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SUMMARY OF CHANGES

For Protocol Revision #11 to GOG-0261

NCI Protocol #: GOG-0261
Local Protocol #: GOG-0261

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 #1-11. Lead Organization has been added. Revised footer has been added.
	ICD		NCI version date has been update on the Informed Consent

PROTOCOL GOG-0261

A RANDOMIZED PHASE III TRIAL OF PACLITAXEL PLUS CARBOPLATIN VERSUS IFOSFAMIDE PLUS PACLITAXEL IN CHEMOTHERAPY-NAIVE PATIENTS WITH NEWLY DIAGNOSED STAGE I-IV, PERSISTENT OR RECURRENT CARCINOSARCOMA (MIXED MESODERMAL TUMORS) OF THE UTERUS, FALLOPIAN TUBE, PERITONEUM OR OVARY **(06/1/10) (11/19/2012)** NCT #00954174
(05/05/2014)

NCI Version Date: 12/19/2014
Includes Revision #1-11
POINTS:
PER CAPITA – 20
MEMBERSHIP -6

TRANSLATIONAL RESEARCH PER CAPITA – Award based on specimen submission with 1.0 point for formalin-fixed, paraffin-embedded primary, metastatic, or recurrent tumor and 0.5 point for whole blood (MAX = 1.5). **(04/02/2012)**
Lead Organization: NRG/NRG Oncology

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OPEN TO PATIENT ENTRY AUGUST 17, 2009; REVISED SEPTEMBER 7, 2009; REVISED JUNE 1, 2010; REVISED DECEMBER 20, 2010; REVISED; MARCH 21, 2011; REVISED SEPTEMBER 6, 2011; REVISED APRIL 2, 2012; REVISED NOVEMBER 19, 2012; REVISED OCTOBER 21, 2013; CLOSED TO PATIENT ENTRY MARCH 24, 2014; REVISED MAY 5, 2014; REVISED

PROTOCOL GOG-0261

A RANDOMIZED PHASE III TRIAL OF PACLITAXEL PLUS CARBOPLATIN VERSUS IFOSFAMIDE PLUS PACLITAXEL IN CHEMOTHERAPY- NAIVE PATIENTS WITH NEWLY DIAGNOSED STAGE I-IV, PERSISTENT OR RECURRENT CARCINOSARCOMA (MIXED MESODERMAL TUMORS) OF THE UTERUS, FALLOPIAN TUBE, PERITONEUM OR OVARY **(06/1/10) (11/19/2012)**

NCI Version Date: 12/19/2014

Includes Revision #1-11

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION (06/1/10)

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206	Please refer to the patient enrollment section for instructions on using the OPEN system.	GOG Statistical and Data Center at Roswell Park Cancer Institute Elm and Carlton Streets Buffalo, NY 14263 Phone: 716-845-5702 ***Call GOG User support 716-845-7767 to obtain user name and password to submit electronic data*** Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.		
For patient eligibility or treatment-related questions contact the Study PI of the Coordinating Group.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites, please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org		
The CTSU Web site is located at https://www.ctsu.org		

OPEN TO PATIENT ENTRY AUGUST 17, 2009; REVISED SEPTEMBER 7, 2009; REVISED JUNE 1, 2010; REVISED DECEMBER 20, 2010; REVISED: MARCH 21, 2011; REVISED SEPTEMBER 6, 2011; REVISED APRIL 2, 2012; REVISED NOVEMBER 19, 2012; REVISED OCTOBER 21, 2013; CLOSED TO PATIENT ENTRY MARCH 24, 2014; REVISED MAY 5, 2014; REVISED

SCHEMA (12/20/2010)

A RANDOMIZED PHASE III TRIAL OF PACLITAXEL PLUS CARBOPLATIN VERSUS IFOSFAMIDE PLUS PACLITAXEL IN CHEMOTHERAPY-NAÏVE PATIENTS WITH NEWLY DIAGNOSED STAGE I-IV, PERSISTENT OR RECURRENT CARCINOSARCOMA (MIXED MESODERMAL TUMORS) OF THE UTERUS, FALLOPIAN TUBE, PERITONEUM OR OVARY
(11/19/2012)

Stage I- IV, Persistent or Recurrent Carcinosarcoma (chemotherapy-naïve)

Patients may have prior pelvic and/or vaginal radiation therapy

Stratification:
- History of Pelvic Radiation
- Disease Status/Stage at time of Study registration
- Measurable Disease

TREATMENT RANDOMIZATION

REGIMEN I

Paclitaxel 175 mg/m^2* IV over 3 hours Day 1
Carboplatin (AUC=6*) IV Day 1

Repeat q 3 weeks x 6-10 cycles (see Section 5.21)

REGIMEN II

Ifosfamide 1.6 g/m^{2**} IV days 1, 2, 3 Mesna***
Paclitaxel 135 mg/m^2 by 3-hour infusion on Day 1

Repeat q 3 weeks x 6-10 cycles (see Sections 5.22 and 6.3 for dose modifications AS EACH CYCLE DOSE MAY CHANGE BASED ON NADIR COUNTS.)

G-CSF Support: Filgrastim or Pegfilgrastim beginning Day 4-6 (See Section 5.22.)

*Initial dose reduced to Paclitaxel 135 mg/m^2 and Carboplatin (AUC=5) if prior whole pelvic radiotherapy (may be escalated if patient tolerates lower dose—see Section 6.134)

** Initial dose reduced to Ifosfamide 1.2 g/m^2/day x 3 days if prior whole pelvic radiotherapy (subsequent dosing MAY INCREASE OR DECREASE EACH CYCLE BASED ON NADIR COUNTS) **(11/19/2012)**

*** See Sec. 5.22 for Mesna administration information.

PLEASE NOTE THAT REGIMEN II UTILIZES DOSE ESCALATIONS—See Section 6.3 for details **(11/19/2012)**

Translational Research requirements include formalin-fixed, paraffin-embedded tumor and pre-treatment whole blood for banking. See Section 7.3 for details. **(04/02/2012)**

Quality of Life assessments required at: Baseline; approximately Week 6 (prior to Cycle 3); Week 15 (prior to Cycle 6); Week 30 post initiation of therapy. See Section 7.4 for details.

TABLE OF CONTENTS

1.0 OBJECTIVES

1.1 Primary Objectives

1.11 To determine if treatment with combination paclitaxel and carboplatin (TC) chemotherapy does not result in an inferior death rate when compared to ifosfamide, mesna, and paclitaxel chemotherapy.

1.2 Secondary Objectives

1.21 To determine if treatment with combination paclitaxel and carboplatin (TC) chemotherapy does not result in an inferior progression-free survival when compared to ifosfamide, mesna, and paclitaxel chemotherapy.

1.22 To determine if acute toxicity, specifically physician-assessed neurotoxicity and infection, associated with combination paclitaxel and carboplatin chemotherapy is reduced compared to that of ifosfamide, mesna, and paclitaxel chemotherapy.

1.23 To determine if treatment with combination paclitaxel and carboplatin chemotherapy is associated with superior patient-reported quality of life and neurotoxicity scores compared to that of ifosfamide, mesna, and paclitaxel chemotherapy.

1.3 Translational Research Objective

To bank formalin-fixed, paraffin-embedded (FFPE) tumor tissue and DNA extracted from whole blood for future research. **(04/02/2012)**

2.0 BACKGROUND AND RATIONALE

Uterine sarcomas represent 2-6% of all uterine malignancies. In a review of tumor registries in Britain, carcinosarcomas (CS) and leiomyosarcomas (LMS) made up almost 90% of all uterine sarcomas registered over a 15-year period. The overall five-year survival for patients with these tumors was 31%.[1,2] In a prospective staging study by the GOG, 53% of patients with clinical Stage I-II carcinosarcoma of the uterus recurred within five years of initial therapy.[3] Studies have confirmed recurrence rates of 53 –56%, the majority of which include an extra-pelvic component.[4,5] Post-operative therapy in the form of pelvic radiotherapy or chemotherapy is often prescribed but neither has been proven beneficial. Of the multiple GOG trials evaluating response to chemotherapy in patients with CS of the uterus, cisplatin, ifosfamide, paclitaxel, and doxorubicin have demonstrated the greatest tumor response. In a Phase II trial using cisplatin alone as first-line chemotherapy for advanced and recurrent uterine sarcomas, including 63 CS, Thigpen et al reported 12/63 (19%) overall responses with 5/63 (8%) achieving a Complete Response (CR).[6] The median survival was 7 months for all patients and 9.3 months for complete responders. Twenty-eight of 63 (44%) of these patients were treated with prior

pelvic RT. Significant hematologic and gastrointestinal toxicities were noted. Another GOG Phase II trial evaluated ifosfamide-mesna as first-line chemotherapy in patients with advanced or recurrent CS.[7] The investigators reported 9/28 (32%) overall responses and a 5/28 (18%) CR. Eight of 28 (29%) of these patients were treated with prior pelvic RT. The median PFI was 3.8 months. There was a significant incidence of Grade 3-4 neutropenia and neurotoxicity, as well as one treatment-related death. GOG-0108 evaluated the combination of ifosfamide-mesna with or without cisplatin as first-line therapy in patients with advanced, persistent, or recurrent CS.[8] The combination regimen demonstrated a significantly improved overall response rate (54%) when compared to the single-agent regimen (36%). The combination regimen demonstrated only a two-month prolongation (statistically significant) in the median progression free interval (six vs. four months) with no improvement in overall survival. Grade 3-4 toxicities were two-ten times more toxic in the combination arm. This data serves to underscore the lack of curative adjuvant and salvage therapy in this setting and the current need for less toxic alternatives in the treatment of uterine CS.

Findings from GOG-0161 were recently published.[9] There was a 31% decrease in the adjusted hazard of death (hazard ratio (HR) = 0.69; P = 0.03) and a 29% decrease in the adjusted hazard of death or progression (HR = 0.71; P = 0.03) in those patients receiving paclitaxel-ifosfamide- mesna-growth factor relative to ifosfamide alone. Sensory neuropathy was significantly worse with the combination regimen (Grades 1–4: 8% vs. 30%).

Results of GOG-0150 were recently published. The combination of cisplatin, ifosfamide, and mesna (CIM) given for three cycles as treatment for patients with Stage I-IV uterine CS (resected to <1cm and disease confined to the abdomen) was favored over whole abdominal irradiation (WAI).[10] Although not statistically significant, adjusting for stage, the recurrence rate was 21% lower for CIM patients relative to WAI patients (hazard ratio: 0.79, p = 0.245). Similarly, the estimated death rate for CIM is 29% lower relative to WAI (Hazard ratio: 0.71, p = 0.085). The investigators concluded that, due to a high relapse rate and poor OS, the imperative for new adjuvant therapies remains.

There is also evidence for activity of a third combination chemotherapy regimen: paclitaxel plus carboplatin. The rationale for the frequent use of paclitaxel-carboplatin in treating carcinosarcoma is based on the following:

1. Retrospective studies have shown high response rates, and median progression-free survival of 18 months, and overall survival of 25 months among patients with Stage III or IV, mostly measurable, disease.[11,12, 13]
2. Carboplatin-paclitaxel is equivalent to cisplatin-paclitaxel in advanced ovarian cancer in terms of efficacy, and is better tolerated (GOG-0158).[14]
3. Paclitaxel as a single agent achieved an 18% response rate as second-line therapy in advanced carcinosarcoma.[15]
4. Tolerability and convenience of paclitaxel-carboplatin is considered to be better than that of ifosfamide-cisplatin, especially in light of the toxicities observed with ifosfamide-cisplatin in GOG-0108.[8]

5. The GOG Phase II trial (GOG-0232B) formally testing the efficacy of this regimen in advanced disease has been completed and accepted for publication in the Journal of Clinical Oncology. The proportions of patients with confirmed complete and partial responses were 13% and 41%, respectively, resulting in a total overall response rate of 54% (95% CI, 37% to 67%) with a median progression-free survival of 7.0 months and median survival was 14.4 months. **(06/1/10)**

Since we now have evidence from two randomized Phase III trials that treatment with combination chemotherapy improves survival in women with carcinosarcoma, it is reasonable to compare combination chemotherapy regimens with respect to overall survival.

Given the survival advantage achieved with paclitaxel-ifosfamide for advanced disease compared to ifosfamide alone, the known activity of platinum agents, the activity of single-agent paclitaxel as second-line therapy, and the growing evidence for efficacy and known excellent tolerability of paclitaxel-carboplatin, we propose a randomized Phase III trial with the following treatment arms: paclitaxel plus ifosfamide versus paclitaxel plus carboplatin. We hypothesize that paclitaxel-carboplatin will be associated with a non-inferior survival compared to paclitaxel-ifosfamide. Both activity against the disease and lesser toxicity may contribute to this hypothesized non-inferiority.

Paclitaxel-carboplatin is a very commonly used cytotoxic regimen that has evidence for efficacy in over nine different solid tumor types. Looking to the future, one of the goals of this trial is to develop an acceptable "cytotoxic backbone" regimen that biologic therapies could be added to with acceptable toxicity. Paclitaxel-carboplatin appears to be just such a regimen. If in fact paclitaxel-carboplatin is found to be non-inferior to ifosfamide-paclitaxel, then further development of cytotoxic plus biologic regimens should be expedited. Development of these regimens could be much more efficient as the cytotoxic backbone would be shared among ovarian, perhaps endometrium (GOG-0209) and uterine carcinosarcoma. Thus, this trial is a vital step forward in the future development of therapies for this rare tumor type.

Inclusion of Ovarian, Fallopian Tube and Peritoneal Carcinosarcomas **(06/1/10) (11/19/2012)**

Ovarian carcinosarcomas are even more rare than the uterine counterparts that represent an aggressive cancer that are routinely widely metastatic at the time of initial presentation.[16] There is no uniform agreement about the optimal treatment of these malignancies except that achieving optimal debulking at the time of initial surgery is associated with significantly improved overall survival.[17,18] Most published data are limited to retrospective reviews, and because of the rarity of the disease, few institutions are able to accrue a sufficient number of patients for prospective studies. A prior Gynecologic Oncology Group study presented data involving 136 patients with ovarian carcinosarcomas treated with cisplatin 50 mg/m2 every 3 weeks until disease progression or unacceptable toxicity occurred.[19] Cisplatin was found to be active as initial therapy for

these tumors. The median survival in 130 patients was 11.7 months. Silasi et al. recently published (2007) their experience and review of the literature (nine other studies included) for a total of 417 patients.[20] They compared the patients receiving cisplatin / ifosfamide to the group receiving carboplatin / paclitaxel and there was no statistically significant difference in survival. A power analysis was performed utilizing their retrospective findings and 58 patients were needed to see a difference in progression-free-survival and 558 for a difference in overall survival. These tumors are felt to be too rare to study as part of an independent trial. Ovarian carcinosarcomas are currently excluded from other GOG ovarian cancer trials. Both uterine and ovarian carcinosarcomas share similar biologic, pathologic and clinical management questions and thus it is reasonable to combine this tumor type into this current ongoing clinical trial (GOG 261). Fallopian tube and peritoneal carcinomas are even more rare than ovarian carcinosarcomas but share a similar clinical management dilemma with the ovarian and uterine carcinosarcomas and thus will be included in this trial. **(11/19/2012)**

Quality of Life Assessment: **(06/1/10)**

Since the regimens differ in schedule, convenience, and side effect profile, the toxicities and the quality of life impact of the two regimens will be compared.

