overall, the study would have 89% power to declare paclitaxel and carboplatin to be superior to BEP.

GCIG participation is also anticipated, which would increase the accrual and decrease the duration of the trial.

Table 2: Operating Characteristics of the Study for Various Median PFS Values and HRs (11/22/2010)

Hazard Ratio	Interim†				Final‡			
	Expected Analysis Time (yr)	Pr (futility)	Pr (indeterminate) → Continue to 2nd stage?	Pr (superiority) [Power]	Expected Analysis Time (yr)	Pr (Noninferiority) Overall	Pr (superiority)	Pr (Superiority or Noninferiority) Overall [Power]
Median PFS = 60 months								
0.667	7.1	6%	85%	10%	11.1	10%	76%	86%
0.80	7.0	16%	81%	3%	11.1	15%	48%	63%
1.00	6.8	38%	61%	1%	11.1	11%	16%	27%
1.10	6.7	50%	50%	0%	11.1	7%	8%	α = 15%
Median PFS = 30 months								
0.667	5.4	4%	87%	9%	8.2	10%	78%	88%
0.80	5.3	13%	85%	2%	8.2	15%	50%	65%
1.00	5.2	36%	63%	0%	8.2	12%	15%	27%
1.10	5.1	50%	50%	0%	8.3	8%	7%	α = 15%

† PFS Events required at interim analysis: 20 in either arm (i.e., control or experimental, not total). Decision rules at interim analysis are based on the following: superiority will be declared if $p \leq 0.01$ for test against null *HR*=1.00, and futility will be declared if the observed *HR* >1.10.

‡ PFS Events required at final analysis: 38 in control arms. Decision rule at final analysis is based on a 85% CI for *HR* excluding HR values of 1.10 and 1.00 for noninferiority and superiority, respectively.

Notes: Accrual = 1.25 /month = 15/year.
N projected overall = 128 (8.5 years of accrual [if necessary]).
Based on 10,000 simulations for each scenario.
Based on Cox proportional hazards model.

11.5 Secondary and Exploratory Analyses

Secondary Analyses

The relationship of treatment to overall survival will be assessed using the proportional hazards model described above for PFS. The relationship of treatment to tumor response rate will be assessed using logistic regression models adjusted for age and stratification factor (measurable disease status).

All patients who receive any therapy will be evaluated for both treatment efficacy and toxicity, except for the evaluation of response, in which the minimum length of trial to

evaluate response is defined as receiving 2 cycles of therapy and living at least 3 weeks after the second cycle for repeat assessment to be performed. However, if a patient has global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be considered evaluable and should be classified as having "symptomatic deterioration."

Translational Research

The translational component of this study will be developed based on technology existing nearing the completion of patient accrual.

Exploratory Analyses

Pre-treatment levels of inhibin A and inhibin B will be examined in relation to overall and progression-free survival in Cox proportional hazards models. Changes from baseline in inhibin levels will be compared between treatment groups using mixed effects models accounting for the longitudinal nature of the data. The repeated measures of inhibin also will be explored versus overall survival and PFS using time-dependent covariates in Cox proportional hazards models.

11.6 Interim Analysis

An interim analysis will be done that will allow for stopping early due to superiority, futility, or inconclusiveness. The interim analysis will occur after 20 PFS events have been observed in either arm (i.e., control or experimental, not total). The decision rules are based on p-values or the estimated hazard ratio from the analysis of PFS and are as follows **(11/22/2010)**:

- $p \leq 0.01$ → superiority declared for paclitaxel and carboplatin vs. BEP
- $HR > 1.10$ → futility
- otherwise → go to second stage or stop or deem study inconclusive.

More details regarding the interim analysis and its expected timing are given in section 11.4 and Table 2 above.

These rules control the overall α for the PFS endpoint to be 0.15.

11.7 Anticipated Gender and Minority Inclusion: This study restricts entry to women by nature of the site of disease.

11.8 The table below lists the anticipated percentages of patients by racial and ethnic subgroups (based on previous studies in this patient population).

Ethnic Category	Sex/Gender				
	Females		Males		Total
Hispanic or Latino	5	+	0	=	5
Not Hispanic or Latino	123	+	0	=	123
Ethnic Category: Total of all subjects	128	+	0	=	128
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0

Asian	8	+	0	=	8
Black or African American	24	+	0	=	24
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	96	+	0	=	96
Racial Category: Total of all subjects	128	+	0	=	128

Accrual Rate: 1.25 pts/mont h

Total Expected Accrual: 105 Min 128 Max

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