Larry J. Copeland, M.D.
President

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

Laura L. Reese
Executive Director of Operations

GOG® FOUNDATION, INC.

Robert S. Mannel, M.D.
Vice President

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

Mary C. Sharp
Chief Financial Officer

SUMMARY OF CHANGES

For Protocol Amendment #3 to: GOG-0277

NCI Protocol #: GOG-0277
Local Protocol #: GOG-0277

NCI Version Date: 12/07/2017

#	Section	Page(s)	Change
1.	Title Page	1	• NCI Version Date is now 12/07/2017. • Includes Revisions #1-3. • Danielle Enserro, PhD is now the Study Statistician.
2.	ICD	1	NCI Version Date is now 12/07/2017. No additional changes have been made to the ICD.

PROTOCOL GOG-0277 (IRCI 001)

A PHASE III RANDOMIZED TRIAL OF GEMCITABINE (NSC# 613327) PLUS DOCETAXEL (NSC# 628503) FOLLOWED BY DOXORUBICIN (NSC# 123127) VERSUS OBSERVATION FOR UTERUS-LIMITED, HIGH-GRADE UTERINE LEIOMYOSARCOMA **(10/28/2013)**

NCI Version Date 12/07/2017

Includes Revisions #1-3

POINTS:
PER CAPITA - 20
MEMBERSHIP -6

Lead Organization: NRG/NRG Oncology **(02/16/2015)**

STUDY CHAIR: GOG **(10/28/2013)**	STUDY CO-CHAIR
MARTEE L. HENSLEY, M.D.	JAMES HOFFMAN, MD.
MEMORIAL SLOAN-KETTERING CANCER CENTER	See GOG Website Directory
300 E. 66th Street, Suite 1355	
NEW YORK, NY 10065	PATHOLOGIST
646-888-4222	HELEN E. MICHAEL, M.D.
FAX: 212-717-3272	See GOG Website Directory
hensleym@mskcc.org	
	STATISTICIAN
NURSE CONTACT **(10/28/2013)**	DANIELLE ENSERRO, Ph.D.
KATHLEEN O'CONNOR, RN	NRG ONCOLOGY SDMC-BUFFALO
MEMORIAL SLOAN-KETTERING CANCER CENTER	ELM AND CARLTON STREETS
1275 YORK AVE, H907	BUFFALO, NY 14263
NEW YORK, NY 10065	716-845-5702
212-639-2252	FAX: 716-845-8393
FAX: 212-639-8895	enserrod@nrgoncology.org
oconnor@mskcc.org	
	STUDY CHAIR: NCRN **(10/28/2013)**
	HELEN HATCHER, M.D.
	UNIVERSITY OF CAMBRIDGE
	ONCOLOGY DEPARTMENT
	BOX 193 (R4)
	ADDENBROOKE'S HOSPITAL
	HILLS ROAD
	CAMBRIDGE CB2 0QQ.
	ENGLAND, UNITED KINGDOM
	T: +44 01223 769309
	hh321@medschl.cam.ac.uk

OPEN TO PATIENT ENTRY JUNE 4, 2012
REVISED OCTOBER 28, 2013
REVISED FEBRUARY 16, 2015
CLOSED TO PATIENT ENTRY SEPTEMBER 20, 2016

PROTOCOL GOG-0277 (IRCI 001)

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NCI Version Date 12/07/2017
Includes Revisions #1-3

STUDY CHAIR: EORTC Gynecological Cancer Group (GCG) **(10/28/2013)**	STUDY CHAIR: EORTC (Soft Tissue Bone Sarcoma Group (STBSG) **(10/28/2013)**
PETRONELLA BEATRIX OTTEVANGER	ANDERS KRARUP-HANSEN
RADBOUD UNIVERSITY NIJMEGEN	HERLEV HOSPITAL –UNIVERSITY COPENHAGEN
MEDICAL CENTRE	HERLEV RINGVEJ
PO BOX 9101-GEERT GROOTEPLEIN 10	2730 HERLEV
6500 HB NIJMEGEN	DENMARK
NETHERLANDS	+45 44535300
+31 243610353	Anders.Krarup-Hansen@regionh.dk
FAX: +31 243540788	
E-MAIL: p.ottevanger@onco.umcn.nl	PATHOLOGIST: EORTC **(10/28/2013)**
	CYRIL FISHER
	DEPT OF HISPATHOLOGY
	ROYAL MARSDEN HOPSITAL-CHELSEA, LONDON
	FULHAM ROAD 203
	GB LONDON SW3 6JJ
	UNITED KINGDOM
	+44 2078082631
	FAX: +44 2078082578
	E-MAIL: Cyril.fisher@rmh.nhs.uk

OPEN TO PATIENT ENTRY JUNE 4, 2012
REVISED OCTOBER 28, 2013
REVISED FEBRUARY 16, 2015
CLOSED TO PATIENT ENTRY SEPTEMBER 20, 2016

PROTOCOL GOG-0277 (IRCI 011)

A PHASE III RANDOMIZED TRIAL OF GEMCITABINE (NSC# 613327) PLUS DOCETAXEL (NSC# 628503) FOLLOWED BY DOXORUBICIN (NSC# 123127) VERSUS OBSERVATION FOR UTERUS-LIMITED, HIGH-GRADE UTERINE LEIOMYOSARCOMA

NCI Version Date 12/07/2017
Includes Revisions #1-3

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

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 **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		

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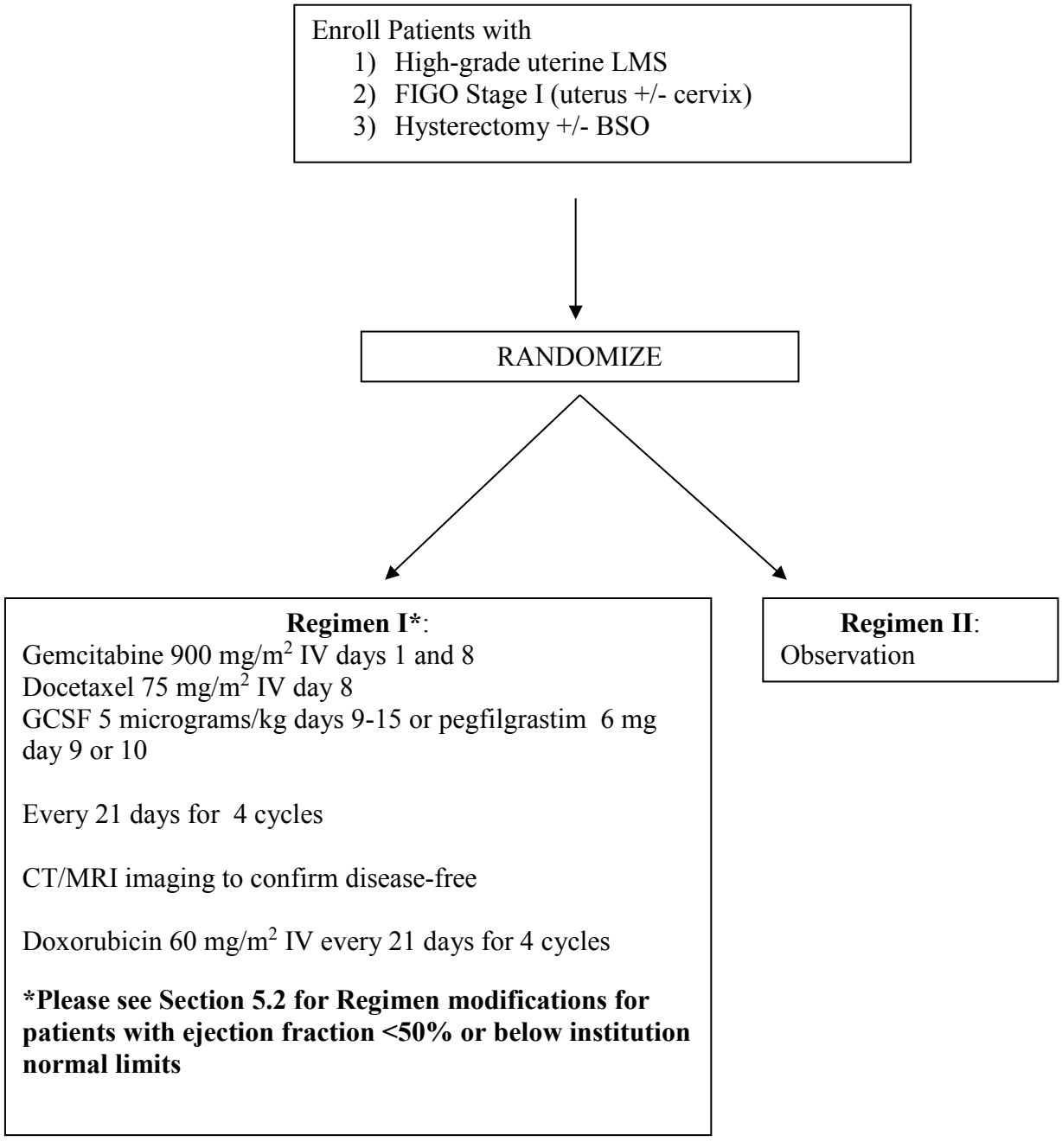
SCHEMA **(10/28/2013)**

ATTENTION: EORTC and NCRN Sites: Please refer to your site-specific appendices (Appendices III and IV) for important site-specific protocol information



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1.0 OBJECTIVES

1.1 Primary Objectives

1.11 To determine whether overall survival of patients with uterus-limited high-grade leiomyosarcoma is superior among patients assigned to treatment with adjuvant gemcitabine plus docetaxel followed by doxorubicin compared to patients assigned to observation.