Rationale for assessment of patient-reported quality of life and neurotoxicity:

Physical well-being, functional well-being, and neurotoxicity will be assessed using patient-reported outcomes, given the potential differences in short- and longer-term toxicities between the two treatment arms.

The regimens being tested in this trial will differ in treatment schedule, patient convenience, and expected side effect profile. Ifosfamide will be given daily for 3 days in a row, with mesna for bladder protection, in combination with paclitaxel on Day 1. This regimen will require granulocyte growth factor support, and in some institutions, this 3-day regimen may be given as inpatient therapy. In contrast, the paclitaxel-carboplatin regimen is given all on Day 1, does not routinely require granulocyte growth factor support, and is an outpatient treatment. While both regimens can cause myelosuppression, it is possible that the paclitaxel-ifosfamide arm will be more myelosuppressive. The requirement of granulocyte growth factor with the paclitaxel-ifosfamide treatment means that patients in that arm may have more bone pain and physical discomfort. While the paclitaxel that is part of both regimens can be associated with peripheral neurotoxicity (which may be reversible), ifosfamide is associated with reversible, central neurotoxicity (confusion, hallucinations). Because of these differences in the schedule and side effect profile, and since it is possible that the survival difference between the two arms may not be very great, understanding the impact of the two regimens on patient-reported quality of life and neurotoxicity is very important.

This study will include patients with Stage I, II, III, and IV disease, many of whom will have had their disease completely removed by surgery prior to starting study treatment. Such patients may have few or no symptoms related to their cancer. Therefore, a formal

evaluation of the patient-reported impact of treatment on quality of life is particularly important in this group.

The Functional Assessment of Cancer Therapy, including the endometrial subscale will be used as the measure of patient-reported quality of life. The trial outcome index (TOI) will comprise the 7-item physical well-being subscale (PWB) plus the 7-item functional well-being subscale (FWB) plus the 16-item endometrial cancer subscale. This is the same TOI that was chosen for GOG-0209.

Patient-reported neurotoxicity will be measured using the GOG-NTX (neurotoxicity) subscale of the FACT. The NTX subscale efficiently measures patient perception of neurotoxicity such as pain and paresthesias.[21]

Rationale for delivering 6 cycles of therapy (maximum of 10 allowed):

The duration of chemotherapy has differed across GOG trials for patients with carcinosarcoma. GOG-0150 enrolled patients with Stage I, II, III, or IV carcinosarcoma whose disease had been resected to less than 1 cm residual. The chemotherapy arm comprised only three cycles of ifosfamide plus cisplatin. Even with this relatively short course of chemotherapy, a survival benefit was observed, compared with whole abdominal radiation. This benefit occurred in patients in all disease-stage subgroups. Subsequent to the design of this study, it has become commonplace to offer more cycles of chemotherapy to patients, particularly those patients with more advanced disease, as we have determined that chemotherapy is active in carcinosarcoma, and also as we have developed better supportive care measures that help ameliorate toxicities.

In GOG-0161, patients with advanced, measurable disease were treated with a total of eight cycles of therapy, and then observed. This trial design was able to yield a superior outcome in terms of progression-free and overall survival among women with advanced carcinosarcoma.

In GOG-0209, the advanced endometrial cancer trial, patients may have measurable or non-measurable disease since the primary endpoint is overall survival. In that study all patients are offered a total of seven cycles of therapy, and are then observed for progression-free and overall survival. The rationale for offering seven cycles in this trial is at least partly to limit the cumulative dose of doxorubicin in order to limit the risk of cardiotoxicity.

In GOG-0232B, patients with advanced, measurable carcinosarcoma are treated with an unlimited number of cycles of paclitaxel-carboplatin. This is a Phase II trial in which objective response, rather than survival, is the primary endpoint. In general, GOG Phase II trials have permitted patients to remain on active therapy until progression or unacceptable toxicity.

For patients with a partial response and persistent disease at the completion of 6 cycles of chemotherapy the treating physician may elect to continue therapy for a maximum of 10

cycles. Patients will come off the active treatment portion of study with progression or if dictated by toxicity.

Rationale for chemotherapy dosing:

The dosing of the paclitaxel-ifosfamide arm will mirror GOG-0161 with the dose reduction for prior radiation therapy. The dosing of the paclitaxel-carboplatin arm will be similar to GOG-0232B (paclitaxel 175 mg/m^2 IV plus carboplatin AUC = 6 IV every 21 days). GOG-0209 has noted increased myelosuppression in patients who have previously received pelvic radiotherapy. Therefore for these patients the initial dosing will be paclitaxel 135 mg/m^2 IV plus carboplatin AUC = 5 IV every 21 days. Scudder et al. reported on the SWOG protocol S9720 that used carboplatin (AUC = 6), paclitaxel (175 mg/m^2) and amifostine (740 mg/m^2) every 4 weeks for endometrial cancer patients most of whom had previously received radiation therapy.[13] The toxicity of this regimen was tolerable.

2.1 Banking Tumor Tissue and Whole Blood for Future Research **(04/02/2012)**

FFPE tumor and whole blood will be collected from women who agree to participate in this optional translational research study. Tumor and DNA extracted from whole blood will be banked for future research.

2.2 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 carcinosarcoma population with Stage I-IV, persistent or recurrent disease treated by participating institutions. **(11/19/2012)**

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

3.11 Patients must have newly diagnosed Stage I-IV, persistent or recurrent (including unstaged) uterine carcinosarcoma (malignant mixed mullerian tumor-MMMT or with ovarian, fallopian tube or peritoneal carcinosarcoma and an enrollment date prior to 10/21/2013; pathology confirmed by site/institutional pathologist prior to enrollment) and be chemotherapy naïve as directed against their carcinosarcoma. Unstaged patients (patients who have not had hysterectomy or ovarian surgery) are eligible and should be included as "unstaged" if the only histologic (pathology) documentation of the disease is a biopsy or curettage of the uterus. If these patients have documented metastatic disease, it should be assigned the appropriate Stage (III/IV). **(06/1/10) (11/19/2012) (10/21/2013)**

3.12 Patients may have received prior adjuvant external beam radiation therapy and/or vaginal brachytherapy. Patients should be at least 4 weeks from the completion of external beam radiotherapy prior to beginning protocol chemotherapy. Patients do not need to be delayed if receiving vaginal brachytherapy only. **(12/20/2010)**

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

3.14 Patients must have recovered from effects of recent surgery, radiotherapy or other therapy.

3.15 Patients must be free of active infection requiring antibiotics.

3.16 Any hormonal therapy directed at the malignant tumor must be discontinued at least one week prior to beginning protocol chemotherapy. Continuation of hormone replacement therapy is permitted. **(06/1/10)**

3.17 Patients must have adequate:

Bone marrow function: Platelet count greater than or equal to 100,000/mcl, and ANC count greater than or equal to 1,500/mcl, equivalent to CTCAE v3.0 Grade 1.

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

Hepatic function: Bilirubin less than or equal to 1.5 x ULN (CTCAE v3.0 Grade 1). SGOT and alkaline phosphatase less than or equal to 2.5 x ULN (CTCAE v3.0 Grade 1). Serum Albumin should be equal to or greater than 3g/dL.

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

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

3.19 Patients of childbearing potential must have a negative serum pregnancy test prior to study entry and be practicing an effective form of contraception.

3.110 Patients may have measurable disease or non-measurable disease. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be ≥ 20 mm when measured by conventional techniques, including palpation, plain x-ray, CT, and MRI, or ≥ 10 mm when measured by spiral CT. Measurable disease patients must have at least one "target lesion" to be used to assess progression on this protocol as defined by RECIST (Section 8). 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.

3.111 Patients must be 18 years of age or older. **(09/07/09)**

3.2 Ineligible Patients

3.21 Patients who have received prior cytotoxic chemotherapy for management of uterine or ovarian carcinosarcoma. **(06/1/10)**

3.22 Patients with a history of other invasive malignancies or with a concomitant invasive malignancy, with the exception of non-melanoma skin cancer, if there is any evidence of other malignancy being present within the last five years. Patients are also ineligible if their previous cancer treatment contraindicates this protocol therapy.

3.23 Patients for whom radiotherapy is planned after or during study chemotherapy prior to progression of cancer.

3.24 Patients with a known hypersensitivity to E. coli-derived drug preparations (Pegfilgrastim and Filgrastim).

3.25 Patients with a known hypersensitivity to mesna or other thiol compounds.

3.26 For enrollment prior to 10/21/2013, patients who are not biopsy proven to have carcinosarcoma of the uterus, fallopian tube, peritoneum or ovary. For

enrollment after 10/21/2013, patients who are not biopsy proven to have carcinosarcoma of the uterus. **(06/1/10) (11/19/2012) (10/21/2013)**

4.0 STUDY MODALITIES

4.1 Paclitaxel (NSC #673089)

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

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

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

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

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

All patients should be premedicated with corticosteroids, diphenhydramine, and H_2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

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

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

4.16 Administration: See Section 5.2.

4.2 Carboplatin (Paraplatin® - NSC #241240)

4.21 Formulation: Carboplatin is supplied as a sterile, pyrogen-free, 10mg/mL aqueous solution in multi-dose vials containing 50mg/5mL, 150mg/15mL, 450mg/45mL, or 600mg/60mL of carboplatin. **(12/20/2010)**

4.22 Storage: Unopened vials of carboplatin are stable to the date indicated on the package when stored at 25°C (77°F). Excursions from 15 to 30°C (59 to 86°F) are permitted. Protect from light. Carboplatin multidose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries.

4.23 Preparation: Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5mg/mL with 5% Dextrose in Water or 0.9% Sodium Chloride for Injection, USP. When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C / 77°F). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded 8 hours after dilution.

See Appendix IV for current dosing instructions. (12/20/2010)
Note that carboplatin dose will be recalculated if patient has weight change of greater than or equal to 10% from baseline. **(3/21/2011)**

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

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

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

4.26 Administration: See Section 5.2.

4.3 Ifosfamide - (IFEX® - NSC #10724)

4.31 Formulation: Ifosfamide is available as a white crystalline powder in 1 gram or 3 gram single-dose vials.

4.32 Preparation: Injections are prepared by adding sterile water for injection, USP or bacteriostatic water for injection, USP to the vial and shaking to dissolve. Use the quantity of diluent below for reconstitution.

Strength	Quantity of diluent	Final concentration
1 gram	20 ml	50 mg/ml
3 grams	60 ml	50 mg/ml

4.33 Storage: The dry powder may be stored at room temperature. The sterile reconstituted solution is stable for 1 week at 30°C or 3 weeks at 5°C.

4.34 Adverse effects: Myelosuppression, genitourinary (hemorrhagic cystitis, dysuria, urinary frequency and other symptoms of bladder irritation), nausea and vomiting, CNS (somnolence, confusion, depressive psychosis and hallucinations), alopecia and liver dysfunction. Other less frequent side effects include phlebitis, pulmonary symptoms, fever of unknown origin, allergic reactions, stomatitis, cardiotoxicity, and polyneuropathy.

4.35 Supplier: Commercially available from Bristol-Myers Oncology. Please refer to
the package insert for additional information.

4.36 Administration: See Section 5.2

4.4 Mesna - (Mesnex® - NSC #113891)

4.41 Formulation: Mesna is available in a sterile preservation-free aqueous solution (100 mg/mL) and as oral tablets (400 mg). The colorless solution is supplied in clear glass ampules for IV or oral administration.

4.42 Preparation: For IV administration, the drug can be diluted by adding the contents of a mesna ampule to any of the following solutions: 5% D/W, 5% D/NaCl injection, 0.9% NaCl injection, and lactated ringers injection. The vial should be inspected visually for particulate matter and discoloration prior to administration. For oral administration of the intravenous formulation, prepare and dispense mesna undiluted in BD syringe

4.43 Storage: When mesna is exposed to oxygen, mesna is oxidized. Any unused drug remaining in the ampules after dosing should be discarded and new ampules used for each administration. Store ampules and vials at

room temperature. Multidose vials may be stored and used for up to 8 days after initial entry. Syringes prepared for oral administration are stable for 9 days at room temperature and under refrigeration. Diluted solution is sterile for 24 hours at 25°C (77°F). It is recommended that solutions of mesna be refrigerated and used within six hours.

4.44 Adverse effects: Mesna should not be given to patients known to be hypersensitive to mesna or other thiol compounds. Mesna in high doses can cause acetone in the urine, occasional irritation at the infusion site and nausea and vomiting.

4.45 Supplier: Commercially available from Baxter Healthcare Corp. Please refer to the package insert for additional information. **(12/20/2010)**

4.46 Administration: See Section 5.2

4.5 Filgrastim (G-CSF, Neupogen®)

4.51 Formulation: Filgrastim (G-CSF) is available at a concentration of 300 mcg/ml in 1.0 and 1.6 single-use glass vials. It is formulated as a sterile, clear, colorless liquid in a 10 mm sodium acetate buffer at pH 4.0. The quantitative composition (per ml) is:

Filgrastim (G-CSF)	300 mcg
Acetate	0.59 mg
Sorbitol	50.0 mg
Tween 80™	0.004%
Sodium	0.035 mg
Water for injection USP q.s. ad.	1 ml

4.52 Preparation: For this protocol, filgrastim will be given subcutaneously. It can be used directly from the vial.

4.53 Storage: The intact vials of filgrastim should be stored under refrigeration (2-8ºC). Avoid shaking.

4.54 Adverse Effects: The adverse effects associated with Filgrastim (G-CSF) are usually mild and include bone pain and, rarely, splenomegaly. Laboratory effects include increases in alkaline phosphatase, LDH, WBC and uric acid. Filgrastim should not be used in patients with known hypersensitivity to E. Coli-derived drug preparations.