1.2 Secondary Objectives

1.21 To determine whether treatment with adjuvant gemcitabine plus docetaxel followed by doxorubicin improves recurrence-free survival of patients with uterus-limited high-grade leiomyosarcoma compared to observation.

1.22 To explore the impact of potential predictors of recurrence or death such as patient age, and institution reported tumor size, cervix involvement (yes or no), and mitotic rate.

2.0 BACKGROUND AND RATIONALE

2.1 Rationale for a randomized trial of adjuvant systemic therapy in uterine LMS

Patients with early-stage, high-grade uterine leiomyosarcoma (LMS) have a 50-70% chance of relapse/recurrence of disease. Recurrences may be distant or local or both. In one GOG study of prognostic factors for recurrence of LMS, only 14% of patients with stage I or II disease had isolated pelvic recurrences as the site of first recurrence. Adjuvant pelvic radiation can decrease local recurrence rates, but has not been shown to increase overall survival. In the EORTC randomized trial of adjuvant whole pelvic radiation v. observation for FIGO stage I and II uterine sarcomas, the recurrence rates were approximately 50% in both arms of the study. The percentage of leiomyosarcoma patients remaining progression-free at 2 years in that study was approximately 58%, and the percentage of all patients (both uterine LMS and uterine carcinosarcoma) that remained progression-free at 3 years was 52%.

A recent prospective phase II study of adjuvant gemcitabine plus docetaxel followed by doxorubicin for women with uterus-limited high-grade LMS was conducted by the Sarcoma Alliance for Research through Collaboration (SARC) and the results were presented at the American Society of Clinical Oncology (Hensley, ASCO 2010). In that study (SARC005), 47 women with uterus-limited high-grade LMS were enrolled over 3 years' time. All patients were treated with adjuvant gemcitabine + docetaxel for four cycles. Provided that repeat CT imaging showed no evidence of disease, patients then received four cycles of doxorubicin. All patients were followed with CT imaging every 3 months for 2 years, then every 6 months for 3 years.

The primary endpoint of that study was the progression-free survival at 2 years. 12/46 evaluable patients recurred (26%) at a median time of 12.6 months (range 3-39). Recurrence sites: lung-5, liver-1, pelvis-4, both-1, bone+liver-1. With median follow-up of 27.3 months, 78.4% of women remain progression-free at 2 years from diagnosis (95% confidence interval 67-99%). Median progression-free survival (PFS) is 39.3 months (95% confidence interval 31.6-not yet reached). The probability that 2-year PFS is ≥50% is > 0.999. The probability that 2-year PFS is ≥70% is 0.855. The conclusion was that 78% of women with uterus-limited LMS treated with adjuvant GT followed by D remain progression-free at 2 years, with median follow-up of 27.3 months. This compares favorably with historical estimates of PFS. The updated results of this study have been submitted to the Connective Tissue Oncology Society (CTOS, annual meeting October 2011). Although these data are not yet published, the principal investigator (Hensley) provided personal communication that the 3 year PFS is about 52%.

Despite these promising data, SARC005 is still, at best, a single-arm study without a control group, and the 3-year disease-free survival rate does not appear to be substantially better than the outcomes observed in the EORTC adjuvant radiation study. The research question of whether adjuvant chemotherapy improves survival for women with early stage high grade LMS remains unanswered. The ideal strategy for answering this research question is with a randomized trial with observation as the control arm.

2.2 Rationale for gemcitabine + docetaxel followed by doxorubicin as the experimental arm of an adjuvant treatment trial

Doxorubicin remains a standard first-line treatment for patient with advanced soft tissue sarcoma. Because of its proven activity in metastatic disease, doxorubicin has been studied as adjuvant therapy. Adjuvant doxorubicin or epirubicin-based chemotherapy has been beneficial in some trials of soft-tissue sarcomas, but these studies have included patients with differing histologies and differing disease sites. Adjuvant chemotherapy with doxorubicin (60 mg/m^2 every 3 weeks for 8 cycles) has been studied in one randomized trial that enrolled patients with either carcinosarcoma of the uterus or leiomyosarcoma of the uterus. Patients enrolled on the study may have had pelvic radiation at physician discretion. In this study, adjuvant doxorubicin did not improve survival in the total patient population. However, among the subgroup of patients with leiomyosarcoma, adjuvant therapy with doxorubicin decreased the risk of relapse (44% v. 61%). The sample size was not large enough for this difference in this subgroup to be statistically significant. These data may, however, be used to support the inclusion of doxorubicin in an adjuvant therapy strategy for LMS.

The rationale for testing gemcitabine and docetaxel as part of an adjuvant strategy for uterus-limited LMS is that gemcitabine-docetaxel achieves moderately high

objective response rates in patients with measurable metastatic disease. The Gynecologic Oncology Group conducted a phase II trial for women with advanced, unresectable uterine leiomyosarcoma who had progressed after one prior cytotoxic regimen (gemcitabine-docetaxel as second-line therapy). Ninety percent of the patients had received prior doxorubicin-based therapy. Three of 48 patients (6.3%) achieved complete responses, and 10 (20.8%) achieved partial responses (assessed by RECIST) for an overall objective response rate of 27%. An additional 50% of women had stable disease lasting a median duration of 5.4 months. The median number of cycles per patient was 5.5 (range 1-22). The percentage of patients remaining progression-free at 3 months was 73%, and the percentage progression-free at 6 months was 52%. Median progression-free survival was 5.6+ months (range 0.7 – 27+ months). The median duration of objective response was 9+ months (range 3.9 – 24.5+ months).

The Gynecologic Oncology Group subsequently conducted a prospective phase II trial to assess the efficacy of fixed dose-rate gemcitabine plus docetaxel in women with advanced uterine leiomyosarcoma who had received no prior cytotoxic treatment (first-line treatment). Objective responses were observed in 35.8% of patients with complete responses in 4.8%, and partial responses in 31%, (90% confidence interval for the overall response rate, 23.5 to 49.6%). An additional 26.2% had stable disease. Half of the patients received six or more cycles of study treatment. The median progression-free survival was 4.4 months (range 0.4 to 37.2+ months). Among the patients with objective response, median response duration was six months (range 2.1 to 33.4+ months). Median overall survival was 16+ months (range 0.4 - 41.3 months).

2.3 Rationale for observation as the control arm of an adjuvant treatment trial

The current standard of care for management of women with completely resected, uterus-limited, high grade LMS is observation. No intervention has been proven in a prospective, randomized trial to improve recurrence-free or overall survival. In a discussion among potential international collaborators (EORTC and Cancer Research-NCRN (UK), the consensus of the group was that the scientifically correct control arm is observation. **(10/28/2013)**

2.4 Rationale for every 4 month imaging

With a secondary endpoint of recurrence-free survival (RFS), we will need to image patients in order to determine whether there is evidence of recurrence. Although SARC005 had patients undergo imaging every 3 months, an increase in the imaging interval to every 4 months to decrease resource use and radiation exposure is reasonable. Surveillance imaging for soft tissue sarcoma is in accordance with published guidelines from the American College of Radiology (http://www.acr.org/SecondaryMainMenuCategories/quality_safety/app_criteria.aspx). Patients on this study will have approximately 16 CT scans over 5 years. This level of radiation exposure is not expected to significantly increase the risk

of cancer, particularly in a population that is at high risk to die of the existing cancer (Zondervan, Lee, 2011)[1].

Provided that imaging occurs at the same time point in both arms, RFS will be a reliable endpoint.

While it has traditionally been thought that most recurrences of LMS happen within the first 2 years of diagnosis, we have observed a shift in the timing of recurrences among patients treated on SARC005. There were few recurrences in years 1 and 2, but more recurrences in year 3. Thus, every 4 month imaging for 3 years, then every 6 months for 2 additional years (total of 5 years of required imaging) is a reasonable schedule. This schedule was agreed upon among the international collaborators at the June 2011 meeting.

International collaborators requested the flexibility of using MRI of the abdomen and pelvis plus CT of the chest as a surveillance strategy. Thus, the surveillance imaging on this study will be either CT chest/abdomen/pelvis or MRI abdomen/pelvis + CT chest.

2.5 Rationale for international collaboration with EORTC and Cancer Research-NCRN (UK) **(10/28/2013)**

Although there are some concerns about whether a phase III trial with observation as the control arm may be difficult to accrue, discussion with international collaborators led to the consensus that observation as the control arm is the best scientific design, and that most patients, when told that chemotherapy has not been shown to benefit in terms of either disease-free or overall survival, would be comfortable enrolling on a trial that has an observation arm. The group discussed that in order to facilitate accrual, it is useful to reassure patients that if there is evidence of recurrence then chemotherapy or resection or other appropriate therapy would be offered at that time.

International collaboration raises some logistical issues, which were discussed at the June 2011 meeting. We plan to allow each group (GOG, EORTC, and NCRN) to use their current standards for review of eligibility criteria, histologic review, and imaging for both eligibility and evidence of recurrence. We do not plan for central review of imaging studies. RECIST will be used for determination of recurrence.

We do plan for central histologic review: each group will assign a pathologist to be a co-investigator for the group for this study. The three pathologists will set up a mechanism for review of slides or digital images of slides among the pathologists of the three groups. This could be done with digital images or in person in conjunction with a meeting. We will not plan on real-time review of pathology slides prior to enrollment. Each group will follow its current standards for pathology review. On a once or twice a year basis, designated pathologists

from each group will arrange to review representative patient slides from the already-enrolled patients. This cross-group pathology review may be done in person or with digital images.

2.6 Rationale for primary endpoint of overall survival

Many recurrences among patients with uterine LMS are not accompanied or signaled by symptoms and only detected on scans. This suggests that patient benefit may be more appropriately measured by survival. Relative activity of the combination arm can be evaluated by recurrence-free survival assuming surveillance is standardized across arms. In the observation control arm, treatment will be delayed until recurrence is documented. In the absence of a survival benefit with multi-agent chemotherapy, with or without a RFS benefit, adjuvant treatment of all patients upfront with such chemotherapy would be called into question. This would be even more so if the recurrences on the observation arm were treated with the study regimen. Treatment at the time of recurrence may be highly variable: some patients have late, isolated recurrences which are resectable; other patients may recur quickly but respond well to treatment with chemotherapy; and still others will have rapidly progressive-treatment-refractory disease. In this rare tumor, we would not be able to control for the down-stream management of recurrences.

While a RFS endpoint requires smaller sample size and study duration, with international collaboration, overall survival will be the primary endpoint. The study is designed to detect an increase in overall survival to 48 months with adjuvant chemotherapy versus 30 months without. It is thought that living an average of eighteen months longer is likely to be worth the six months spent on chemotherapy for most women. The RFS endpoint will help us estimate the difference between treatment arms in the median number of months alive and recurrence-free.

Uterine leiomyosarcoma is a rare disease with a high risk of recurrence. Currently, the standard of care after complete resection of uterus-limited disease is observation, although it is recognized that the recurrence rate is 50-70%. No adjuvant intervention has been shown in a prospective randomized trial to diminish this risk. Adjuvant whole pelvic radiation was no better than observation in a prospective phase III trial [4]. Adjuvant chemotherapy as delivered in the prospective phase 2 trial SARC005 showed a promising 2-year progression-free survival rate but in the absence of a control arm we cannot conclude that adjuvant chemotherapy improves recurrence-free or overall survival.

The proposed trial would establish the standard of care for adjuvant treatment of high-risk uterus-limited LMS. If the study shows a clinically meaningful improvement in overall survival with chemotherapy compared with observation, adjuvant chemotherapy can be recommended to women after resection of uterus-limited disease. If chemotherapy shows no improvement in overall survival, then

women can be spared the toxicities of chemotherapy in the adjuvant setting, with subsequent treatment delayed until recurrence.

2.7 Inclusion of Women and Minorities

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

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

3.11 Patients with high risk uterine LMS, FIGO stage I (confined to corpus +/- cervix). Patients with known uterine serosa involvement are not eligible. Patients should have had, at least, a complete hysterectomy (including removal of the cervix). Bilateral salpingo-oophorectomy is not required.

3.111 Institutional pathology review calls the uterine leiomyosarcoma "high grade."

3.112 Additionally, if the pathology report indicates a mitotic rate, the mitotic rate should be greater than or equal to 5 mitoses/10 high power field.

All patients must be no longer than 12 weeks (3 months) from surgical resection of cancer at the time of enrollment on study. If a patient requires a second operation to complete her surgery, i.e. trachelectomy to remove the cervix and/or BSO, the 12 weeks may be counted from the time of the second operation.

Patients who had a "morcellation" hysterectomy procedure that involved morcellation within the peritoneal cavity are eligible IF a second operation is performed and biopsies from the second procedure show no evidence of leiomyosarcoma. **(10/28/2013)**

3.12 All patients must have no evidence of persistent or metastatic disease as documented by a post-resection CT of the chest/abdomen/pelvis or by CT chest + MRI abdomen/pelvis. The post-resection imaging studies should be performed within 4 weeks of registration on study.

3.13 Patients must have adequate:

3.131 Bone marrow function: Absolute neutrophil count (ANC) greater than or equal to 1,500/mcl (ANC 1.5 x 10^9/liter (L).
Platelets greater than or equal to100,000/mcl (Platelets 100 x 10^9/L).
Hemoglobin greater than 8.0 g/dl (= 80 g/L; or 4.9 mmol/L).

3.132 Renal function: creatinine less than or equal to 1.5 x institutional upper limit normal (ULN.)

3.133 Hepatic function: Bilirubin within normal range. SGOT (AST), SGPT (ALT), and alkaline phosphatase less than or equal to 2.5 x ULN. Patients with a history of Gilbert's syndrome may be eligible provided total bilirubin is less than or equal to 1.5 x ULN and the AST, ALT, Alkaline phosphatase meet the criteria detailed.

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

3.14 Patients with GOG performance status of 0 or 1; ECOG performance status of 0 or,1; or KPS >= 80%.

3.15 Patients who have met the pre-entry requirements specified in Section 7.0.

3.16 Patients must have signed an approved informed consent.

3.17 Patients participating through U.S. sites must sign an approved and authorization permitting release of personal health information.

3.18 Patients must be a minimum of 18 years of age.

3.19 Patients should be free of active infection requiring antibiotics (with the exception of an uncomplicated UTI).

3.2 Ineligible Patients

3.21 Patients who have had prior therapy with docetaxel or gemcitabine or doxorubicin at any time in their history.

3.22 Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer, are ineligible 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 with a history of severe hypersensitivity reaction to Taxotere® (docetaxel) or other drugs formulated with polysorbate 80.

3.24 Patients with GOG performance status of 2, 3 or 4; or ECOG performance status of 2, 3 or 4.

3.25 Patients who are breast-feeding.

3.26 Patients with a known history of congestive heart failure or cardiac ejection fraction < 50% (or less than institutional normal limits). ECHO or MUGA is not required prior to enrollment. For patients assigned to the chemotherapy arm, an ECHO or MUGA must have been done within 6 months of day 1 of gemcitabine-docetaxel treatment.

Patients who enroll on study and are randomized to Regimen I (chemotherapy) and then are found on baseline ECHO or MUGA to have cardiac ejection fraction <50% or below institutional normal will remain ON study. Such patients will

receive gemcitabine + docetaxel for 4 cycles, as detailed in Section 5.2, but will NOT receive any doxorubicin treatment. They will continue treatment follow-up as outlined for all patients assigned to Regimen I. **(10/28/2013)**

3.27 Patients with a history of prior whole pelvic radiation.

3.28 Concurrent treatment with hormone replacement therapy is permitted at the discretion of the treating physician. Patients who have been taking hormonal/hormone blocking agents for breast cancer or breast cancer prevention or other indication are eligible. Use of anti-hormonal agents (tamoxifen, medroxyprogesterone, aromatase inhibitors) is permitted at the discretion of the treating physician. Documentation of concurrent medications is required.

3.29 Patients with recurrent uterine LMS.

3.210 Patients who are known to be HIV (human immunodeficiency virus) positive are not eligible due to the high risk for infectious complications of the myelosuppressive therapy used in the experimental arm of this study.

3.211 Patients with gross residual or metastatic tumor findings following complete surgical treatment for uterine LMS.

4.0 STUDY MODALITIES

4.1 Docetaxel (Taxotere® RP-56976, NSC #628503)

4.11 Formulation: Docetaxel is supplied as a sterile, non-pyrogenic, non-aqueous viscous solution in single dose vials containing 20mg/0.5mL or 80mg/2mL of docetaxel. Each mL contains 40mg docetaxel (anhydrous) and 1040mg polysorbate 80.

4.12 Docetaxel requires dilution prior to use. A sterile, non-pyrogenic, single dose diluent is supplied for this purpose. The diluent for docetaxel contains 13% (w/w) ethanol in water for injection and is supplied in vials.

4.13 Storage: Unopened vials of docetaxel are stable to the date indicated on the package when stored between 2 and 25°C (36 and 77°F). Protect from light.

4.14 Preparation: Docetaxel must be combined with its supplied diluent (final concentration = 10mg/mL) and then further diluted prior to infusion. Docetaxel should be diluted in 0.9% Sodium Chloride for Injection, USP or 5% Dextrose Injection, USP to produce a final concentration of 0.3 to 0.74mg/mL. The fully prepared docetaxel infusion solution should be used within 4 hours (including the infusion duration).NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.

4.15 Administration: Docetaxel is given intravenously as a one-hour infusion. All patients should be pre-medicated with oral corticosteroids (for example: dexamethasone 16 mg per day (8 mg BID)) for three days starting one day prior to docetaxel administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions

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

4.17 Supplier: Docetaxel is commercially available. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

4.2 Gemcitabine, Gemzar ® (NSC #613327)

4.21 Formulation: Gemcitabine HCl is a nucleoside analog that exhibits anti-tumor activity.

4.22 Supplier/How Supplied: Gemcitabine HCl is commercially available. Gemcitabine is supplied as a white lyophilized powder in sterile single use vials containing 200mg (10 ml) or 1000 mg (50 ml) of gemcitabine as the hydrochloride salt.

4.23 Stability/Storage: Unopened vials of gemcitabine are stable until the expiration date indicated on the package when stored at controlled room temperature between 20 to 25°C (68 to 77° F).

4.24 Preparation: To reconstitute, add 5 ml of 0.9% Sodium Chloride Injection to the 200 mg vials or 25 ml to the 1000 mg vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/ml which includes accounting for the displacement volume of the lyophilized powder. The total volume upon reconstitution will be 5.26 ml or 26.3 ml, respectively. Complete withdrawal of the contents will provide 200 mg or 1 g of gemcitabine, respectively. The appropriate amount of drug may be administered as prepared or further diluted with 0.9% Sodium Chloride Injection to concentrations as low as 0.1 mg/ml. The solution should be clear, colorless to slightly straw colored. Do not administer if discoloration or particulate matter is found. Once the drug has been reconstituted, it should be stored at controlled room temperature and used within 24 hours.