4.55 Supplier: Commercially available from Amgen.

4.56 Administration: See Section 5.2.

*Refer to Package Insert for additional information.

4.6 Pegfilgrastim (G-CSF, Neulasta®)

4.61 Formulation: Pegfilgrastim (G-CSF) is available commercially at a concentration of 6 mg /0.6 ml solution in a premeasured sterile syringe.

4.62 Preparation: For this protocol, Pegfilgrastim will be administered subcutaneously directly from the premeasured syringe.

4.63 Storage: Syringes of Pegfilgrastim should be stored in a refrigerator at 2-8° C and protected from light.

4.64 Adverse Effects: The adverse effects associated with Pegfilgrastim are usually mild and include bone pain, flu-like symptoms, nausea, vomiting, adult respiratory distress syndrome, splenomegaly, and sickle cell crisis (in patients with sickle cell anemia). Laboratory effects include increases in alkaline phosphatase, LDH, WBC, and uric acid. Pegfilgrastim should not be used in patients with known hypersensitivity to E. Coli-derived drug preparations.

4.65 Supplier: Commercially available from Amgen.

4.66 Administration: See Section 5.2.

*Refer to Package Insert for additional information

4.7 Quality of Life assessments:

The Functional Assessment of Cancer Therapy – General (FACT-G) Trial Outcome Index (FACT-TOI) will be used to assess the physical dimension of health-related quality of life. The FACT-G is a validated instrument that assesses the multidimensional aspects of QOL including: physical well-being, social/family well-being, emotional well-being, and functional well-being. In this study, three subscales that are clinically relevant to the physical and functional well-being of cancer patients will be used, two of which are general to cancer, and one that is targeted specifically to endometrial cancer. These three subscales comprise approximately three-fourths of the FACT-Endometrial (FACT-En), and are referred to as the "Trial Outcome Index," or TOI. Therefore, the FACT-En TOI, comprised of a 7-item Physical Well-being (PWB) scale, a 7-item Functional Well-being (FWB) scale, and a 16-item Endometrial Cancer Subscale (EnCS) will be administered at each time point.

The FACT-En has been utilized in two recent Phase III GOG endometrial cancer trials. In GOG-0122, quality of life (QOL) outcomes were prospectively compared in patients with advanced endometrial cancer treated with whole abdominal

irradiation (WAI) or doxorubicin-cisplatin (AP) chemotherapy.[22] Reliability of the FACT-G was assessed in the GOG-0122 study population and demonstrated a high internal consistency (Cronbach's alpha=0.89 at pretreatment). Health-related QOL is currently being assessed in GOG-0209, which is a randomized Phase III trial of doxorubicin/cisplatin/paclitaxel and G-CSF Versus carboplatin/paclitaxel in patients with Stage III and IV or recurrent endometrial cancer. Since GOG-0209 continues to accrue, patient-reported outcome data are not available. However, psychometric data on the FACT-TOI will provide meaningful information for future endometrial cancer trials, and will substantiate support for use of the proposed subscales in this study.

Patient-reported neurotoxicity will be measured using the FACT/GOG-Ntx subscale (11 items).

4.8 Pathology Requirements:

See Section 3.1 for eligibility requirements:

4.81 Pathology Eligibility Criteria:

Patients must have newly diagnosed Stage I-IV, persistent or recurrent (including unstaged) uterine carcinosarcoma (malignant mixed mullerian tumor-MMMT) or ovarian, fallopian tube or peritoneal carcinosarcoma with an enrollment date prior to 10/21/2013 and be chemotherapy-naïve as directed against carcinosarcoma. **(06/1/10) (12/20/2010) (11/19/2012) (10/21/2013)**

4.82 Pathology Ineligibility Criteria:

For enrollment prior to 10/21/2013, patients who are not biopsy proven to have carcinosarcoma of the uterus, fallopian tube, peritoneum or ovary. For enrollment after 10/21/2013, patients who are not biopsy proven to have carcinosarcoma of the uterus. **(06/1/10) (11/19/2012) (10/21/2013)**

4.83 Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility. See Section 7.2 and 10.2

4.84 See Section 7.3 and Appendix III for information and instructions regarding the specimen requirements for Translational Research.

5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE (06/1/10)

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group or a CTSU CICRS site. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for GOG-0261 site registration:
- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

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:

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 **(12/20/2010)**

5.1 Patient Entry and Registration **(06/1/10)**

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the

CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

All baseline laboratory tests and pre-study evaluations must be performed, including tumor and blood samples, within the time period specified in the protocol.

All site staff (Lead Group and CTSU Sites) will use OPEN to enroll patients to this study. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following: **(06/1/10)**

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPPA authorization form (if applicable).

Access requirements for OPEN: **(06/1/10)**

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent 'Registrar' role on the Lead Group roster. Role assignments are handled through the Groups in which you are a member
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations), you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

  Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records. The confirmation provides the patient identification number, treatment arm and if applicable, any necessary instructional information. To print a copy of the completed Fast Fact Sheet, go to the confirmation page and open the "view summary" box.

  Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

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 must be gathered, which can be downloaded from the CTSU GOG-0261 web page in the Patient Enrollment section of the registered members' web site at https://www.ctsu.org **(06/1/10)**

5.14 The institution will enter the patient's name, GOG number, and assigned regimen in the appropriate place in their Log Book to verify the patient's entry.

5.2 Treatment Plan

Stratification factors for randomization **(11/19/2012)**

1. History of pelvic radiation: any or none
2. Disease status at time of study registration: **(06/1/10) (12/20/2010)**
   a) FIGO clinical Stage I-II carcinosarcoma
   b) FIGO surgical Stage I-II (pelvic lymph nodes not surgically and pathologically assessed), carcinosarcoma
   c) FIGO surgical Stage I-II (pelvic lymph nodes surgically and pathologically assessed), carcinosarcoma
   d) FIGO Stage III-IV carcinosarcoma or
   e) recurrent carcinosarcoma
3. Measurable disease at time of study registration: any or none

Baseline Quality of life forms must be filled out prior to starting treatment.

MAXIMUM BODY SURFACE AREA USED FOR DOSE CALCULATION WILL BE 2.0 m^2 AS PER GOG CHEMOTHERAPY PROCEDURES MANUAL. DOSING FOR THE REGIMENS SHOULD NOT BE CHANGED FROM CYCLE TO CYCLE UNLESS MANDATED BY THE PROTOCOL. All modifications are relative to the actual starting doses for the specific regimen. For application of individual dose modifications, see specific guidelines below. **(06/1/10)**

All patients should be premedicated with corticosteroids, diphenhydramine, and H_2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Patients who experience severe hypersensitivity

reactions to paclitaxel should not be re-challenged with the drug.

5.21 **Regimen I**:

Paclitaxel 175 mg/m^2 IV* with a 3-hour infusion time, Day 1 followed by Carboplatin AUC 6 IV* Day 1 with a 30-60 minutes infusion time **(06/1/10)**

Carboplatin Dosing: Refer to Appendix IV for current instructions. (12/20/2010)

Note that carboplatin dose will be recalculated if patient has weight change of
greater than or equal to 10%. **(3/21/2011) (04/02/2012)**

Doses of paclitaxel or carboplatin may be rounded according to institutional standard or to the nearest 5 mg. After initial treatment, doses of paclitaxel should be re-calculated based only on body weight change of ≥ 10%. **(06/1/10)(12/20/2010)**

***Prior Radiotherapy: Patients who have had prior external beam radiotherapy involving the whole pelvis or abdomen or over 50% of the spine for this or any other cancer must initiate Regimen I (Paclitaxel-Carboplatin) at the -1 reduced dose.**

5.22 **Regimen II**:

Ifosfamide 1.6 g/m^2* IV Days 1, 2, 3 with a one-hour infusion time with Mesna (multiple dosing options available and allowed) (oral [tablets or liquid] or IV-see dosing below) pre ifosfamide and at hours 4 and 8 (oral liquid) or at 2 and 6 hours for tablets). **(11/19/2012)**

The Ifosfamide infusion is followed by Paclitaxel 135 mg/m^2 IV over 3 hours Day 1 **(06/1/10)**

Filgrastim (Neupogen®) 5 mcg/kg/day beginning Day 4-6 and given for at least 10 days **OR** pegfilgrastim (Neulasta®) 6 mg day 4**
NOTE: *Japanese institutions will use 2 mcg/kg/day dosing of G-CSF. Rounding of Filgrastim (G-CSF) dose to the nearest vial size is acceptable.*

***Prior Radiotherapy: Patients who have had prior external beam radiotherapy involving the whole pelvis or abdomen or over 50% of the spine for this or any other cancer must initiate Regimen II (Ifosfamide-Paclitaxel) dose of Ifosfamide 1.2 g/m^2 IV Days 1, 2, 3.**

Doses of paclitaxel and ifosfamide may be rounded according to institutional standard or to the nearest 5 mg. After initial treatment, doses of paclitaxel and ifosfamide should be re-calculated based only on body weight change of ≥ 10%. See Section 6.3 for dose modifications FOR EACH CYCLE BASED ON NADIR COUNTS. **(06/1/10)(12/20/2010)**

****Pegfilgrastim can be given between 24-72 hours after chemotherapy is administered. Pegfilgrastim should not be administered within 14 days of subsequent chemotherapy.**

Repeat cycle every 3 weeks for 6 planned cycles. Patients who entered the study with measurable disease and have a partial response after 6 cycles many continue on therapy to a maximum of 10 cycles until progression or unacceptable toxicity develops.

Mesna dosing: Mesna can be given either IV (bolus or infusional) or by mouth (liquid or table). Dosing suggested below is recommended dosing, but minor variances in institutional methods of the dosing of Mesna are acceptable. Below is suggested dosing for Mesna. Please read carefully as this is complicated by the multiple options available: **(06/1/10)**

For IV continuous infusional mesna, begin mesna 15 minutes before ifosfamide infusion at the rate of 2 g/m^2 IV over 12 hours. For use with continuous infusion ifosfamide, mesna may be administered as a bolus dose equal to 20% of the total ifosfamide dose followed by a continuous infusion of mesna equal to 40% of the ifosfamide dose, continuing for 12 hours after completion of the ifosfamide infusion. **(06/1/10)**

The recommended dose and schedule (ASCO guidelines 2002) is to administer mesna as an IV bolus injection in a dosage equal to 20% of the ifosfamide dosage (weight/weight) at the time of ifosfamide administration. It is suggested that the
daily dose of mesna be calculated to equal 60% of the total daily dose of ifosfamide, administered as three bolus doses given 15 minutes before, and 4 and 8 hours after, administration of each dose of ifosfamide when the ifosfamide dose is less than 2.5 g/m2/d administered as a short infusion. **(06/1/10)**

For oral (liquid) mesna: **(06/1/10)**

For oral (liquid) mesna, the total daily oral dose of mesna is 4 grams divided into three doses (1.33 grams each) given one hour before and four and eight hours after (for oral liquid) or two and six hours after (for tablets) the infusion of ifosfamide on each of the three days of ifosfamide therapy. If outpatient, give mesna in syringe (stable at room temperature for five days) to patient with instructions for time of oral administration.

Often the initial dose of mesna is given IV, with the second and third dose delivered orally. From ASCO guidelines: "Administration of the first dose of mesna intravenously (IV) at a dose equal to 20% of the total daily ifosfamide dose, followed at 2 and 8 hours by 40% weight/weight of the ifosfamide dose administered orally, may be considered an acceptable alternative to the three-dose IV mesna regimen when the total ifosfamide daily dose is less than 2.0 g/m2."[23] **(06/1/10)**

Mesna liquid is bitter and can be mixed 1:10 in milk (regular or chocolate), orange juice, apple juice, Coke, Pepsi, Dr. Pepper, Sprite, Seven-Up, or Ginger Ale. Once mixed for oral intake, mesna is stable for 24 hours. **(06/1/10)**

For mesna tablets: **(06/1/10)**

Mesna tablets have been approved by the United States Food and Drug Administration (FDA) to prevent hemorrhagic cystitis in patients receiving ifosfamide chemotherapy and are encouraged to be used. Mesna tablets are given orally in a dosage equal to 40% of the ifosfamide dose at 2 and 6 hours after each dose of ifosfamide. The total daily dose of mesna is 100% of the ifosfamide dose. Patients who vomit within 2 hours of taking oral mesna should repeat the dose or receive IV mesna.

The dosing schedule should be repeated on each day that ifosfamide is administered. Mesna tablets are supplied as 400 mg tablets. Oral Mesna dosing of the tablets should be rounded up to the next tablet when necessary (excess Mesna is preferred to under dosing).

5.23 Disease Surveillance:

Baseline assessment for all patients: CT or MRI (for contrast allergy patients if non-contrast CT is inadequate to assess) scan of the chest/abdomen/pelvis within 4 weeks prior to starting protocol therapy is required for all patients.

Requirements for Patients WHO DO NOT HAVE MEASURABLE disease ("NON-MEASURABLE") at study entry: CT or MRI scans and CA-125 will be repeated every three cycles for 6 cycles (baseline, then after Cycles 3, and 6) to rule out progression. After the 6th cycle of therapy, patients with no evidence of progression will obtain a CA-125 every 3 months for the next 1 year, then every 6 months for three years, then annually, up until disease progression is documented. Imaging will be performed if there is clinical concern based on a clinically significant rise (in the investigator's opinion) in the CA125 or symptoms develop. Following completion of therapy, surveillance imaging should be obtained

every 6 months for 2 years then annually thereafter until disease progression is documented. **(04/02/2012) (11/19/2012)**

Requirements for Patients WITH MEASURABLE DISEASE at study entry: CT or MRI scans and CA-125 will be repeated every other cycle while on therapy for a planned 6 cycles (maximum of 10) (baseline, then after 2, 4, 6, (continued every other if additional therapy is given to maximum of 10 cycles) to rule out progression. After the last cycle of therapy, patients with no evidence of progression will be imaged and obtain CA-125 every 3 months for the next 2 years, then every 6 months for three years, then annually, up until disease progression is documented. Imaging will be performed if there is clinical concern based on a clinically significant rise (above institutional normal) in the CA-125 or symptoms develop.

Patients with evidence of progression of disease will remain on study in terms of determining overall survival but are permitted to receive treatment for the progression of disease, and are no longer required to have imaging for the purposes of this study.

5.24 QOL evaluations: baseline; approximately Week 6 (prior to Cycle 3); Week 15 (prior to Cycle 6); Week 30.

5.3 Criteria for removal from study treatment

5.31 Inability to tolerate the lowest doses because of toxicity.

5.32 Patients may withdraw from the study at any time for any reason. Patients with evidence of disease progression or significant side effects will be removed from study therapy.