4.25 Administration: The mixed solution will be continuously infused over 70-90 minutes, depending on the dose (See Section 5.2 and Section 6.1).

4.26 Adverse effects:

Hematologic: The following Grade 3 and 4 toxicities can be expected after single agent therapy with doses between 800 and 1250 mg/m^2: neutropenia 25%, leukopenia 9%, anemia 8%, and thrombocytopenia 5%. Infection occurred in 16% of patients; sepsis occurred in less than 1%. 17% of patients experienced hemorrhage of Grade 2 or less.
Gastrointestinal: Nausea and vomiting is frequent, up to 69%, but usually mild to moderate. Grade 3 and 4 nausea and vomiting were noted in 14%. Diarrhea was seen in 19%, stomatitis in 11%, and constipation in 23%.
Pulmonary: Dyspnea was seen in 23%, severe in 3%. Rarely parenchymal toxicity including pneumonitis has been reported. Treatment should be discontinued immediately, if suspicious symptoms occur.
Hepatic: Transient elevation of hepatic enzymes was seen in 70%, however, this was not dose dependent and no increase was noted during prolonged therapy. Serious hepatotoxicity, including liver failure and death, has been reported very rarely.

Fever: This is seen in up to 41%, but usually of a mild degree. Fever may be accompanied by flu-like symptoms in 19%.
Renal: Reversible proteinuria, hematuria are frequent; increased BUN and creatinine in 16% and 8% of patients, respectively. However, renal insufficiency or hemolytic uremic syndrome is very rare. If suspicious symptoms are noted therapy should be discontinued immediately.
Dermatologic/Skin: Alopecia is seen in 15%; a reversible macular or macular-papular rash is seen in 30%; pruritus occurs in 13%. Peripheral edema is seen in up to 20% of the patients treated. Infusion site reactions occurred in 4% of patients.
Neurologic: There was a 10% incidence of mild paresthesias; somnolence occurred in 11% of patients.
Pain at the site of injection: Seen in 48% of patients; Grade 3 in 9%.
Other: Cardiovascular or allergic reactions are seen very rarely.

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

4.3 Filgrastim (G-CSF), Neupogen® (NSC #614629)

4.31 Formulation: Filgrastim (G-CSF), Neupogen® (recombinant granulocyte-colony stimulating factor) is a protein produced by E. Coli into which has been inserted the human G-CSF gene. Filgrastim differs from the natural protein in that the N-terminal amino acid is a methionine and it is not 0-glycosylated. G-CSF functions as a hematopoietic growth factor; it increases the proliferation, differentiation, maturation and release of precursor cells into mature blood cells of the neutrophil lineage. G-CSF has demonstrated *in vitro* effects on mature neutrophils, including an increase expression of chemotactic receptors, enhanced phagocytosis and intracellular killing of certain organisms, as well as enhanced killing of target cells that are bound by antibodies.

Approximately 6,400 patients in US and international based trials have participated in clinical trials of filgrastim to date, and the worldwide commercial populations receiving filgrastim totaled approximately 190,000. The drug has been found to be well tolerated at dosages up to 69 mcg/kg/d given IV or subcutaneously, with no toxic effects attributable to filgrastim. A maximum tolerated dose has not yet been determined.

4.32 Supplier/How Supplied: Filgrastim is commercially available. Filgrastim is supplied as a clear, colorless preservative-free liquid for parenteral administration. The product is available in single use vials and pre-filled syringes.

Single use vials: Single use vials contain filgrastim 300 mcg/ml in a preservative-free solution with 0.59 mg/ml acetate, 50 mg/ml sorbitol, 0.004% Tween 80, 0.035 mg/ml sodium, and water for injection, USP, pH 4.0 to make 1

ml filgrastim. Filgrastim (G-CSF) is commercially available in two vial sizes: 300 mcg/1ml and 480 mcg/1.6 ml.

Single use pre-filled syringes: Single use pre-filled syringes contain either 300 mcg or 480 mcg of filgrastim at a fill volume of 0.5 ml or 0.8 ml, respectively.

4.33 Storage and Stability: Filgrastim should be stored in the refrigerator at 2 - 8°C (36 to 46° F). Avoid shaking. Prior to injection, filgrastim may be allowed to reach room temperature for a maximum of 24 hours. Any vial or pre-filled syringe left at room temperature for greater than 24 hours should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit; if particulates or discoloration are observed, the container should not be used.

4.34 Administration: Filgrastim is administered as a single daily injection by subcutaneous bolus injection, by short IV infusion (15-30 minutes), or by continuous subcutaneous or continuous IV infusion. Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, do not use filgrastim in the period 24 hours before through 24 hours after the administration of cytotoxic chemotherapy.

4.35 Dilution: If required, filgrastim may be diluted in 5% dextrose. Filgrastim diluted to concentrations between 5 and 15 mcg/ml should be protected from adsorption to plastic materials by addition of albumin (human) to a final concentration of 2 mg/ml. When diluted in 5% dextrose or 5% dextrose plus albumin, filgrastim is compatible with glass bottles, PVC and polyfilm IV bags, and polypropylene syringes. Dilution of filgrastim to a final concentration of less than 5 mcg/ml is not recommended at any time. Do not dilute with saline at any time; product may precipitate.

4.36 Precautions: Filgrastim should be used with caution in patients with pre-existing cardiac conditions such as hypertension, angina pectoris and cardiac dysrhythmias. Until further data become available, precaution should be exercised if filgrastim is administered to those patients with myeloid malignancies.

4.37 Pregnancy and lactation: No clinical trials have been performed in pregnant or lactating women. Therefore, administration of filgrastim during pregnancy or lactation is not recommended until further data are available.

4.38 Contraindications: Filgrastim is contraindicated in these patients with known hypersensitivity to *E. coli* -derived proteins.

4.39 Adverse Effects:

Medullary bone pain: Occurring in 20-25% of patients in phase II and III trials. When bone pain was reported it often preceded a rise in the

circulating neutrophil count; it occurred more frequently in patients treated with 20-100 mcg/kg/d of intravenously administered filgrastim, and less often in lower subcutaneous doses. The pain was generally mild to moderate in severity, and usually controlled with non-narcotic analgesics such as acetaminophen.

Other side effects include transient but reversible increases of alkaline phosphatase, lactate dehydrogenase, and uric acid levels. These occurred in 27-58% of patients, without clinical sequelae observed. Transient decreases in blood pressure that did not require clinical treatment were reported in 7/176 patients in Phase III clinical studies following administration of filgrastim. Cardiac events (myocardial infarctions, arrhythmias) have been reported in 11/375 cancer patients receiving filgrastim in clinical studies but the relationship to filgrastim therapy is unknown.

Less frequently reported adverse events related to filgrastim administration include subclinical splenomegaly, exacerbation of pre-existing skin rashes, alopecia, and thrombocytopenia, and cutaneous vasculitis. Ischemic or infarcted colon, sometimes with involvement of other parts of the gastrointestinal tract, has been seen in patients receiving paclitaxel and G-CSF therapy. Patients reporting abdominal discomfort should be monitored closely. The specific etiologic role of paclitaxel, other chemotherapeutic agents, or G-CSF is not entirely defined. It is conceivable that the high doses of chemotherapy used in these studies induced sufficiently severe neutropenia that these patients were at risk for complications based on the myelotoxicity alone. If this is the case, then the use of G-CSF may actually assist in preventing this occurrence in other patients receiving high-dose paclitaxel chemotherapy. A review of the Amgen database of over 10,000 patients treated on company-sponsored trials revealed the occurrence of only one case of typhlitis, two instances of intestinal ischemia, and six occurrences of intestinal perforation. However, it is remotely possible that the G-CSF may have contributed in some unforeseen way to these events.

Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving filgrastim, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving filgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, filgrastim should be discontinued until resolution of ARDS and patients should receive appropriate medical management for this condition.

Rare cases of splenic rupture have been reported following the administration of filgrastim in both healthy donors and patients with cancer. Some of these cases were fatal. Patients who report left upper

abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Rarely, allergic-type reactions have occurred. Since the commercial introduction of filgrastim there have been reports (< 1 in 4,000 patients) of symptoms suggestive of an allergic-type reaction, but in which an immune component has not been demonstrated. These have generally been characterized by systemic symptoms involving at least two body systems, most often skin (rash, urticaria, edema), respiratory (wheezing, dyspnea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first thirty minutes after administration and appeared to occur more frequently in those patients who received filgrastim intravenously. Rapid resolution of symptoms occurred in most cases after administration of standard supportive care, and symptoms recurred in more than half the patients when re-challenged.

*Please see the FDA-approved filgrastim package insert for a comprehensive list of adverse events associated with filgrastim.

4.4 Pegfilgrastim (Neulasta®) (NSC #725961)

4.41 Formulation: Pegfilgrastim is a covalent conjugate of recombinant methionyl human G-CSF (filgrastim) and monomethoxypolyethylene glycol. To produce pegfilgrastim, a 20 kD monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of filgrastim. The average molecular weight of pegfilgrastim is approximately 39 kD.

4.42 Supplier/How Supplied: Pegfilgrastim is commercially available. Pegfilgrastim is supplied in 0.6 ml pre-filled syringes for subcutaneous injection. Each syringe contains 6 mg pegfilgrastim (based on protein weight), in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), sorbitol (30.0 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in water for injection, USP.

4.43 Storage and Stability: Pegfilgrastim should be stored refrigerated at 2 to 8° C (36 to 46° F); syringes should be kept in their carton to protect from light until time of use. Shaking should be avoided. Before injection, pegfilgrastim may be allowed to reach room temperature for a maximum of 48 hours but should be protected from light. Pegfilgrastim left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen, pegfilgrastim should be allowed to thaw in the refrigerator before administration. If frozen a second time, it should be discarded.

4.44 Administration: Pegfilgrastim is a single subcutaneous injection of 6 mg administered once per chemotherapy cycle.

Because of the potential sensitivity of rapidly dividing myeloid cells to cytotoxic chemotherapy, do not use pegfilgrastim for 24 hours after the administration of cytotoxic chemotherapy.

4.45 Precautions: Pegfilgrastim should be visually inspected for discoloration and particulate matter before administration and should not be administered if discoloration or particulates are observed.

4.46 Pregnancy and lactation: No clinical trials have been performed in pregnant or lactating women. Therefore, administration of pegfilgrastim during pregnancy or lactation is not recommended until further data are available.

4.47 Contraindications: Pegfilgrastim is contraindicated in patients with known hypersensitivity to *E. coli* -derived proteins, pegfilgrastim, filgrastim, or any other component of the product.

4.48 Adverse Effects:

Medullary bone pain: The most common adverse event attributed to pegfilgrastim in clinical trials was medullary bone pain, reported in 26% of subjects. This bone pain was generally reported to be of mild-to-moderate severity. Approximately 12% of all subjects utilized non-narcotic analgesics and less than 6% utilized narcotic analgesics in association with bone pain.

Other side effects include reversible elevations in LDH, alkaline phosphatase, and uric acid, which did not require treatment intervention.

One case of splenic rupture has been reported following the administration of pegfilgrastim. Patients who report left upper abdominal and/or shoulder tip pain should be evaluated for an enlarged spleen or splenic rupture.

Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving filgrastim, the parent compound of pegfilgrastim, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving pegfilgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, pegfilgrastim should be discontinued until resolution of ARDS and patients should receive appropriate medical management for this condition.

Allergic-type reactions, including anaphylaxis, skin rash, and urticaria, occurring on initial or subsequent treatment have been reported with filgrastim. In some cases, symptoms have recurred with re-challenge, suggesting a causal relationship. Allergic-type reactions to pegfilgrastim have rarely been reported in post-marketing experience. If a serious allergic reaction or an anaphylactic reaction occurs, appropriate therapy should be administered and further use of pegfilgrastim should be discontinued.

In subjects receiving pegfilgrastim in clinical trials, the only serious event that was not deemed attributable to underlying or concurrent disease or to concurrent therapy was a case of hypoxia.

*Please see the FDA-approved pegfilgrastim package insert for a comprehensive list of adverse events associated with pegfilgrastim.

4.5 Doxorubicin (Adriamycin) NSC #123127)

4.51 Formulation: Doxorubicin is supplied as a sterile, red-orange, freeze-dried powder in 10, 20 and 50 mg single dose vials and a 150 mg multidose vial as doxorubicin hydrochloride for injection only. Doxorubicin is also available as a sterile parenteral, isotonic solution for intravenous injection only, containing no preservative, available in 10, 20, 50 and 75 mg single dose vials and a 200 mg multidose vial.

4.52 Preparation: Doxorubicin hydrochloride for injection 10, 20,50 and 150 mg vials should be reconstituted with 5, 10, 25 and 75 ml respectively, of sodium chloride injection, USP (0.9%) to give a final concentration of 2 mg/dl of doxorubicin hydrochloride. An appropriate volume of air should be withdrawn from the vial during reconstitution to avoid excessive pressure build-up. Bacteriostatic diluents are not recommended. After adding the diluent, the vial should be shaken and the contents allowed to dissolve.

4.53 Storage: The reconstituted solution is stable for 7 days at room temperature and normal light and 15 days under refrigeration (2° to 8°C). It should be protected from sunlight. Discard any unused solution.

4.54 Adverse Events: Severe local tissue necrosis will occur if there is extravasation during administration. Doxorubicin must not be given by the intra-muscular or subcutaneous route.

Dose-limiting toxicities are myelosuppression and cardiotoxicity. Serious irreversible myocardial toxicity with delayed congestive heart failure often unresponsive to any cardiac supportive therapy may be encountered as total dosage approaches 550 mg/m^2. This toxicity may occur at lower cumulative doses in patients with prior mediastinal irradiation or on concurrent cyclophosphamide therapy.

Adverse reactions may include: acute nausea, vomiting, mucositis, and reversible and complete alopecia. Facial flushing may occur if the injection is given too rapidly. Severe cellulitis, vesication and tissue necrosis will occur if doxorubicin is extravasated during administration. Fever, chills and urticaria have been reported occasionally.

Doxorubicin imparts a temporary red coloration to the urine.

4.55 Supplier: Commercially available.

4.56 Administration: Doxorubin is administered by slow IV push through a free-running intravenous access. It is recommended but not required that doxorubicin be given through a central access device in order to decrease the risk for extravasation injury.

It is recommended that doxorubicin be slowly administered by IV push into the tubing of a freely running intravenous infusion of sodium chloride injection, USP or 5% dextrose injection, USP. The tubing should be attached to a Butterfly® needle inserted preferably into a large vein. If possible, avoid veins over joints or in extremities with compromised venous or lymphatic drainage. Doxorubicin should not be mixed with heparin or fluorouracil since it has been reported that these drugs are incompatible to the extent that a precipitate may form.

*Refer to Package Insert for additional information

4.6 Pathology Requirements

4.61 Eligibility Criteria: Patients must have "high grade" leiomyosarcoma of the uterus diagnosed on the institutional pathology report. The tumor must be FIGO stage I (confined to the uterus with or without involvement of the cervix.) Patients with involvement of the uterine serosa are not eligible. If the mitotic rate is reported, it must be at least 5 mitotic figures/10HPF. Patients must have had a complete hysterectomy with removal of the uterine cervix (trachelectomy after supracervical hysterectomy is acceptable if needed to remove the cervix).

The following patients are not eligible: Patients with recurrent uterine leiomyosarcoma, patients with residual, persistent or metastatic leiomyosarcoma after hysterectomy, and patients with a history of other invasive malignancies within the past 5 years (with the exception of non-melanoma skin cancer).

4.62 Requirements: Stained pathology slides are required for central review by the GOG pathology committee to confirm eligibility. At least one H&E stained slide is required to demonstrate the primary high grade uterine leiomyosarcoma with adequate mitotic rate ($\geq$5 MF/10 HPF), nuclear atypia and tumor necrosis (if present).

4.63 See Section 7.2 and 10.2 for additional instructions for submitting the stained pathology slides to the GOG Statistical and Data Center in Buffalo, NY.

5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE

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. 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-0277 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)
Suite 1100
1818 Market Street
Philadelphia, PA 19103
FAX: 1-215-569-0206
CTSURegulatory@ctsu.coccg.org

5.1 Patient Entry and Registration

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

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 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.

OPEN Registration: All site staff 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:

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

Access requirements for OPEN:

- 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 GOG 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.

  Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions

contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

5.2 Treatment Plan

5.21 Randomization will be stratified by country of treating site.

Patients diagnosed with high grade uterine LMS and who have had a hysterectomy will be randomized into one of the two management arms:

REGIMEN I: (10/28/2013)

Patients randomly assigned to Regimen I will be treated as follows:

Gemcitabine 900 mg/m^2 IV over 90 minutes on days 1 and 8

Docetaxel 75 mg/m^2 IV day 8 (pre-medication dexamethasone 4-8 mg p.o. bid for 3 days, starting 12-24 hours prior to docetaxel)

(Gemcitabine is administered prior to docetaxel on day 8)

Filgrastim (GCSF) 5 micrograms/kg (may round to nearest vial size of 300 micrograms or 480 micrograms) subcutaneously days 9-15 or pegfilgrastim 6 mg subcutaneously day 9 or 10

Each cycle is 21 days
Treat for 4 cycles

Repeat CT chest/abdomen/pelvis (or CT chest + MRI abdomen/pelvis) imaging after 4 cycles (no sooner than 3 months from start of study treatment, but no later than 4 months from start of study treatment) of gemcitabine plus docetaxel to confirm continued no evidence of disease (NED).

If NED, no sooner than 3 weeks, but no longer than 8 weeks from cycle 4 day 1 of gemcitabine/docetaxel start:

Doxorubicin 60 mg/m^2 IV every 21 days for 4 cycles (use of central venous catheter access recommended, but not required).

Filgrastim (GCSF) 5 micrograms/kg (may round to nearest vial size of 300 micrograms or 480 micrograms) subcutaneously days 2-8 or pegfilgrastim 6 mg subcutaneously day 2 or 3 is OPTIONAL.

NOTE: Patients who are found, after enrollment, to have a cardiac ejection fraction of <50% or below institutional normal limits will

conclude their adjuvant chemotherapy at the completion of 4 cycles of gemcitabine + docetaxel. They will NOT receive any doxorubicin. They will remain ON STUDY and proceed with follow-up as detailed for all patients assigned to Regimen I.

Follow-up:
Follow patients for recurrence by physical examination and CT chest/abdomen/pelvis (or CT chest +MRI abdomen/pelvis) every 4 months from study entry until 3 years out from the start of study treatment, then every 6 months for the next 2 years. There is a maximum of 5 years of imaging for initial recurrence.

At time of documented recurrence: management of recurrent disease will be at the discretion of the treating physician. Documentation of the site(s) of recurrence and management plan will be required (surgical resection, chemotherapy, radiation, best supportive care, etc).

Chemotherapy administration: See Appendix II for GOG General Chemotherapy Guidelines.