6.0 TREATMENT MODIFICATIONS

6.1 Hematologic Toxicity: **REGIMEN I** (Paclitaxel and Carboplatin)

6.11 Dose reduction levels:

Study Drug	**-2 Level reduction**	**-1 Level reduction***	**Initial dose level**
Carboplatin	AUC = 4	AUC = 5	AUC = 6
Paclitaxel	105 mg/m^2	135 mg/m^2	175 mg/m^2
*Initial dose for prior pelvic RT patients			

6.12 Treatment modifications will be based on the absolute neutrophil count (ANC) rather than the total white cell count (WBC). Subsequent cycles of therapy will not begin until the ANC is greater than or equal to1,500 cells/mcl and the platelet count is ≥100,000 cells/mcl. Therapy will be delayed on a week-by-week basis until these values are achieved. Treatment modifications will be employed in a sequential manner using cycle delay and dose reduction. If greater than a 3-week delay (6 weeks from last chemotherapy administration) occurs, the patient will be removed from study therapy.

6.13 Dose reductions will be as follows:

6.131 Dose-limiting thrombocytopenia, defined as Grade 4 thrombocytopenia (<25,000/mcl) or bleeding associated with Grade 3 thrombocytopenia (25,000/mcl to <50,000/mcl), will have a dose reduction of carboplatin only to one level less without a change in paclitaxel dosage. **(06/1/10)**

6.132 There will be no dose modifications based on uncomplicated nadirs.

6.133 Dose-limiting neutropenia, defined as febrile neutropenia (ANC < 1,000/mcl and fever ≥38.5° C, per CTCAE v 3.0) or Grade 4 neutropenia lasting ≥ 7 days will receive a dose reduction of one level using the table above without addition of G-CSF. If dose-limiting neutropenia occurs after prescribed dose reductions to the dose level -2, then G-CSF or Pegfilgrastim may be utilized.

6.134 There will be an initial dose reduction based on prior pelvic radiotherapy to the "-1" level. This includes patients with prior radiotherapy **involving the whole pelvis or abdomen or over 50% of the spine for this or any other cancer,** dose re-escalation

is allowed and their subsequent dose may be escalated, providing these patients exhibited no hematologic or non-hematologic toxicity > Grade 1 except alopecia.

6.135 Patients who have been dose reduced will not be re-escalated under any circumstances for **Regimen I** on this study other than if initial reduction was due to history of prior radiotherapy.

6.14 Grade 4 neutropenia uncomplicated by fever or lasting < 7 days will not require a dose reduction.

6.15 Patients with uncomplicated Grade 4 neutropenia, who are already at the lowest reduced dose level, may remain on current protocol therapy if counts recover on time and if platelet toxicity ≤ Grade 2. **(06/1/10)**

6.16 Protocol therapy will be discontinued in patients who require a delay of > 21 days.

6.2 Non-Hematologic Toxicity: **REGIMEN I** (Paclitaxel and Carboplatin)

6.21 Grade 2 (or greater) peripheral neuropathy requires reduction of one dose level of both paclitaxel and carboplatin and delay in subsequent therapy for a maximum of 2 weeks until recovered to Grade 1. If Grade 2 or greater peripheral neuropathy persists beyond the two-week period of delay, the paclitaxel will be discontinued and treatment will be allowed with carboplatin at the reduced dose level.

6.22 Grade 2 (or greater) renal toxicity requires reduction of one dose level of carboplatin and delay in subsequent therapy for a maximum of 2 weeks until recovered to Grade 1. Should Grade 3 or unusual toxicity occur, the study chair must be notified. If creatinine rises to > 2.0 mg/dL, a calculated creatinine clearance (CalCcr) should be obtained. If CalCcr is less than 50 ml/min, hold treatment and check weekly CalCcr. Resume therapy when CalCcr is ≥ 50 ml/min. If CalCcr is < 50 ml/min or serum creatinine is > 2 mg/dL after treatment has been held for 2 weeks, protocol therapy will be discontinued and the study chair must be notified. No treatment is to be given to a patient with CalCcr < 50 ml/min.

Selective renal tubular defects are observed with platinum compounds. Hypocalcemia, hypomagnesemia, and hypokalemia are common and potentially severe. Replacement of calcium, magnesium, and potassium is usually effective. Severe defects, although uncommon, may require chronic replacement therapy and, rarely, discontinuation of current protocol drugs.

6.23 Grade 3 (or greater) hepatic toxicity with elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin requires reduction of one dose level of the agent felt to be responsible for the elevation (usually paclitaxel) and delay in subsequent therapy for a maximum of 2 weeks until recovered to Grade 1. Patients whose treatment is delayed > 14 days because of such toxicity should have protocol therapy discontinued. Bilirubin must have recovered to Grade 1 or 0 prior to further therapy. **(06/1/10)**

6.24 There will be no dose modifications for alopecia, fatigue, or myalgias. Myalgias in the several days following paclitaxel treatment may be severe, and should receive aggressive symptomatic treatment, including narcotics or steroids as required. They are not, however, an indication for dose reduction.

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

6.26 Paclitaxel hypersensitivity reaction: If hypersensitivity reactions to paclitaxel or its vehicle (Cremophor) occur, it will usually be during the first few minutes of infusion. Appropriate symptomatic therapy should be given. Continued treatment may be considered if the reaction is not life threatening; however, patients must be cautioned about potential recurrences of the reaction. Should the patient decide to continue with treatment, it is preferable that this be done on the same day as the occurrence. A suggested procedure would be to administer the drug first with 1 cc of the original IV solution diluted in 100 ml over one hour, then 5 cc in 100 ml over one hour, then 10 cc in 100 ml over one hour, and finally, the original solution at the original speed. Patients who elect not to have continued treatment with paclitaxel after experiencing a hypersensitivity reaction may continue on protocol therapy with carboplatin only.

6.27 Supportive Care: In addition to other aspects of supportive care, particular attention should be paid to the likely development of non-hemolytic anemia after several cycles of treatment. The patient should be transfused as necessary while continuing therapy. No treatment delays are permitted for anemia. Erythropoietin therapy in addition to iron supplementation is permitted to ameliorate anemia, at the investigator's discretion.

6.28 Other non-hematologic toxicities with an impact on organ function of Grade 2

(or greater) require reduction of one dose level and delay in subsequent therapy for a maximum of 2 weeks until recovered to Grade 1, or pre-therapy baseline.

6.29 For patients with prior radiotherapy **involving the whole pelvis or abdomen or over 50% of the spine for this or any other cancer,** dose escalation (from the initial "-1" level) is allowed and their subsequent doses may be escalated, providing these patients exhibited no hematologic or nonhematologic toxicity > Grade 1 except alopecia. **(11/19/2012)**

6.3 Hematologic Toxicity: **REGIMEN II** (Ifosfamide + Paclitaxel) **(11/19/2012)**

	Dose Level					
Study Drug	**-3**	**-2**	**-1***	**Start**	**+1**	**+2**
Ifosfamide g/m^2	0.5	0.8	1.2	1.6	2	2
Paclitaxel mg/m^2	100	100	135	135	175	200
*starting dose for patients with prior pelvic RT						

*Starting dose for patients with prior pelvic radiation therapy should be the "-1" level.

DOSE MODIFICATIONS ARE BASED UPON BOTH INTERIM NADIRS (see Section 6.31) AND PRE-TREATMENT COUNTS (see Section 6.32). If both criteria warrant a dose reduction, the lowest dose indicated should be given. Dose Reductions and Dose Escalations are for BOTH ifosfamide and paclitaxel except where specified in Sections 6.41 and 6.44. **(06/1/10)**

6.31 Interim Nadirs (Note: Dose modification may also be required due to pretreatment counts—see Section 6.32.)

6.311 Grade III or IV bleeding or infection requires a 1-level dose reduction regardless of documented ANC or platelet values.

6.312 No dose escalation (increase) above the maximum dose levels (+2) indicated in the table below (6.313) is allowed. Dose escalation is mandated by the ANC Nadir grade (0 or 1) and the platelet nadir is 0, 1, or 2. **(06/1/10)**

6.313 No reduction below the lowest dose level specified above is allowed. If a patient is already at the "-3" dose and counts call for further reduction, the patient is to be removed from the study therapy and the study chair notified.

ANC Nadir Grade	**Action for BOTH ifosfamide and paclitaxel**
0 (≥ LLN)	Escalate dose by 1 Level
1 (< LLN to 1500/mcl)	Escalate dose by 1 Level
2 (<1,500/mcl to 1,000/mcl)	No Change
3 (<1,000/mcl to 500/mcl)	No Change
4 (<500/mcl)	Reduce dose by 1 Level

Platelet Nadir Grade	**Action for BOTH ifosfamide and paclitaxel**
0 (≥ LLN)	No Change or escalate dose based on ANC nadir
1 (<LLN to 75,000/mcl)	No Change or escalate dose based on ANC nadir
2 (<75,000/mcl to 50,000/mcl)	No Change or escalate dose based on ANC nadir
3 (<50,000/mcl to 25,000/mcl)	Reduce dose by 1 Level
4 (<25,000/mcl)	Reduce dose by 1 Level

6.32 Pre-treatment Counts (Note: dose modification may also be required due to interim nadirs laboratory values – see Section 6.31.)

6.321 No subsequent course of therapy should be given until the ANC is greater than or equal to 1,500/mcl and the platelet count is greater than or equal to 100,000/mcl. If dose is held due to pre-treatment myelosuppression, recheck counts weekly. If therapy is delayed 3 weeks or longer from scheduled administration, the Study Chair should be notified and the patient should be removed from study therapy.

6.322 ANC and/or platelet nadir values dictate treatment doses for each cycle, according to the above table for interim counts if no other significant (Grade 2 or greater) organ toxicity is noted. Treatment-related alopecia, fatigue, or myalgias will typically not be used as reasons for NOT escalating doses.

6.323 If treatment is delayed greater than 1 week but less than three from scheduled administration due to pre-treatment counts, the dosage modification is a one dose level reduction.

6.4 Non-Hematologic Toxicity: **REGIMEN II** (Ifosfamide + Paclitaxel)

6.41 Patients experiencing significant ifosfamide-related (i.e., not related to ureteral stents, tumor infiltration, or infection) microscopic hematuria (defined at 1+ or greater on urine dipstick or greater than 25 red blood cells per 1 high power field) should have the dose of ifosfamide reduced 1 level. If the microscopic hematuria persists on the urinalysis prior to the next cycle, reduce one additional level. If symptoms persist, remove patient from study therapy. If the patient develops gross hematuria at any ifosfamide dose level, remove from study therapy. **(11/19/2012)**

If hematuria develops during the three-day treatment cycle, other sources of bleeding should be investigated (infection, tumor-related, etc) and dose should be held only if hematuria is thought to be ifosfamide-related and Mesna was taken properly. Daily urinalysis during the 3-day infusion is not required by this protocol (only prior to the beginning of a new cycle). **(11/19/2012)**

6.42 If the serum albumin drops below 3 g/dL, hold therapy until albumin is at least 3g/dL. If > 6 weeks pass from the last dose of ifosfamide, remove patient from study therapy.

6.43 There will be no dose adjustment based on serum albumin.

6.44 If Grade 2 ifosfamide-related neurologic symptoms develop (e.g., confusion), reduce ifosfamide dose 1 level. If symptoms recur (Grade 2 or worse), remove patient from study therapy. If Grade 3 or 4 neurologic symptoms develop, remove patient from study therapy.

6.45 Grade 2 (or greater) peripheral neuropathy requires reduction of one dose level of both paclitaxel and ifosfamide and delay in subsequent therapy for a maximum of 2 weeks until recovered to Grade 1. If Grade 2 or greater peripheral neuropathy persists beyond the two-week period of delay, the paclitaxel will be discontinued and treatment will be allowed with ifosfamide dose reduced one level.

6.46 Grade 3 (or greater) hepatic toxicity with elevations in SGOT (AST), SGPT (ALT), alkaline phosphatase or bilirubin requires reduction of one dose level of the agent felt to be responsible for the elevation (usually paclitaxel) and delay in subsequent therapy for a maximum of 2 weeks until recovered to Grade 1. Patients whose treatment is delayed > 14 days because of such toxicity should have protocol therapy discontinued. Bilirubin must return to within normal limits prior to further therapy.

6.47 There will be no dose modifications for alopecia, fatigue, or myalgias. Myalgias in the several days following paclitaxel treatment may be severe,

and should receive aggressive symptomatic treatment, including narcotics or steroids as required. They are not, however, an indication for dose reduction or lack of dose escalation. **(11/19/2012)**

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

6.49 Paclitaxel hypersensitivity reaction: If hypersensitivity reactions to paclitaxel or its vehicle (Cremophor) occur, it will usually be during the first few minutes of infusion. Appropriate symptomatic therapy should be given. Continued
treatment may be considered if the reaction is not life threatening; however, patients must be cautioned about 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. A suggested procedure would be to administer the drug first with 1 cc of the original IV solution diluted in 100 ml over one hour, then 5 cc in 100 ml over one hour, then 10 cc in 100 ml over one hour, and finally, the original solution at the original speed. Patients who elect not to have continued treatment with paclitaxel after experiencing a hypersensitivity reaction may continue on protocol therapy with ifosfamide only.

6.410 Supportive Care: In addition to other aspects of supportive care, particular attention should be paid to the likely development of non-hemolytic anemia after several cycles of treatment. The patient should be transfused as necessary while continuing therapy. No treatment delays are permitted for anemia. Erythropoietin therapy in addition to iron supplementation is permitted to ameliorate anemia, at the investigator's discretion.

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

7.0 STUDY PARAMETERS

7.1 Observations and Tests

The following observations and tests are to be performed and recorded on the appropriate form(s). **See Section 7.2 and 10.2 for a description of the stained pathology slides that are required for central review by the GOG Pathology Committee to confirm eligibility and for instructions for shipping that material to the GOG Statistical and Data Center. See Section 7.3 for a description of the specimen requirements for translational research for this study. (06/1/10)**

PARAMETER	Pre-Treatment	Weekly	Prior to Each Cycle	Disease Surveillance	Follow-up, Post Therapy
History & Physical, including pelvic examination	1		X		9
Toxicity Assessment*	1		X		
CBC/Differential/Platelets, Creatinine	3	4	5		
Urine Analysis (U/A)	3		5		
Bilirubin, SGOT, Alkaline Phosphatase, Electrolytes, BUN, Ca, Mg, PO4, Albumin	3		5		
CA-125	1			6, 8	6, 8
Chest, Abdomen and Pelvic Imaging (CT scan or MRI)	1			6, 8	6, 8
Pregnancy test (if childbearing potential exists)	2				
Electrocardiogram (EKG)	1				
Audiogram	X[7]				
Clinical and/or Radiographic Tumor Measurement	1,8				6, 8
QOL Evaluations: FACT TOI-En, FACT/GOG-Ntx Subscale	1		10		10

* Including neurotoxicity assessment

Notes:

1. Must be obtained within 28 days prior to initiating protocol therapy.
2. Must be obtained within 72 hours of initiating protocol therapy if childbearing potential exists.
3. Must be obtained within 14 days prior to initiating protocol therapy.
4. If Grade 4 neutropenia is documented (ANC < 500/mcl), obtain twice per week until resolved to Grade 3.

5. CBC/Differential/Platelets, creatinine, and U/A (U/A for patients receiving ifosfamide only) must be obtained within 4 days of re-treatment with protocol therapy. Calcium, Magnesium, PO4 and Albumin within 7 days of re-treatment.
6. For patients who do not have measurable disease (NON-MEASURABLE) at study entry, they will be imaged by CT or MRI (for contrast allergy patients if non-contrast CT is inadequate to assess) scan of the chest/abdomen/pelvis within 4 weeks before starting protocol therapy. CT or MRI scans and CA-125 will be repeated prior to every three cycles for 6 cycles (baseline, then after cycles 3, and 6) to rule out progression. After the 6th cycle of therapy, patients with no evidence of progression will obtain a CA-125 every 3 months for the next 1 year, then every 6 months for three years, then annually, up until disease progression is documented. Imaging will be performed every 6 months for 2 years then annually thereafter until disease progression is documented or if there is clinical concern based on a clinically significant rise (above institutional normal) in the CA-125, or symptoms develop. **(04/02/2012)**
7. Audiogram is necessary if there is a history of hearing loss or new onset hearing loss. Audiograms should be repeated at the physician's discretion.
8. For patients with MEASURABLE DISEASE at study entry, they will be imaged by CT or MRI (for contrast allergy patients if non-contrast CT is inadequate to assess) scan of the chest/abdomen/pelvis within 4 weeks of starting protocol therapy. CT or MRI scans and CA-125 will be repeated every other cycle until protocol chemotherapy is completed at a maximum of 10 cycles (baseline, then after cycles 2, 4, 6, 8, 10) to rule out progression. After the final protocol cycle of therapy, patients with no evidence of progression will undergo imaging and obtain CA-125. Tumor imaging, clinical examination and CA-125 will be repeated every 3 months for the next 2 years, and then every 6 months for 3 years, and then annually, up until disease progression is documented. Imaging will be performed if there is clinical concern based on a clinically significant rise (above institutional normal) in the CA-125 or symptoms develop. **(06/1/10)**
9. Every 3 months x 2 years, then every 6 months x 3 years, then every year until death; all subsequent antitumor therapies administered must be reported.
10. Patients will complete the QOL Survey at **FOUR** times
    1) Baseline (within 28 days prior to initiation of therapy)
    2) Prior to Cycle 3 (week 6)
    3) Prior to Cycle 6 (week 15)
    4) 30 weeks following initiation of therapy

    NOTE: **QOL assessments should be administered at ALL 4 assessment times, REGARDLESS of whether the patient progresses or is removed from study therapy for any reason.** If there are treatment delays, the QOL assessment timing should be adjusted to follow the timing of the cycles

7.2 Stained Pathology Slide Requirements for Central Review to Confirm Protocol 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 and **histologic cell types including the presence of heterologous elements** will be required. In addition, at least one representative H&E stained slide documenting the most advanced stage of disease will be required if the most advanced stage is documented by histology or cytology. 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, two 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 4.8 and 10.2 for additional requirements and instructions.**

7.3 Translational Research **(04/02/2012)**

7.31 Specimen Requirements **(04/02/2012)**

If the patient gives permission for her specimens to be collected and used for this optional translational research component, then participating institutions within the United States are required to submit the patient's specimens as outlined below (unless otherwise specified).

A detailed description of the specimen requirements can be found in Appendix III.

Required Specimen (Specimen Code)	**Collection Time Point**	**Ship To**
FFPE Primary, Metastatic, or Recurrent Tumor (FT01) 1st Choice: block 2nd Choice: 10 unstained slides (charged, 5µm)	Prior to initiating chemotherapy	GOG Tissue Bank within 8 weeks of registration[1]
Whole Blood (WB01) 7-10mL drawn into a purple top (EDTA) tube	Prior to or after initiating chemotherapy	GOG Tissue Bank the day the specimen is collected[1]

1 Ship specimens to: GOG Tissue Bank / Protocol GOG-0261, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: GOGBanc@nationwidechildrens.org

7.32 Laboratory Testing **(04/02/2012)**

FFPE tumor and DNA extracted from whole blood will be banked for future research.

7.33 Future Research **(04/02/2012)**

Details regarding the banking and use of specimens for future research can be found in Appendix III.

7.4 Quality of Life

7.41 Patients will complete the QOL Survey at **FOUR** times
1) Baseline (within 28 days prior to initiation of therapy)
2) Prior to Cycle 3 (week 6)
3) Prior to Cycle 6 (week 15)
4) 30 weeks following initiation of therapy

NOTE: **QOL assessments should be administered at all 4 assessment times, REGARDLESS of whether the patient progresses or is removed from study for any reason.**

7.42 The QOL Survey is also available in French and Spanish. Requests for the translated versions should be made to the GOG Statistical and Data Center.

7.43 Whenever possible the QOL Survey should be administered at the clinic visit before the patient is seen by the physician, before evaluations are performed and before test results are shared with her. In the event that the questionnaires are not administered at the clinic visit, the QOL data can be collected by telephone or mail as backup methods, with telephone data collection being the preferred back-up method.

7.44 The Quality of Life Liaison (GOG Nurse/Data Manager) at each institution has overall responsibility for the administration of the study questionnaires.

7.45 The GOG Nurse/Data Manager should read the instructions printed on the questionnaire to the patient and ensure the patient understands the instructions. It is important to assure the patient that all material on the questionnaire is confidential, and will not be shared with the health care team and that it will not become part of the medical record.

7.46 Assistance in reading the questionnaire is permitted if the patient is unable to complete the questionnaire on her own (e.g., difficulty in reading, elderly). It is important not to influence the response of the patient. Note why the patient required assistance and what assistance was given.

7.47 Patients should be instructed to answer all the questions regardless of whether the symptoms or conditions asked about are related to the cancer or cancer treatment. Discourage family members from being present during questionnaire completion or from influencing the patient's response.

7.48 Review the questionnaire for completeness before the patient leaves.

7.481 If the patient has marked more than one answer per question, ask the patient which answer best reflects how she is feeling

7.482 If the patient has skipped a question or questions, assure that she noted in the space provided that she has chosen not to answer those questions.

7.49 It is essential that the questionnaires be completed according to the schedule described in Section 7.41.

7.410 If the patient refuses or cannot complete the questionnaire at any time point, she should be asked to do so at the next scheduled administration time.

7.411 The patient may withdraw from the Quality of Life portion of the protocol for any reason. The reason must be documented on the form.

7.412 Prior to submitting the QOL Scantron to the GOG Statistical and Data Center, be sure the following information is recorded and coded in:
a) patient's complete GOG number
b) date of form completion
c) study time point for which the form is being completed

8.0 EVALUATION CRITERIA

8.1 Parameters of Outcome – GOG RECIST Criteria

8.11 Measurable disease

Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest dimension to be recorded). Each lesion must be ≥ 20 mm when measured by conventional techniques, including palpation, plain x-ray, CT, and MRI, or ≥ 10 mm when measured by spiral CT.

8.12 Baseline documentation of "Target" and "Non-Target" lesions

All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest dimension) and their suitability for accurate repetitive measurements by one consistent method of assessment (either by imaging techniques or clinically). A sum of the longest dimension (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the progression of the measurable dimension of the disease. Tumor 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.

All other lesions (or sites of disease) should be identified as *non-target* lesions and should also be recorded at baseline. Measurements are not required and each of these lesions should be followed as stable **(t**he persistence of a non-target lesion), complete response **(t**he disappearance of a non-target lesion) or progressive disease (the unequivocal progression of a non-target lesion).

All baseline evaluations of disease status should be performed as close as possible to the start of treatment and never more than 4 weeks before the beginning of treatment.

Measurement of the longest dimension of each target lesion size is required for follow-up. Change in the sum of these dimensions affords some estimate of change in tumor size and hence therapeutic efficacy. All disease must be assessed using the same technique as baseline.

8.13 Definition of disease progression

Progression for patients with measurable disease at baseline is defined as ANY of the following:

- At least a 20% increase in the sum of LD target lesions taking as reference the smallest sum LD recorded since study entry
- In the case where the ONLY target lesion is a solitary pelvic mass measured by physical exam which is not radiographically measurable, a 50% increase in the LD is required taking as reference the smallest LD recorded since study entry
- The appearance of one or more new lesions
- Death due to disease without prior objective documentation of progression
- Global deterioration in health status attributable to the disease requiring a change in therapy without objective evidence of progression
- Unequivocal progression of existing *non-target* lesions, other than pleural effusions without cytological proof of neoplastic origin, in the opinion of the treating physician (in this circumstance an explanation must be provided)

Progression for patients with non-measurable disease at baseline is defined as increasing clinical, radiological, or histological evidence of disease since study entry.

8.14 Survival is the observed length of life from entry into the study to death or the date of last contact.

8.15 Progression-Free Survival is the period from study entry until disease progression, death, or date of last contact.

8.16 Subjective Parameters including performance status, specific symptoms, and side effects are graded according to the CTCAE.

9.0 DURATION OF STUDY

9.1 A total of 6 cycles of chemotherapy is planned for all patients in the absence of disease progression or unacceptable toxicity. Patients who entered the study with measurable disease and meet the criteria for a partial response at the end of 6 cycles may continue on therapy up to a maximum of 10 cycles in the absence of disease progression or unacceptable toxicity.

9.2 Follow-up is required as outlined in Section 7.0. In brief, patients will be followed (with physical exams and histories) every three months for the first two years and then every six months for the next three years, then annually. Scheduled imaging varies based on patients having measurable or non-measurable disease at enrollment (see Section 7.0) Patients will be monitored for progression, delayed toxicity, non-protocol therapy and survival for this 5-year period with D2M and Q forms submitted to the GOG Statistical and Data Center, unless consent is withdrawn.

9.3 A patient is considered off study therapy when the patient has either completed the prescribed number of cycles of study therapy, has progressed or died prior to completion of study therapy, a non-protocol drug or therapy (directed at the disease) is initiated or all study therapy is totally discontinued. Report all treatment received on Form D2R and adverse events on Form T up until the patient qualifies as being off study therapy.

10.0 STUDY MONITORING AND REPORTING PROCEDURES

10.1 ADVERSE EVENT REPORTING FOR A COMMERCIAL AGENT **(05/05/2014)**

10.11 Definition of Adverse Events (AE) **(09/06/2011)**

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

10.12 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 Adverse Event Reporting System (CTEP-AERS). All CTEP-AERS submissions are reviewed by GOG before final submission to CTEP. CTEP staff will not be evaluating submissions to these databases. Submitting a report through CTEP-AERS 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: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of Any Commercial Study Agent

From the period of protocol activation through September 30, 2011, Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (CTCAE v3.0) are utilized for defining and grading specific adverse events reported through the CTEP-AERS system. **(09/06/2011)**

Beginning October 1, 2011, the NCI Common Terminology Criteria for Adverse Events (CTCAE) v 4.0 will be utilized for AE reporting through the CTEP-AERS system. CTCAE v 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of this Version of CTCAE. CTCAE v 4.0 definition is also available on

the GOG member web site (https://gogmember.gog.org under MANUALS). **(09/06/2011)**

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:

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

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 7 calendar day report:

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

[2] Although a CTEP-AERS 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 CTEP-AERS 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 CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 3 calendar days of the initial 24-hour report.

  "7 calendar days" – A complete CTEP-AERS 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 CTEP-AERS 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 CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent:

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

10.14 Procedures for Expedited Adverse Event Reporting:

10.141 CTEP-AERS Expedited Reports: Expedited reports are to be submitted using CTEP-AERS available at http://ctep.cancer.gov. The NCI guidelines for expedited adverse event reporting requirements are also available at this site.

Up until September 30, 2011, AML/MDS events must be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v3.0, the event can be reported as: "Secondary malignancy-Other (specify)". **(09/06/2011)**

Starting October 1, 2011 when use of CTCAE v4.0 begins: AML/MDS events must be reported via CTEP-AERS (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. **(09/06/2011)**

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to GOG by telephone at: 215-854-0770. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted. **(12/20/2010)**

10.2 GOG DATA MANAGEMENT FORMS

The following forms must be completed for all patients registered and submitted to the GOG Statistical and Data Center (SDC) in accordance with the schedule below. Use the SDC Electronic Data Entry System (SEDES) online application found at the GOG Web Menu page, to view and print a copy of each form along with instructions, and to submit forms electronically. All amendments to forms submitted through SEDES must also be submitted through SEDES. The original form and required copies for forms NOT submitted online must be mailed to the GOG SDC. **Note: Pathology material (Form F, path report and slides) may be submitted together via postal mail. The GOG Uploader Application in SEDES is an alternate method for submitting Form F and pathology reports to the GOG SDC (stained slides must be shipped via postal mail).See Sec. 4.8 and 7.2 for additional requirements and instructions. (06/1/10) (3/21/2011)**

Form±	**Due within**		**Copies***	**Comments**
	Weeks	**Event**		
Form R (Registration Form)	2	Registration	1	Mandatory submission via SEDES
Specimen Consent Application	1	Registration	N/A	Complete online
Form OSR (Recurrent Gynecologic Cancer On-Study Form) or Form OSU (Uterine Cancer On-Study Form) or Form OSO (Primary Ovarian Cancer- On Study Form)✦	2	Registration	1	Mandatory submission via SEDES
Form DR (Treatment Summary Form) Operative Report Discharge Summary	2 6 6	Registration Registration Registration	1 2 2	Mandatory submission via SEDES Submit via postal to SDC or upload via SEDES
Form BMR (Biomarker Reporting Form)	2	Registration	1	Mandatory submission via SEDES; report CA-125
Form D2M (Solid Tumor Reporting Form) - baseline assessment)	2	Registration	1	Mandatory submission via SEDES
Quality of life: *** Scantron Form – baseline Scantron Form-6 weeks Scantron Form-15 weeks Scantron Form-30 weeks	 2 8 17 34	 Start of study therapy Start of study therapy Start of study therapy Start of study therapy	 1 1 1 1	Submit Scantron from by postal mail***
Primary disease**: Form F (Pathology Form)	6	Registration	2	Available in SEDES for print only