The initial **recommended pre-medication for the docetaxel** is: dexamethasone 8 mg orally X 2 doses the day prior to chemotherapy (Day 7), and 8 mg orally twice daily for the next 2 days (Days 8-9). The dexamethasone dosing schedule may be adjusted at the discretion of the treating physician.

Patients who develop **peripheral edema as a side effect of docetaxel and/or gemcitabine** may be treated with diuretics at the discretion of the treating physician. Recommended treatment for edema includes starting with Hydrochlorothiazide/triamterene (25/37.5) or (25/50) up to 3 times a day, or hydrochlorothiazide (HCTZ) 25-50 mg once or twice daily. Furosemide may be used if Hydrochlorothiazide/triamterene or HCTZ does not adequately control the edema.

REGIMEN II: (10/28/2013)
Observation only

RN (nurse) or MD (physician) telephone call every 3-4 weeks for approximately 24 weeks to document patient-reported toxicities or adverse events (see Section 7.1, Regimen II table).

CT chest/abdomen/pelvis (or CT chest +MRI abdomen/pelvis) imaging after 3 to 4 months from study entry to confirm continued no evidence of disease.

Continue with observation if there is no evidence of disease.

Follow-up:
Follow patients for recurrence by physical examination and CT chest/abdomen/pelvis (or CT chest +MRI abdomen/pelvis) imaging every 4 months from study entry until 3 years out from the start of study treatment, then every 6 months for the next 2 years. There is a maximum of 5 years of imaging for detection of first recurrence.

At time of documented recurrence: management of recurrent disease will be at the discretion of the treating physician. Documentation of the site(s) of recurrence and management plan will be required (surgical resection, chemotherapy, radiation, best supportive care, etc).

5.3 Criteria for removal from treatment

5.31 Inability to tolerate the lowest doses because of toxicity.

5.32 Disease recurrence which is defined by RECIST in section 8.

5.33 Patients may refuse further intervention or completely withdraw consent from the study at any time for any reason. If a patient elects to discontinue further study treatment and/or intervention prior to documentation of recurrent disease and elects to receive alternate therapy, this information should be specifically documented as consent allows.

6.0 TREATMENT MODIFICATIONS

Note: Version 4.0 of the NCI Common Terminology for Adverse Events (CTCAE) is the reference for all grade specifications included in this study's dose modification sections.

6.1 Gemcitabine and Docetaxel Dose level definitions

Study Drug	**1 Level reduction**	**Initial dose level**
Gemcitabine	675 mg/m^{2}over 70-90 minutes	900 mg/m^2 over 90 minutes
Docetaxel	60 mg/m^2	75 mg/m^2

6.2 Doxorubicin Dose level definitions: **(10/28/2013)**

Study Drug	**1 Level reduction**	**Initial dose level**
Doxorubicin	45 mg/m^2	60 mg/m^2

Note: Patients who require a dose reduction because of a toxicity meeting criteria below are permitted ONE dose reduction. If toxicity recurs of a severity that would require another dose reduction, a second dose reduction is NOT permitted. Instead, treatment with the regimen that caused the additional toxicity should be discontinued.

6.3 Hematologic toxicity during EITHER **gemcitabine + docetaxel** OR **doxorubicin (10/28/2013)**

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

6.311 Patients will receive prophylactic growth factors [filgrastim (G-CSF), or pegfilgrastim (Neulasta)] on Day 9 of each cycle of treatment with gemcitabine + docetaxel as detailed in Section 5.2. Use of [filgrastim (G-CSF), or pegfilgrastim (Neulasta)] on Day 2 of treatment with doxorubicin is optional.

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

6.313 Patients may receive erythropoietin (EPO), iron supplements, and/or transfusions as clinically indicated for management of anemia.

Treating physicians should be aware of the recent changes in prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit); this information notes a potential risk of shortening the time to tumor progression or disease-free survival and recommends that these agents be administered only to avoid red blood cell transfusions. They do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted.

6.314 Patients may NOT receive amifostine or other protective reagents, as this would be considered a protocol violation.

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

6.33 Subsequent cycles of therapy will not begin until the ANC is ≥ 1000 /mcl (ANC ≥ 1.0 x 10^9/liter (L). and the platelet count is ≥ 100,000/mcl (100 x 10^9/L) Gemcitabine and docetaxel, or doxorubicin (whichever is applicable) will be delayed for a maximum of two weeks until these values are achieved. Patients whose counts fail to recover adequately within a two week delay will not receive further study treatment with that regimen. If the patient was on the gemcitabine + docetaxel section of the adjuvant treatment, and the ANC and platelets recover after no longer than a 3 week delay, the patient may proceed on to the doxorubicin portion of the study. If again there is a failure to recover ANC and platelets within a 2 weeks delay during treatment with doxorubicin, then study treatment will be discontinued.

6.34 For first occurrence of febrile neutropenia (ANC < 1,000/mcl and fever ≥ 38.5 C), and/or documented Grade 4 neutropenia persisting ≥ 7 days, OR Grade 3 thrombocytopenia (platelet count 25,000 to < 50,000/mcl) that is associated with bleeding or need for transfusion, OR Grade 4 thrombocytopenia (platelet count < 25,000/mcl), reduce the doses of both gemcitabine and docetaxel, or doxorubicin (whichever is applicable), by one dose level on all subsequent cycles. For a second episode of febrile neutropenia occurring despite dose reduction with the current regimen, treatment with that regimen should be discontinued. As in section 6.23, if the febrile neutropenia events occurred during treatment with gemcitabine + docetaxel, and patient has recovered from the toxicity after no longer than a 3 week delay, the patient may proceed on to the doxorubicin portion of the study. If the patient experiences a febrile neutropenia event during doxorubicin, study treatment should be discontinued.

If treatment with gemcitabine + docetaxel is stopped for toxicity, the patient may proceed on to treatment with doxorubicin provided blood counts, liver function, and other toxicities permit chemotherapy treatment with doxorubicin within 3 weeks of the discontinuation of the gemcitabine + docetaxel.

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

6.35 In addition to the dose modifications listed above **Day 8 Gemcitabine and Docetaxel** dose adjustments should be made according to the table below:

Study Drug	**ANC ≥ 1000**/mcl **AND Plt ≥ 100,000**/mcl	**ANC 500-999**/mcl **OR Plt 50,000-99,000**/mcl	**ANC < 500**/mcl **OR Plt < 50,000**/mcl
Gemcitabine	100% of dose	For patients at the initial dose level of Table 6.1, give 675 mg/m^2 over 70-90 minutes. For patients at the 1 level dose reduction dose of Table 6.1, give 500 mg/m^2	Omit on day 8
Docetaxel	100% of dose	For patients at the initial dose level of Table 6.1, give 60 mg/m^2. For patients at the 1 level dose reduction dose of Table 6.1, give 50 mg/m^2	Omit on day 8

Note: ANC (absolute neutrophil count) ≥1000/mcl = ANC 1.0 x 10^9/liter (L).
Plt (platelets) ≥ 100,000/mcl = Plt 100 x 10^9/L.

Dose reduction on Day 8 does not count as one of the two permitted protocol dose reductions for toxicity. The next cycle may be started at previous doses, provided that blood counts have recovered as detailed in 6.23. If a dose reduction is required on Day 8 of a cycle, subsequent Day 8 doses should only be reduced in subsequent cycles if the criteria for reduction or omission of the day 8 doses are met on that cycle's Day 8 of treatment.

6.4 Hepatic Dysfunction during **gemcitabine + docetaxel (10/28/2013)**

6.41 If bilirubin increases to greater than institutional upper limits of normal when checked on Day 1, repeat the bilirubin on or prior to Day 8, prior to giving the docetaxel. If the bilirubin has returned to normal, proceed with docetaxel on Day 8. If the bilirubin remains greater than institutional normal limits on Day 8, give only gemcitabine on Day 8. The patient will thus receive no docetaxel that cycle. If the bilirubin does not recover by Day 8 of the next cycle, study treatment may be continued but will continue without docetaxel until the bilirubin returns to within institutional normal limits. If the bilirubin returns to within institutional normal limits, the docetaxel may be added back to the regimen.

6.42 Elevations of 5 x ULN or higher in SGOT (AST), SGPT (ALT), or alkaline phosphatase requires delay in subsequent study treatment for a maximum of 2 weeks until recovered to less than or equal to 2.5 x ULN, AND reduction of one dose level for all subsequent cycles. Treatment with gemcitabine and docetaxel will be discontinued in patients whose SGOT (AST), SGPT (ALT), or alkaline phosphatase elevations fail to recover to less than or equal to 2.5 x ULN within 2 weeks.

6.5 Hepatic Dysfunction during **doxorubicin (10/28/2013)**

If bilirubin increases to greater than 1.5 x institutional upper limits of normal, delay the doxorubicin by up to 2 weeks. If the bilirubin does not recover after two weeks delay, the patient will be removed from study treatment.

6.6 Hypersensitivity reactions to **Docetaxel (10/28/2013)**

There are no dose reductions for hypersensitivity reactions.