Pathology Report Stained Path Slides to confirm eligibility Recurrent or Persistent Disease**: Form F (Pathology Form) Pathology Report Stained Path Slides to confirm eligibility, if histologically-documented	6 6 6 6 6	Registration Registration Registration Registration Registration	2 ** 2 2 **	Submit via postal mail to GOG SDC in Buffalo, New York or submit using the report upload of SEDES Available in SEDES for print only. Submit via postal mail to GOG SDC in Buffalo, New York or submit using the report upload of SEDES
Form D2R (Cycle Dose Drug Form)	2	Completion of each cycle of therapy	1	Mandatory submission via SEDES
Form BMR (Biomarker Reporting Form)	2	Completion of study treatment; each required follow-up CA-125 assessment	1	Mandatory submission via SEDES; report CA-125
Form D2M (Solid Tumor Reporting Form)	2	Every clinical/radiographic disease assessment	1	Mandatory submission via SEDES
Form SP-FT01-0261 for FFPE tumor **(04/02/2012)**	8	Registration	1	Mandatory submission via SEDES*ƒ* **(04/02/2012)**
Form SP-WB01-0261 whole blood **(04/02/2012)**	26 **(04/02/2012)**	Registration **(04/02/2012)**	1	Mandatory submission via SEDES*ƒ* **(04/02/2012)**
Form T (Common Toxicity Form)	2	Beginning of each subsequent treatment cycle and 3 weeks after final treatment cycle	1	Mandatory submission via SEDES
Form Q0 (Treatment Completion Form)	2	Completion of study treatment and change in treatment	1	Mandatory submission via SEDES
Form Q (Follow-Up Form)	2	Disease progression; death; normal follow-up; change in treatment	1	Mandatory submission via SEDES quarterly for 2 years, semi-annually for 3 more years

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

** Stained pathology slides are required for central review by the GOG Pathology Committee to confirm eligibility. See Sections. 4.8 and 7.2 for additional requirements and instructions. All stained slides must be submitted via postal mail.

ƒ Form SP must be submitted regardless of whether the specimen is submitted for research. **(04/02/2012)**

*** The schedule in Section 10 provides the time that forms are due in the SDC. See Section 7.4 for the times that each QOL assessment should be completed by the patient. Use only Scantron forms with the header of "GOG Protocol 0261." Quality of life forms will be provided by the SDC upon request. If the assessment is not performed, submission of the form is still required documenting the reason the assessment was not performed.

- ✦ Form OSR is required for all patients with measurable or persistent or recurrent disease; Form OSU is required for patients with non-measurable and primary uterine carcinosarcoma and Form OSO is required for patients with non-measurable and primary ovarian carcinosarcoma. **(06/1/10)**

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.

This study utilizes the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) for defining and grading adverse events to be reported on GOG case report forms. A GOG CTCAE v3.0 Manual is available on the GOG member web site (http://www.gog.org under MANUALS) and can be mailed to the institution registering a patient to this study if requested. **(09/06/2011)**

11.0 STATISTICAL CONSIDERATIONS

11.1 Study design overview and registration:

This study is designed as a randomized open-label Phase III clinical trial. This design will provide a direct assessment of the null hypothesis that survival among patients with uterine or ovarian carcinosarcoma treated with paclitaxel and carboplatin chemotherapy is not inferior to survival among patients treated with ifosfamide, mesna, and paclitaxel chemotherapy. Prior to activation of Revision 2 of this study, patients were registered to this study and obtained random treatment assignment centrally at the GOG Statistical and Data Center. Following the effective date of Revision 2, patients are to be registered to this study through OPEN and treatment randomization will be carried out centrally by the GOG Statistical and Data Center. Prior to registration, eligibility will be reviewed via Fast Fact Sheet verification. The sequence of treatment assignments will be concealed from institutions and patients until registration with verification of eligibility. Treatment randomization is to be carried out following study registration. A minimization procedure will be used that tends to balance the treatment allocation equally within patient-level stratification factors. Stratification is defined by three factors; disease status or stage at entry (recurrent, Clinical FIGO Stage I or II, surgical FIGO Stage I or II with or without pelvic nodal assessment, surgical FIGO Stage III or IV) and tumor status at entry (measurable or non-measurable) and pelvic radiation history (any or none). All interim and final reports will include a complete accounting of all patients registered to this protocol. **(06/1/10) (10/21/2013)**

11.2 Data collection:

The principal parameters to be collected, analyzed and reported to determine the relative therapeutic effect of the two treatment regimens are:

11.21 ***Outcome measures:*** Primary: Duration of overall survival; Secondary: Duration of progression-free survival.

11.22 ***Tumor characteristics:*** Stage or status of disease (persistent, recurrent, Stage I-IV), tumor status at entry (measurable or non-measurable), primary site of disease (uterine vs ovarian). **(06/1/10)**

11.23 ***Host characteristics:*** Age at entry, performance status, prior treatment (pelvic, vaginal, and extended field radiation, hormonal) and racial/ethnic designation.

11.24 ***Adverse effects:*** The frequency and severity of acute and late adverse effects graded by CTCAE version 3.0.

11.25 ***Treatment:*** The number of cycles of study therapy administered; for those not completing the prescribed study therapy, and the reason for discontinuation of assigned therapy.

11.26 ***Quality of life***: FACT TOI-En and FACT/GOG-Ntx subscale (11 items).

11.3 Accrual rate, sample size, and study duration:

Based upon accrual to GOG-0161 (a Phase III randomized trial of ifosfamide and mesna and ifosfamide, mesna, paclitaxel and G-CSF) and GOG-0232B (a Phase II study of carboplatin and paclitaxel), the anticipated accrual for the advanced/recurrent measurable disease population for this study is 48 patients per year. Based upon accrual to GOG-0150 (a Phase III randomized trial of radiation and ifosfamide, cisplatin and mesna) the anticipated accrual for the non-measurable Stage I-IV population for this study is 30 patients per year; an expected 50% increase over what was observed in GOG-0150.

Based upon previous GOG experience with studies involving uterine carcinosarcoma, it is expected that 14% of patients registered to this study will be deemed ineligible. The planned sample size for this study is 364 eligible patients with uterine carcinosarcoma; a minimum of 424 total study registrants. Starting with the implementation of Revision #2, patients with ovarian carcinosarcoma will be eligible. The accrual rate for ovarian carcinosarcoma is not well defined but is expected to be very low. Therefore, the current study size will be determined strictly by uterine carcinosarcoma accrual. The ovarian carcinosarcoma accrual will be monitored for 24 months to determine the impact on the total sample size. It is anticipated that this study will require approximately 5.5 years of accrual assuming a uniform accrual rate of 78 patients with uterine carcinosarcoma per year. It is estimated that 24 months of post accrual follow-up will be necessary to observe the minimum number of events required for the final primary analysis. **(09/07/2009) (06/1/10)**

Revision 9: This study was initially developed to include only uterine carcinosarcoma patients and the design parameters were based on data from GOG 0150 and 0161. The study was activated in September 2009. In June 2010, the study was amended to include patients with ovarian carcinosarcoma. Subsequently the study was open to fallopian tube and peritoneal carcinosarcoma; however these cases are even rarer than ovarian carcinosarcoma. At the time of the June 2010 amendment, it was not known how many patients with non-uterine carcinosarcoma would be enrolled and to what degree it would impact the design of GOG-0261. There remains very little data in the literature regarding ovarian, fallopian tube and peritoneal carcinosarcoma.

As of August 15, 2013 there are 92 patients with ovarian carcinosarcoma and three patients with fallopian tube or peritoneal carcinosarcoma enrolled. Accrual rates within subgroups of uterine and ovarian carcinosarcoma can now be

accounted for in the statistical study design in revision 9. Additionally, the original design assumptions have been reviewed. Specifically, the proportion of early stage or lower risk patients is much higher than originally anticipated. Thus, at revision 9, the sample size has been upwardly adjusted to account for this. **(10/21/2013)**

11.4 Primary hypotheses, planning parameters, and sample size justification:

Ifosfamide has been a standard treatment in the GOG for women with advanced or recurrent measurable uterine carcinosarcoma. Recently, results from GOG-0161 have shown a survival advantage favoring the combination of ifosfamide, mesna and paclitaxel (TIM) over ifosfamide alone (death hazard ratio=0.69; two-tail test p=0.03). The combination of carboplatin and paclitaxel (TC) has been a standard treatment for ovarian cancer and is now being used in the community for treating many other gynecologic malignancies. It is currently being tested in advanced or recurrent uterine carcinoma. This combination, TC, has never been studied in a Phase III setting in advanced or recurrent uterine carcinosarcoma. There appears to be an obvious preference for TC in terms of ease of administration since TC can be given in a matter of a few hours, whereas TIM requires a two-day administration followed by 10 days of G-CSF (filgrastim) or a single day dose of pegfilgrastim on Days 4 to 6. Since growth factor is given as part of the TIM regimen, differences in neutropenia are not expected to be significant.

Primary Hypothesis: This study will evaluate the effect of 6 cycles of carboplatin and paclitaxel relative to 6 cycles of ifosfamide, mesna and paclitaxel with G-CSF support. The primary endpoint for this evaluation is overall survival. The purpose of this study is to determine whether TC can be considered not inferior and potentially superior to TIM with regard to overall survival duration. Toward this end, the final analysis will evaluate the hypothesis:

$$H_0 : \lambda_{TC} \geq 1.2 * \lambda_{TIM}$$

where $\lambda_{(\cdot)}$ is the true death rate for each treatment. Alternately, a translation of the hypothesis in terms of proportion surviving at time t can be written as:

$$H_0 : p_{TC}(t) \leq (p_{TIM}(t))^{1.2}$$

where $p_{(\cdot)}$ is the true proportion surviving at time t in each treatment arm.

Planning parameters: Data are available from GOG-0161 to estimate the overall survival distribution among women with advanced or recurrent uterine carcinosarcoma. The median survival time from GOG-0161 on the TIM regimen is 13.5 months. The percentages of patients enrolled on GOG-0161 assigned to receive TIM alive at 1, 2 and 3 years are 55%, 22% and 10%, respectively. Known prognostic factors include performance status recorded at entry.

Similarly, data from GOG-0150 are used to estimate the overall survival time distribution among women with optimally debulked Stages I-IV carcinosarcoma.

The percentages of patients with Stage I or II disease enrolled on GOG-0150 alive at 1, 2 and 5 years are 86%, 76% and 59%, respectively. The percentages of patients with Stage III or IV disease enrolled on GOG-0150 alive at 1, 2 and 5 years are 64%, 46% and 26%, respectively. Known prognostic factors include surgical stage and age at study entry.

Initial sample size justification: Originally**,** this trial was to be considered sufficiently mature for a final analysis when there were at least 264 deaths reported among all eligible patients (combining uterine and ovarian carcinosarcomas together). If the true death rate on TIM is 13% greater than the death rate associated with TC then this study provides 80% chance of rejecting H_0 and concluding that TC is not inferior to TIM when Type I error is limited to 5% for a one-tail test. If the true death rates are equal on both arms then there is a 45% chance of concluding that TC is not inferior to TIM.[24] A stratified log rank test will be used to assess the null hypothesis, stated above, between the two regimens with the assumption that the hazards are proportional. A graph of the power curve for possible alternatives in terms of the hazard ratio and a graph of the absolute differences in the proportion surviving among treatment arms within each population for possible alternatives in terms of hazard ratio are provided below.

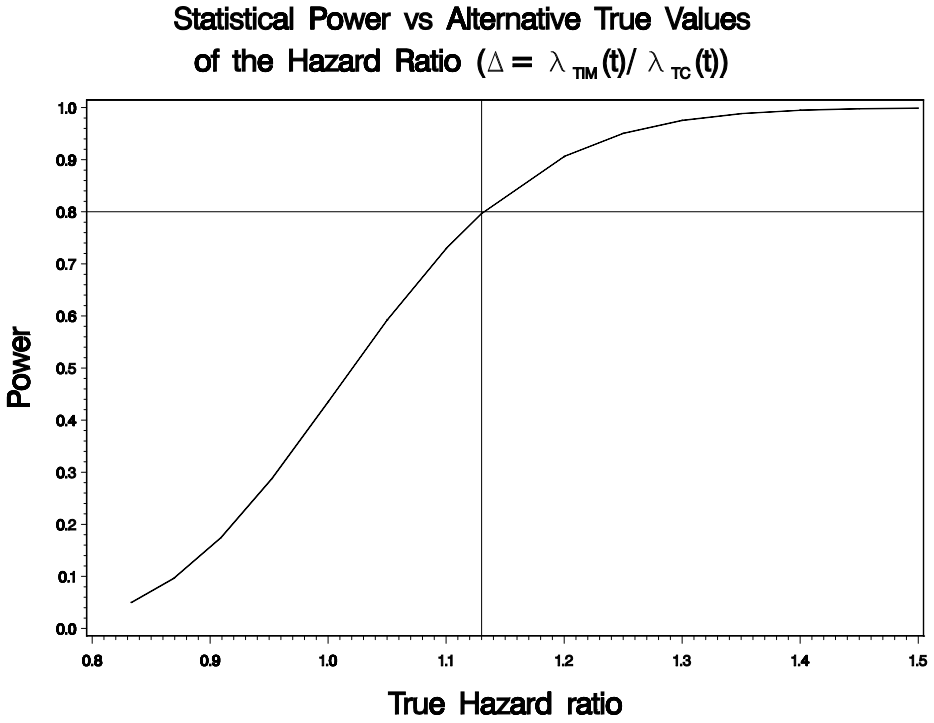
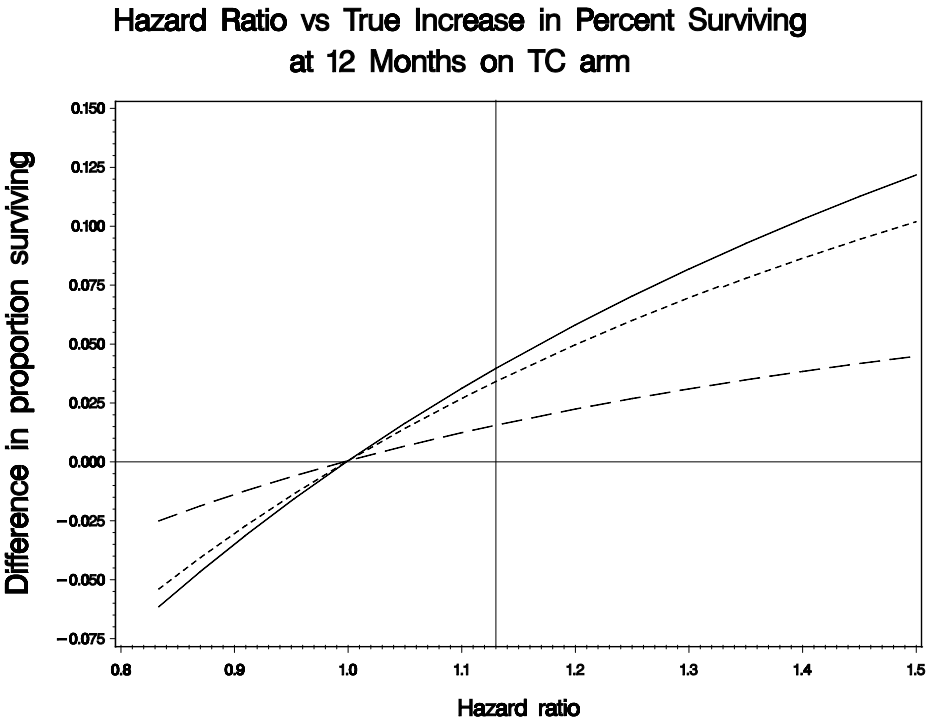


Figure 11.A



Solid line: measurable Stages III, IV or recurrent population; *short dashed line:* non-measurable Stages III or IV population; *long dashed line:* non-measurable Stages I or II population

Figure 11.B

Assuming a decrease in the hazard of death, it is anticipated that 73% of patients will have died at the time of planned analysis. The sample size necessary to observe 264 deaths is estimated to be 364 eligible uterine carcinosarcoma patients or a minimum of 424 enrolled patients. These assumptions and the impact of ovarian carcinosarcoma eligibility on accrual were assessed prior to the first interim analysis and reported to the GOG Data and Safety Monitoring Board (DSMB). The DSMB approved the changes to the statistical considerations included in revision 9 on 10/17/2013. **(09/07/2009) (06/1/10) (10/21/2013)**

Revised target accrual goal - revision 9: (10/21/2013)
Maintaining the same characteristics used above and using the same failure rates assumed at the original study design, the target accrual was recalibrated based on the current distribution of risk groups (see Table 11.A) and the proportion of cases with uterine carcinosarcoma (80%). The study will target 437 patients with uterine carcinosarcoma deemed eligible following central review (508 total patients with uterine carcinosarcoma); anticipated total enrollment accounting for both uterine and non-uterine carcinosarcoma will be approximately 603 participants. The accrual rate was much faster than originally expected (see Table 11.B). The accrual duration from study activation is estimated to be 56 months and the total study duration is expected to be 80 months; 10 months shorter than originally expected (see Table 11.C).

Table 11.A Risk Group Distribution

Risk Group	Original study design proportion	Revised proportion among uterine carcinosarcoma
Optimal, Stage I or II	16.7%	39%
Optimal, Stage III or IV	21.3%	26%
Measurable, recurrent or persistent	62.0%	35%

Table 11.B Current Average Accrual Rates

	Average accrual
Uterine Carcinosarcoma	9.07/month or 108.8/year

Table 11.C Revised Accrual and Study duration in months

Study population	Revised total accrual	Revised accrual duration (original)	Revised follow-up duration	Revised study duration (original)
All carcinosarcoma	**603**	**56 (66)**	**24**	**80 (90)**
Uterine Carcinosarcoma	508			

Uterine carcinosarcoma design summary

Group	Months of accrual	Expected Sample size	Months of follow-up	Expected number of events
Stage I/II optimal	56	170	24	57 (33%)
Stage III/IV optimal	56	114	24	73 (64%)
Measurable or Recurrent	56	153	24	133 (87%)
Total eligible	56	437	24	263 (60%)
Total enrolled		508	patients	
Study duration		80	months	

Final Analysis: Originally, a pragmatic approach to the comparison of planned therapeutic regimens will be carried out. All eligible enrolled patients will be included in the primary analysis, regardless of the amount of study treatment received *or, after the addition of other tumor sites, primary tumor site*; that is, the primary analysis will be an intention-to-treat analysis among eligible patients. The approach taken in re-designing this study was to leave the original study objectives intact and restrict the primary hypothesis test to include only participants with uterine carcinosarcoma. Since the original study was open only

to those with a diagnosis of uterine carcinosarcoma and they now represent roughly 80% of the current accrual, the accrual goal will be set to allow for 80% power for hypothesis testing within this specific subgroup.

The primary analysis will be stratified by disease status, tumor status, and history of pelvic radiation. Potential confounders, including performance status, age, and racial designation will be considered in a final exploratory model. A forest plot of treatment hazard ratios with confidence intervals within subgroup determined by primary site (uterine and ovarian, assuming estimation is possible) and other covariates will also be reported. **(06/1/10) (10/21/2013)**

11.5 Interim Analyses:

An initial interim analysis of survival data will occur when at least 132 deaths have been reported among all eligible patients with uterine carcinosarcoma enrolled. The results of interim analyses are scheduled to be reviewed by the GOG DSMB at its meetings in January and July each year. Approximately eight weeks prior to each of these meetings, the study database is locked in order to prepare a progress report. If the prerequisite number of events has been attained, an interim analysis report is also prepared and presented to the DSMB at their next scheduled meeting. Overall survival, the accrual rate, adverse events of treatment, treatment compliance, the frequency of treatment termination due to toxicity, non-protocol therapy, the PFS relative hazard estimate, potential confounders and results of external studies will be included in the interim analysis report to the DSMB to be taken into consideration when reaching a decision. It is essential to assess adverse events of treatment at the interim and final analyses since this is a non-inferiority design. **(06/1/10) (04/02/2012) (10/21/2013)**

Interim analysis for efficacy (non-inferiority): The hypothesis testing strategy using the log rank test as described above will be used to test the null hypothesis of inferiority of TC relative to TIM with respect to overall survival. The nominal p-value to stop for efficacy at the interim analysis will be 0.001. If the null hypothesis can be rejected in the test involving the uterine subgroup, terminating accrual will be considered given that the study has not yet reached the target accrual goal. Consideration may also be given to continue accrual in order to test the hypothesis $H_{02} : \lambda_{TC} \geq \lambda_{TIM}$. If the study is closed to accrual early, an additional period of follow-up for data maturity will also be considered prior to releasing the final report. This will require evaluating the benefit of observing additional events with the cost of postponing the release of the final report to observe these events. If additional interim analyses are warranted, then the nominal p-value used to stop for efficacy at each interim analysis will be 0.001. There will be no correction to the nominal p-value in the final report. [25] **(06/1/10) (10/21/2013)**

***Interim analysis for futility (inferiority)*:** Additionally, a futility analysis will be carried out in the uterine carcinosarcoma subgroup. If the observed estimate of

the stratified ratio of the death rate of the experimental arm to the death rate of the control arm equals or exceeds 1.2, then accrual termination will be considered (if still active) with a conclusion that it is unlikely that the experimental arm will be shown to be not inferior to the control arm. The increase in Type II error due to this interim analysis is negligible. Under the null hypothesis, this procedure has a 50% chance of resulting in early termination. **(10/21/2013)**

***Safety monitoring*:** The GOG Safety Review Committee (SRC) reviews accumulating summaries of toxicities and all serious adverse event (SAE) reports on an ongoing basis (not efficacy results). This committee also reviews those deaths in which study treatment may have been a contributing cause. The SRC reports to the DSMB and it may recommend study amendments pertaining to patient safety. **(04/02/2012)**

11.6 Secondary endpoints, hypotheses or analyses: **(10/21/2013)**

Progression-free Survival: Progression-free survival (PFS) will be analyzed as a secondary endpoint. All eligible patients will be included in the intent-to-treat analysis of progression-free survival in the subgroup of uterine carcinosarcoma. A stratified Cox proportional hazards model will be used to assess the treatment comparison with respect to PFS in the uterine subgroup. Potential confounders will also be assessed in exploratory analyses. The same null hypothesis that is used to assess survival will be used to assess PFS.

***Toxicity*:** The maximum grade over the entire course of therapy for any individual effect will be used as a summary of acute toxicity. The Kruskal-Wallis test corrected for ties will be used to compare the maximum grade of acute adverse effects of therapy by treatment arm. The CTCAE v3.0 grading system will be used (i.e., scale from 0 for none to 5 for death). A significance level of 0.01 will be used for each tested AE term or category. No correction for multiple testing will be employed since it is very important to identify moderate increases in the severity of toxicity at the risk of increasing the Type I error. Since some of these toxicities are correlated, the overall type I error is less than calculations would indicate when assuming complete independence. Toxicity is assumed to be independent of primary site of disease.

Quality of Life: The following assessment tools will be used to measure the quality of life prior to and following treatment (baseline, prior to Cycle #3 or 6 weeks following initiation of treatment, prior to Cycle #6 or approximately 15 weeks following initiation of treatment, and 30 weeks following initiation of treatment):

- FACT-G Physical Well-being (PWB) and Functional Well-being (FWB) subscales (14 items),
- FACT-En additional concerns subscale (16 items), and
- FACT/GOG-NTtx subscale (11 items)

Each item in the subscales listed above are scored using a 5-point scale (0=not at all; 1=a little bit; 2=somewhat; 3=quite a bit; 4=very much). Within an individual assessment, one or more items may not be answered. A subscale score will be computed as long as more than 50% of subscale items have been answered. A subscale score S_i with N_i items will be calculated as:

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

Where δ_{ij} is equal to 1 when the j^{th} item has a valid response, otherwise it is equal to 0 and s_{ij} is the response score of the j^{th} item. The total score for the PWB and FWB is the sum of the two subscale scores if at least 80% of PWB and FWB items have been answered. The total score for the TOI-En is the sum of the FWB, PWB, and En subscale if at least 80% of TOI-En items have been answered.

The QOL objectives in this study are to compare treatment regimens with respect to the patient-reported quality of life as measured with PWB+FWB score, and patient-reported neurotoxicity as measured with FACT/GOG-Ntx-11 subscale. It has been suggested by the FACIT author [26, 27,28, 29] that the Trial Outcome Index (TOI) which is the sum of the PWB, FWB, and "additional concerns" of a specific cancer is more responsive to change in QOL outcomes in cancer clinical trials than the FACT-G plus the disease specific concerns. However, limited data are available on the validation of the FACT TOI-En in terms of psychometric properties. For the purposes of this study, the FACT TOI-En will be assessed as an exploratory endpoint. Currently, the FACT TOI-En scale is being used in GOG-0209 and will be validated once the study is completed. By the time of the final QOL report, if the FACT TOI-En is validated to be a reliable scale and sensitive to treatment and change over time, it will be assessed as a definitive endpoint in place of PWB+FWB to measure the quality of life.

A difference of 2-3 points is considered the minimally clinically important difference (MCID) for PWB and FWB respectively and a difference of 6-9 points is considered the MCID for FACT TOI-En scale.[29] For this study, an observed difference of 5.2 points for the total score of PWB and FWB and 7.7 points for TOI-En will be considered as the MID in terms of QOL between the treatment groups. This magnitude of difference is equivalent to an effect size of 0.5 assuming that the standard deviation (SD) is 10.4 for the total score of PWB and FWB and 15.4 for TOI-En as currently observed in GOG-0209. A difference of 3.8 points in FACT-GOG/Ntx subscale (11 items) is considered the MCID between the treatment groups for this study. This difference is approximately equivalent to an effect size of 0.5 assuming a SD of 7.6 as observed in GOG-0184.

	MCID	Estimated SD	Effect size	Study or reference
PWB+FWB	5.2	10.4	0.5	GOG-0209
TOI-En	7.7	15.4	0.5	GOG-0209
FACT-GOG/Ntx subscale	3.8	7.6	0.5	GOG-0184

With the multiple QOL measures, the Type I error is set at $0.025=1-(1-0.05)^{1/2}$ for each two-tail comparison between treatments to ensure the overall Type I error to be 0.05. To evaluate the primary endpoint (overall survival) this study will enroll 603 patients, of which 437 patients with uterine carcinosarcoma are assumed to be eligible with roughly 218 patients in each randomized group. However, death, illness, non-compliance, and missed appointments can lead to missing information that increases over time. Assuming the completion rates of QOL assessments are 90% at 6 weeks, 80% at 15 weeks, and 70% at 7 months, there will be 196 eligible patients at 6 weeks, 174 at 15 weeks, 152 at 7 months in each treatment group for QOL analyses. These sample sizes provide at least 98% power to detect the MCIDs or effect sizes listed above and in the table above at α of 0.025 (two-sided).[30] The statistical power will be higher than the estimated if the correlations among repeated measures are taken into account.

Linear mixed models adjusted for baseline score, age, and performance status at enrollment will be used to test the hypothesis of no difference in PWB+FWB scores (or FACT TOI-En), and in FACT-GOG/Ntx subscale score between assigned treatment arms in an intent-to-treat analysis of all enrolled eligible patients. Since the En subscale in the FACT TOI En is designed specifically for patients with endometrial cancer, the analysis for FACT TOI En will be limited to patients with uterine carcinosarcoma only. These models will account for the correlation between scores measured over time and the compound symmetry correlation is assumed for the repeated measures in this study. The interaction between treatment and assessment time on QOL scores will be tested initially in each model. If this interaction is found to be statistically significant at level of 0.05, treatment comparisons for each assessment tool will be carried out individually at each time point using the model parameter estimates. If there is no evidence of an interaction, then a weighted average of estimates over the three time points will be compared between assigned treatment arms. The empirical sandwich variance will be used to estimate the precision of the parameter estimates. Satterthwaite's DF approximation will be used in significance testing to adjust the degrees of freedom for unequal group variances.

11.7 Anticipated Gender and Minority Inclusion: **(09/07/2009) (10/21/2013)**

This study restricts entry to women by nature of the site of disease. The table below lists the projected percentage of patients by racial/ethnic subgroup. Prior GOG studies of uterine carcinosarcoma populations support no differences in the intervention effect between racial/ethnic subgroups. Therefore, the study design does not involve race. However, subsets defined by white, black/African American and all others will be analyzed in this study to investigate this important question with the current therapies. Additionally the association of race with outcome will be assessed.