MANAGEMENT OF ACUTE HYPERSENSITIVITY TO DOCETAXEL

Severity of Symptoms	Treatment Guidelines
Mild symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash	Consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient; then, complete docetaxel infusion at the initial planned rate
Moderate symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mm Hg	Interrupt docetaxel infusion Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor patient until resolution of symptoms Resume docetaxel infusion after recovery of symptoms; depending on the physician's assessment of the patient, docetaxel infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate*, (e.g. infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, then finally, resume at the initial planned rate.* Depending on the intensity of the reaction observed, additional oral or IV pre-medication with an antihistamine should also be given for the **next cycle** of treatment, and the rate of infusion should be decreased initially and then increased back to initial planned rate, *(e.g. infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5*

	minutes, then at a 2-h rate for 5 minutes, and finally, administer at the initial planned rate.)
Severe symptoms: any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80mm Hg, angioedema	Immediately discontinue docetaxel infusion Give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor patient until resolution of symptoms The same treatment guidelines outlined under moderate symptoms (i.e. the third and fourth bullets) should be followed.
Anaphylaxis (NCI grade 4 reaction)	NO FURTHER DOCETAXEL THERAPY. Patients can continue gemcitabine on study.

6.7 Other Non-hematologic toxicity likely attributable to **gemcitabine and/or docetaxel or doxorubicin (10/28/2013)**

6.71 In the event of **Grade 3 or 4 neurotoxicity**, treatment will be delayed 1 week.
If neurotoxicity has resolved to less than or equal to Grade 1, then the patient may continue on study with docetaxel dose reduction of one dose level in the current and all subsequent cycles (no dose adjustment is required for gemcitabine).

If the Grade 3 or 4 neurotoxicity has not resolved to less than or equal to Grade 1 after a two-week delay, the docetaxel will be discontinued. Patients will continue to receive gemcitabine.

A patient who presents with **Grade 2 peripheral neuropathy** requires a docetaxel dose reduction of one dose level and delay in subsequent therapy for a maximum of 2 weeks until recovery to Grade 1. If the patient is re-treated with a docetaxel dose reduction after recovery from a Grade 2 peripheral neuropathy, the dose reduction should remain in the current and all subsequent cycles.

6.72 Grade 2 (or greater) renal toxicity requires reduction of one dose level for gemcitabine and for docetaxel and delay in subsequent therapy for a maximum of 2 weeks until recovered to Grade 1. Discontinue both gemcitabine and docetaxel (or doxorubicin, if applicable) when Grade 2 or worse renal toxicity does not recover to Grade 1 or less. Since renal toxicity is generally <u>not</u> considered a toxicity of doxorubicin, no dose reduction for doxorubicin is required, unless, in the judgment of the treating physician, the doxorubicin was considered the cause of the renal toxicity. **(10/28/2013)**

HUS (hemolytic uremic syndrome): The diagnosis of HUS should be considered if the patient develops hemolytic anemia with evidence of microangiopathic hemolysis as indicated by elevation of indirect bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of serum creatinine of BUN). Gemcitabine therapy should be discontinued immediately. Renal Failure associated with HUS may not be reversible even with discontinuation of therapy and dialysis may be required. Patients who develop HUS requiring intervention should be removed from study treatment.

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

6.74 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 for both gemcitabine and docetaxel if the toxicity occurs during the gemcitabine + docetaxel treatment, and for doxorubicin if the toxicity occurs during the doxorubicin treatment, and delay in subsequent study treatment for a maximum of 2 weeks until recovered to Grade 1.

6.75 Other non-hematologic toxicities (including mucositis) with an impact on organ function of Grade 2 (or greater) require reduction of one dose level for both gemcitabine and docetaxel if the toxicity occurs during the gemcitabine + docetaxel treatment, and for doxorubicin if the toxicity occurs during the doxorubicin treatment, and delay in subsequent study treatment for a maximum of 2 weeks until recovered to Grade 1, or pre-therapy baseline.

6.76 In patients who develop Grade 4 edema considered likely related to gemcitabine and/or docetaxel, gemcitabine and docetaxel will be discontinued.

7.0 STUDY PARAMETERS

7.1 Observations and Tests

For patients on REGIMEN I Gemcitabine + Docetaxel x 4 cycles, followed by Doxorubicin x 4 cycles:
The following observations and tests are to be performed and recorded on the appropriate form(s)

PARAMETER	Baseline, pre-treatment **(10/28/2013)**	Day 8 of treatment with Gemcitabine /docetaxel	Prior to each cycle of chemotherapy	After 4 cycles Gemcitabine/ docetaxel	Follow up (until evidence of disease recurrence) every 4 months for 3 yrs, then every 6 months for 2 years]†
History & Physical	1		X		5
Review of concurrent medications	1		X		
Serum Pregnancy Test (for patients of childbearing potential)	6				
Electrocardiogram	1				
Toxicity Assessment	3		X		
CBC/Diff/ platelets	3	X	X		
Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase	3,7	7	X		
Electrolytes, BUN, creatinine)	3		X		
CT chest/abdomen/ pelvis or CT chest + MRI abdomen/pelvis	2			8	5
ECHO/MUGA scan **(10/28/2013)**	4				

† **Protocol-specified imaging studies should continue until disease progression or until patient is put on non-protocol cancer therapy. Follow-up for SURVIVAL status should continue for a minimum of 5 years from time of study entry, regardless of whether patient has recurred or not.**

1. Must be obtained within 28 days prior to initiating protocol therapy.

2. CT c/a/p is preferred as there is less reader variation among centers. Baseline imaging to confirm no evidence of disease prior to enrollment should be done within 4 weeks of enrollment.
3. Must be obtained within 14 days prior to initiating protocol therapy.
4. Documentation of cardiac ejection fraction is only required for patients assigned to the chemotherapy arm and may have been done up to six months prior to initiation of study treatment. **(10/28/2013)**
5. Follow patients by physical examination and CT chest/abdomen/pelvis (or CT chest +MRI abdomen/pelvis) imaging every 4 months from study entry until 3 years out from the start of study treatment, then every 6 months for the next 2 years. There is a maximum of 5 years of imaging for detection of first recurrence. Patients who stop study treatment prior to completion of all planned chemotherapy for reasons of toxicity or for any reason (other than withdrawal of consent) should continue with every 4 month imaging to determine date of first recurrence.
6. Obtain within 48 hours prior to patient enrolling into study.
7. Bilirubin should be repeated on or before Day 8 if abnormal on Day 1 of the 4 cycles of Gemcitabine/ docetaxel.
8. The CT scan that occurs after the 4th cycle of gemcitabine + docetaxel should occur approximately 4 months from study enrollment. If a patient stops gemcitabine + docetaxel prior to cycle 4, and plans to proceed on to doxorubicin treatment, no CT is needed until approximately 4 months from study enrollment.

For patients on REGIMEN II-observation:

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

PARAMETER	Baseline, pre-enrollment	Every 3 -4 weeks for months 1-3 on study	At approximately 4 months from enrollment	Every 3 -4 weeks for months 3-6 on study	Follow up (until evidence of disease recurrence) every 4 months for 3 yrs, then every 6 months for 2 years]†
History & Physical	1		X		5
Review of concurrent medications	1		X		
Serum Pregnancy Test (for patients of childbearing potential)	6				
Electrocardiogram	1				
Toxicity Assessment	3	4	X	4	
CBC/Diff/ platelets	3		X		
Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase	3		X		
Electrolytes, BUN, creatinine)	3		X		
CT chest/abdomen/ pelvis or CT chest + MRI abdomen/pelvis	2		X		5
MD or RN telephone call		4		4	

† **Protocol-specified imaging studies should continue until disease progression or until patient is put on non-protocol cancer therapy. Follow-up for SURVIVAL status should continue for a minimum of 5 years from time of study entry, regardless of whether patient has recurred or not.**

1. Must be obtained within 28 days prior to initiating protocol therapy.
2. CT c/a/p is preferred as there is less reader variation among centers. Baseline imaging to confirm no evidence of disease prior to enrollment should be done within 4 weeks of enrollment.
3. Must be obtained within 14 days prior to initiating protocol therapy.
4. Approximately every 3 to 4 weeks, for the first 6 months from enrollment, an RN or MD should obtain vital status, and report of any toxicities from patient by phone or by office visit evaluation.

5. Follow patients by physical examination and CT chest/abdomen/pelvis (or CT chest +MRI abdomen/pelvis) imaging every 4 months from study entry until 3 years out from the start of study treatment, then every 6 months for the next 2 years. There is a maximum of 5 years of imaging for detection of first recurrence.
6. Obtain within 48 hours prior to patient enrolling into study.

7.2 Stained Pathology Slide Requirements for Central Review to Confirm Eligibility

NOTE: The following details about GOG review of pathology apply to GOG participants. For details about submission of slides and pathology review for EORTC and NCRN participants, please see the EORTC and NCRN specific appendices.

Stained pathology slides are required for central review by the GOG pathology committee to confirm eligibility. At least one H&E stained slide is required: 1) at least one representative H&E stained slide demonstrating the primary high grade uterine leiomyosarcoma with adequate mitotic rate, nuclear atypia and tumor necrosis (if present),
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 stained slides, pathology reports and Form F to the GOG Statistical and Data Center. Please see sections 4.6 and 10.2 for additional requirements and instructions.

7.3 Translational Research

Not Applicable

7.4 Quality of Life **(10/28/2013)**

Not Applicable

8.0 EVALUATION CRITERIA

8.1 Antitumor Effect – Solid Tumors

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

8.11 Disease Parameters

This is a study of adjuvant therapy. All patients must have no evidence of measurable disease on baseline imaging in order to be eligible for this study.

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

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

8.12 Methods for Evaluation of Disease

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. In this study of adjuvant therapy, baseline imaging should be performed no longer than 28 days prior to study enrollment. **(10/28/2013)**

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

Chest x-ray: Chest CT is required for thoracic disease surveillance on this study.

Conventional CT and MRI: While CT is preferred, MRI is also acceptable in certain situations (e.g., for body scans), but NOT lung.