Ethnic Category	**Number of patients anticipated**
Hispanic or Latino	18 (2.9%)
Not Hispanic or Latino	566 (93.9%)
Unknown	19 (3.2%)
Total	603 (100%)

Racial Category	**Number of patients anticipated**
American Indian/Alaskan Native	4 (0.6%)
Asian	5 (0.9%)
Native Hawaiian or Other Pacific Islander	2 (0.3%)
Black or African American	143 (23.7%)
White	442 (73.3%)
More than one race	2 (0.4%)
Unknown	5 (0.8%)
Total	603 (100%)

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APPENDIX I **(12/20/2010)**

FIGO STAGING FOR UTERINE CARCINOSARCOMA

Uterine Carcinosarcoma FIGO Surgical Stage Classification based on the Carcinoma of the Endometrium FIGO Classification 2009 [1-3]

Stage I*	Tumor confined to the corpus uteri
IA*	No or less than half myometrial invasion
IB*	Invasion equal to or more than half of the myometrium
Stage II*	Tumor invades cervical stroma, but does not extend beyond the uterus**
Stage III*	Local and/or regional spread of the tumor
IIIA*	Tumor invades the serosa of the corpus uteri and/or adnexae[#]
IIIB*	Vaginal and/or parametrial involvement[#]
IIIC*	Metastases to pelvic and/or para-aortic lymph nodes[#]
IIIC1*	Positive pelvic nodes
IIIC2*	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage IV*	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA*	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

* Either Grade 1, Grade 2, or Grade 3.

**Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.

[#] Positive cytology has to be reported separately without changing the stage.

FIGO **Clinical** Staging for Uterine Corpus Cancer (1971) [4]
To be used only for patients who have not had a hysterectomy

Stage I	Tumor is limited to the uterine body
IA	Uterine cavity measures 8 cm or less
IB	Uterine cavity measures greater than 8 cm
Stage II	Tumor extends to the uterine cervix
Stage III	Tumor has spread to the adjacent pelvic structures
Stage IV	Bulky pelvic disease or distant spread
IVA	Tumor invades the mucosa of the bladder or rectum
IVB	Distant metastasis is present.

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APPENDIX II

OVARIAN CARCINOSARCOMA
FIGO STAGING CRITERIA
Based on
FIGO STAGE GROUPING FOR PRIMARY CARCINOMA OF THE OVARY

(1985)

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

Stage I — Growth limited to the ovaries.

- Stage IA — Growth limited to one ovary; no ascites. No tumor on the external surface; capsule intact.
- Stage IB — Growth limited to both ovaries; no ascites. No tumor on the external surfaces; capsules intact.
- Stage IC* — Tumor either Stage IA or IB but with tumor on the surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.

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

- Stage IIA — Extension and/or metastases to the uterus and/or tubes.
- Stage IIB — Extension to other pelvic tissues.
- Stage IIC* — Tumor either Stage IIA or IIB but with tumor on the surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.

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

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

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

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

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

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

APPENDIX III

Specimen Procedures

I. Summary of Specimen Requirements

Required Specimen (Specimen Code)	Collection Time Point	Ship To
FFPE Primary, Metastatic, or Recurrent Tumor (FT01) 1st Choice: block 2nd Choice: 10 unstained slides (charged, 5μm)	Prior to initiating chemotherapy	Ship to the GOG Tissue Bank within 2 week(s) of registration[1]
Whole Blood (WB01) 7-10mL drawn into a purple top (EDTA) tube	Prior to or after initiating chemotherapy	Ship to the GOG Tissue Bank the day the specimen is collected[1]

1 Ship specimens to: GOG Tissue Bank / Protocol GOG-0261, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: GOGBanc@nationwidechildrens.org

II. Obtaining a GOG Bank ID

Only one GOG Bank ID (# # # # - # # - G # # #) is assigned per patient. All specimens and accompanying paperwork must be labeled with this coded and confidential tracking number. A GOG Bank ID can be obtained online via the Tissue Bank Portal on the GOG website (under Tools on the Web Menu page).

Obtain the GOG patient study ID for any GOG protocol with specimen requirements before requesting a GOG Bank ID from the Tissue Bank Portal.

Please contact GOG User Support at the GOG Statistical and Data Center if you need assistance (Email: support@GOGStats.org; Phone: 716-845-7767).

III. Requesting Specimen Kits

Specimen kits are not provided for this protocol.

IV. Submitting Formalin-Fixed, Paraffin-Embedded (FFPE) Tissue

A. Requirement

If the patient gives permission for her specimens to be used for this optional translational research component, then participating institutions within the United States are required to submit specimens as outlined in Section I.

Every attempt should be made to provide a block; however, if a block cannot be provided, please submit 10 unstained slides**,** 5 micrometers in thickness on charged slides suitable standard immunohistochemistry.

The type of specimen (block or slides) should be specified on Form SP.

B. Purpose

FFPE primary, metastatic, and/or recurrent tumor will be banked for future research.

C. Time Point

FFPE tumor should be collected prior to initiating chemotherapy**.**

D. Format for Labeling the Specimen

Label FFPE tissue specimens with the GOG protocol number (GOG-0261), GOG Bank ID (# # # # - # # - G # # #), specimen code (FT01), and collection date (mm/dd/yyyy). This specimen may also be labeled with the pathology accession number and block identifier, but must not be labeled with personal identifiers like patient name or initials.

V. Submitting Whole Blood

A. **Requirement**

If the patient gives permission for her specimens to be used for this optional research component, then participating institutions within the United States are required to submit specimens as outlined in Section I.

B. **Purpose**

DNA will be extracted from whole blood specimens. DNA will be banked for future research.

C. **Time Point**

Whole blood can be collected prior to or after initiating chemotherapy.

D. **Format for Labeling the Specimen**

Label the specimen with the GOG protocol number (GOG-0261), GOG Bank ID (# # # # - # # - G # # #), specimen code (WB01), and collection date (mm/dd/yyyy).

E. **Instructions for Submitting Whole Blood**

1. Label the purple top whole blood collection tube(s) (containing EDTA) as described above.

2. Draw 7-10mL of blood into the labeled purple top tube(s).

3. Mix the blood with the EDTA by gently inverting the tube 5-10 times.

4. Ship the whole blood specimen to GOG Tissue Bank the day the specimen is collected*. Whole blood specimens should be stored at room temperature until the specimens can be shipped.

   ** If the whole blood absolutely cannot be shipped the day it is collected, the tube may be placed in the refrigerator overnight. Please note that the blood was refrigerated overnight in the comment box on Form SP (item 15).*

VI. Submitting Form SP

A. Form SP Requirements

Form SP must be submitted online via SEDES for each specimen regardless of specimen submission status. Retain a printout for your records.

Include hard copy of the electronically-completed form should be included with the specimen when shipped to the GOG Tissue Bank or alternate laboratory. Form SP does not need to be sent to the GOG Tissue Bank when specimens are not collected.

B. Instructions for Submitting Form SP Online

Specific instructions for completing Form SP are available on SEDES. Questions should be directed to User Support at the GOG Statistical and Data Center (Email: support@gogstats.org, Phone: 716-845-7767).

VII. Shipping Specimens

A. Formalin-Fixed, Paraffin-Embedded Tissue

FFPE tissue should be shipped using your own container at your own expense to:

GOG Tissue Bank / Protocol GOG-0261
Nationwide Children's Hospital
700 Children's Dr, WA1340
Columbus, OH 43205

Phone: (614) 722-2865
FAX: (614) 722-2897
Email: GOGBank@nationwidechildrens.org

B. Whole Blood

Whole blood should be shipped to the GOG Tissue Bank (address above) *the day the specimens are collected**. Please do not ship blood the day before a holiday. **Use your own shipping container to ship specimens via FedEx using a pre-paid GOG Tissue Bank FedEx air bill.**

** If the whole blood absolutely cannot be shipped the day it is collected, the tube may be placed in the refrigerator overnight. Please note that the blood was refrigerated overnight in the comment box on Form SP (item 15).*

When shipping whole blood specimens, **please be aware that your institution must comply with IATA standards** (www.iata.org). If you have questions regarding your shipment, contact the GOG Tissue Bank at GOGBank@NationwideChildrens.org or by phoning 866-GOG-BANC (866-464-2262).

To ship whole blood specimens you will need (1) a sturdy shipping container (e.g., a cardboard or styrofoam box), (2) a leak proof shipping bag with absorbent material*, (3) a puncture and pressure resistant envelope (e.g., Tyvek envelope), (4) an Exempt Human Specimen Sticker, and (5) a pre-paid FedEx air bill.

**If you will be shipping whole blood specimens from more than one patient, please put each specimen in a separate plastic zip-lock bag before placing the specimens in the shipping bag.*

If you do not have these materials available at your Institution, you may order them from any supplier (e.g., Saf-T-Pak; Phone: 800-814-7484; Website: www.saftpak.com).

Instructions for Shipping Whole Blood Using Your Own Shipping Container*

**Please note that you can include up to four different blood specimens in one biohazard envelope.*

1. Place the whole blood specimen in a biohazard envelope containing absorbent material. Expel as much air as possible before sealing the bag.

2. Wrap the biohazard envelope in bubble wrap or another padded material.

3. Place the padded tube(s) into a Tyvek envelope. Expel as much air as possible before sealing the envelope.

4. Place the Tyvek envelope in a sturdy shipping contained (e.g., cardboard FedEx box).

5. Insert a copy of the SP Form(s) into the box.

6. Attach an Exempt Human Specimen Sticker to the outside of the shipping container.

7. Print a pre-paid FedEx air bill using the Kit Management application (found under Data Entry on the Web Menu page) and attach the air bill.

   Make arrangements for FedEx pick-up through your usual institutional procedure or by calling 800-238-5355. Ship the specimens and transmittal forms to the GOG Tissue Bank via FedEx Priority Overnight delivery. **Please ship specimens Monday through Friday for Tuesday through Saturday delivery.** If the whole blood is collected on a Friday, select "yes" for Saturday delivery when completing the FedEx air bill. **Saturday delivery is only available for the shipment of whole blood.**

VIII. Banking Specimens

The GOG Tissue Bank will be responsible for all activities associated with receiving, banking, and distributing clinical specimens.

Upon receipt of specimen shipments, the GOG Tissue Bank will immediately (1) assess the type, quantity, and condition of the specimens received, (2) complete the appropriate fields on Form SP, (3) enter the specimens into their database system, and (4) store the specimens under the appropriate conditions.

As needed, the GOG Tissue Bank will work with the GOG Statistical and Data Center to reconcile specimen identifiers, information, condition, and quality.

A. FFPE Tissue

FFPE tissue will be received as a block or unstained slides. The GOG Tissue Bank will make sure that each block, slide, or scroll is labeled appropriately.

B. Whole Blood

Whole blood will be processed by the Bank to isolate DNA. DNA will be stored at the Bank. Bank staff will make sure each whole blood and subsequent DNA specimen is labeled appropriately.

IX. Distributing Specimens for Laboratory Testing

The GOG Statistical and Data Center and GOG Tissue Bank will coordinate the distribution of specimens to approved investigators for laboratory testing. Specimen selection will be based on information regarding specimen procurement and condition as

well as patient eligibility, evaluation criteria, statistical considerations, and relevant clinical information.

For each shipment, an inventory of all specimens sent will be provided to the investigator and the Statistical and Data Center.

Investigators will not be given access to any personal identifiers.

Investigators will be responsible for the direct supervision and oversight of the laboratory testing performed and for keeping accurate records of all specimen testing.

Investigators will ensure that the laboratory testing results are linked to the appropriate specimen-specific identifiers and are responsible for transferring relevant laboratory data to the Statistical and Data Center.

X. Banking Specimens for Future Research

Specimens will remain banked at the GOG Tissue Bank and made available only for approved research projects if the patient has provided permission for the use of her specimens for future cancer and/or non-cancer research. The patient's choices will be recorded on the informed consent document the patient signs and electronically via the online Specimen Consent Application.
GOG Institutions can amend a patient's choices regarding the future use of her specimens <u>at any time</u> if the patient changes her mind.

If the patient does not give permission for the use of her specimens, the GOG Tissue Bank will be instructed to destroy (incinerate) any remaining specimens to insure that the patient's wishes are honored.

APPENDIX IV

CARBOPLATIN DOSE CALCULATION INSTRUCTIONS **(3/21/2011) (04/02/2012)**

1) The Cockcroft-Gault formula will be used in GOG trials.
2) Conversion of IDMS creatinine levels to "non-IDMS" values will not be permitted.
3) The carboplatin calculation tool is available on the GOG website (Web Menu, Tools).

Dosing of Carboplatin:

1) The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.

2) The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin **will not** need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

3) Carboplatin doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for <10% weight changes.

4) At the time of dose modification, if the patient's age had changed (the patient has had a birthday), the site can use the current age.

5) In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using a **minimum value of 0.7 mg/dl**.

6) For trials where patients enter and are treated within less than or equal to 12 weeks of surgery: If a more appropriate (higher**)** baseline creatinine value is available from the pre-operative period (within 4 weeks of surgery date), that value may also be used for the initial estimation of GFR.

CALVERT FORMULA:
Carboplatin dose (mg) = target AUC x (GFR + 25)
NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.
Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.
The maximum allowed doses of carboplatin are:
AUC 6 = 900 mg
AUC 5 = 750 mg
AUC 4 = 600 mg
For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (ml/min) is calculated by the method of Cockcroft-Gault using the following formula:

$$\textbf{Creatinine Clearance (mL/min)} = \frac{\textbf{[140-Age (years)] x Weight (kg) x 0.85}}{\textbf{72 x serum creatinine (mg/dl)}}$$

Notes:

1) Weight in kilograms (kg):
   a. Body Mass Index (BMI) should be calculated for each patient. A BMI calculator is available at the following link: http://www.nhlbisupport.com/bmi/
   b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25.
   c. **Adjusted** weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**.
   d. Adjusted weight calculation:
      Ideal weight (kg) = (((Height (cm)/2.54) – 60) x 2.3) + 45.5
      Adjusted weight (kg) = ((Actual weight – Ideal weight) x 0.40) + Ideal weight

2) The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor).

At the time of a dose modification for toxicity:

If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose

APPENDIX V **(04/02/2012)**

General Chemotherapy Guidelines:

- For 21 or 28 day cycles, a patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.
- It will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window before and after the protocol-defined date" for "Day 1" treatment of 21 or 28 day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due).
- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window," for example; "Day 8 chemotherapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" can be given on Day 14, Day 15, or Day 16.
- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).
- Chemotherapy doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy does recalculated for <10% weight changes.
- Maximum body surface area used for chemotherapy dose calculations will be 2.0 m^2. For chemotherapy dose calculations that use mg/kg, there will be no maximum kilogram amount used (doses will be calculated on actual weight in kg).