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

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

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

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

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

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

Cytology, Histology: It is mandatory to obtain cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment. This confirmation is necessary to differentiate recurrent disease from a side effect of the treatment.

8.13 Response Criteria

This is a study of adjuvant therapy and thus, by eligibility criteria, all patients will have no evidence of disease at time of enrollment. There will be no evaluation for CR or PR since patients will not have measurable disease.

However, RECIST will be used to determine whether there is radiographic evidence of recurrence.

8.14 Recurrence

Recurrence is defined as newly evident disease for patients who have no evidence of disease at baseline.

8.15 Recurrence-Free Survival

Recurrence-Free Survival (RFS) is defined as the duration of time from study entry to time of recurrence or death, whichever occurs first.

8.16 Survival

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

8.17 Adverse Events

Adverse events will be categorized and graded according to NCI Common Terminology Criteria for Adverse Events version 4.0.

9.0 DURATION OF STUDY

9.1 Patients on Regimen I will receive therapy for a maximum of 8 cycles (4 cycles of gemcitabine + docetaxel, followed by 4 cycles of doxorubicin) or until disease recurrence or toxicity intervenes.

9.2 A patient is considered off study treatment when the patient has recurred or died, 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. Patients on the observation arm, Regimen II, are considered off study treatment at the end of 24 weeks from study entry. Patients who are considered off study treatment remain on study in terms of follow-up for evidence of recurrence and for survival status.

9.3 Patients will be followed for recurrence with physical exam, histories and imaging until recurrence, death or five years of follow-up is reached. If there is evidence of disease recurrence, patients will continue to be followed for survival for at least 5 years from study entry. Patients will be monitored for non-protocol therapy, serious delayed toxicity and survival for this 5 year period with Q forms submitted to the GOG Statistical and Data Center, unless consent is completely withdrawn.

9.4 Patients can refuse study treatment at any time, but can continue to be followed for evidence of recurrence or death as consent allows.

10.0 STUDY MONITORING AND REPORTING PROCEDURES

10.1 ADVERSE EVENT REPORTING FOR A COMMERCIAL AGENT

10.11 Definition of Adverse Events (AE)

NOTE: The following details about GOG reporting of Adverse Events apply to GOG participants. For details about Adverse Event reporting for EORTC and NCRN participants, please see the EORTC and NCRN specific appendices.

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

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov). The CTCAE v4.0 Manual is also available on the GOG member web site (http://www.gog.org under MANUALS).

10.12 Reporting Expedited Adverse Events

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

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

10.13 Phase 2 and 3 Trials Utilizing a Commercial Agent: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of Any Commercial Study Agent **(10/28/2013)**

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]	
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	Unexpected	E
Unrelated Unlikely	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	7 Calendar Days	C
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	C

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

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

- Grade 4 and Grade 5 unexpected events

AdEERS 7 calendar day report:

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

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

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

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

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

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

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

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

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

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

The following events should be excluded from AdEERS reporting although they should still be reported on the routine AE CRFs:

Grade 3 or 4 thrombosis/thrombus/embolism that does not require hospitalization
Grade 3 or 4 neutrophils, anemia, thrombocytopenia that does not require hospitalization
Grade 3 or 4 nausea, diarrhea, fatigue that does not require hospitalization
Docetaxel hypersensitivity reactions that are mild or moderate (grade 2 or 3) but which do not require hospitalization. Grade 4 (anaphylaxis) reaction DO require reporting regardless of whether or not hospitalization is required.
Grade 3 elevations in AST, ALT, alkaline phosphatase, bilirubin that do not require hospitalization.

10.14 Procedures for Expedited Adverse Event Reporting:

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

AML/MDS events must be reported via AdEERS (in addition to 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.

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

10.15 Automated CDUS reporting

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

10.2 GOG DATA MANAGEMENT FORMS

The following GOG forms must be completed for all patients registered and submitted to the GOG Statistical and Data Center (SDC) in accordance with the schedule below. GOG Protocol forms and instructions can be submitted through or printed from the SDC Electronic Data Entry System (SEDES) online application found at the GOG Web Menu page. 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. Pathology material (Form F, pathology reports and slides) should be submitted together via mail. The GOG Uploader Application in SEDES is an alternate method for submitting Form BDR, operative reports, Form F and pathology reports to the GOG SDC.

Form[Δ]	**Due within**		**Copies***	**Comments**
	Weeks	**Event**		
Form R (Registration Form)	2	Registration	1	Mandatory Submission via SEDES
Form OSU (Uterine Cancer - On Study Form)	2	Registration	1	Mandatory Submission via SEDES
Form C (Surgical Reporting Form) Operative report Discharge summary	6 6 6	Registration Registration Registration	1 2 2	Mandatory Submission via SEDES Submit via postal mail or upload online via SEDES labeled with patient identifier
Form DR (Pre-Treatment Summary Form)	2	Registration	1	Mandatory Submission via SEDES
Form D2M (Solid Tumor Evaluation Form) - baseline	4	Registration	1	Mandatory Submission via SEDES
Primary disease: Form F Pathology Report Slides	 6 6 6	 Registration Registration Registration	 2 2 **	 Submit together to SDC via postal mail or upload online via SEDES**
Form D2R (Cycle Dose Drug Form)	2	Completion of each cycle of therapy (Regimen I only)	1	Mandatory Submission via SEDES
Form D2M (Solid Tumor Evaluation Form)	2	each disease assessment	1	Mandatory Submission via SEDES
Form T (Common Toxicity Reporting Form)	2	Beginning of each subsequent cycle for patients on Regimen I (chemotherapy) and every 3-4 weeks for months 1-6, using patient telephone call, for patients on Regimen II	1	Mandatory Submission via SEDES

		(observation)		
Form Q0 (Treatment Completion Form)	2	Completion of study Rx and change in Rx	1	Mandatory Submission via SEDES
Form Q (Follow-Up Form)	2	Disease progression; death; normal follow-up	1	every 4 months for 3 years, then every 6 months for 2 years or more,

* 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 4.6 and 7.2 for additional requirements and mailing instructions.

This study will be monitored by the **Abbreviated** Clinical Data System (CDUS) Version 3.0 CDUS data will be submitted **by the January 31, April 30, July 31 and October 31 due dates** to CTEP by electronic means.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design and Treatment Randomization

The study is designed as a two arm open label randomized phase III superiority trial with an observation only control arm, Regimen II, and experimental arm of multi-agent chemotherapy (Regimen I, 4 cycles of gemcitabine and docetaxel followed by 4 cycles of doxorubicin). The design will provide a direct assessment of the null hypothesis that multi-agent adjuvant chemotherapy offers no increase in survival when compared with observation until recurrence.

Prior to patient registration, eligibility will be reviewed by Fast Fact Sheet verification. The sequence of treatment assignments will be concealed from institutions and patients until registration with verification of eligibility. Patients will be registered by the participating site through OPEN and randomization will be carried out centrally by the GOG Statistical and Data Center. The randomization will be stratified country of treating site using a minimization procedure that tends to allocate two study arms in a ratio of 1 to 1 within strata.

Reports and publications will include a complete accounting of all patients registered to this study.

11.2 Efficacy and toxicity measures

The principal observations for evaluating the therapeutic efficacy and safety of treatments are listed below (see Section 8 for definitions).

11.21 Primary efficacy endpoint: overall survival

11.22 Interim futility endpoint: recurrence-free survival

11.23 Safety endpoints: frequency and severity of adverse events

11.3 Statistical study design and planned analyses of therapeutic efficacy

11.31 Accrual goal: 216 patients are targeted for enrollment on this study.

11.32 Accrual rate: 3 patients per month from GOG sites **(10/28/2013)**

There were 47 patients enrolled on SARC005 (a prospective phase 2 trial of adjvant gemcitabine-docetaxel followed by doxorubicin for high-grade, uterus-limited leiomyosarcoma) in less than 3 years. It is expected that accrual through GOG would potentially be superior to that seen on the SARC trial. Based on data from GOG-0250, a randomized phase III evaluation of docetaxel and gemcitabine plus G-CSF with bevacizumab versus docetaxel and gemcitabine plus G-CSF

with placebo in the treatment of recurrent or advanced leiomyosarcoma of the uterus, the accrual from November 13, 2010 through May 12, 2011 was 23 patients. Furthermore, 47% of patients enrolled on GOG-0250 at the time of recurrence were originally diagnosed with early stage leiomyosarcoma. Assuming that this accounts for 60% of early stage patients, then we can expect at least (0.47*3.8*12/.6) 36 patients per year from the GOG. International collaboration with EORTC and NCRN (as agreed at NCI-EORTC-NCRN Rare Tumor Initiative meeting, June 2011) will likely increase the accrual rate to over 3 patients per month.

EORTC estimates their annual accrual to be no more than 30 patients and NCRN estimates accrual to be no more than 20 patients per year. **(10/28/2013)**

11.33 Study duration:

With an average accrual rate of 36 patients per year, the study accrual time would be 72 months to enroll 216 patients followed by 16 additional months of follow-up. Thus the total study duration is planned as 88 months. If the accrual rate is increased to 3.75 patients per month, the study accrual time would be 58 months to enroll 216 patients with a maximum study duration of 79 months.

Accrual and Study Duration **(10/28/2013)**
For various annual accrual rates and target sample size fixed at 216

Annual accrual	Accrual duration in months	Study duration in months
86	30	63
72	36	66
60	43	70
48	54	77
36	72	88

11.34 Primary hypothesis: The null hypothesis to be tested is that multi-agent adjuvant chemotherapy offers no increase in survival time when compared with observation until recurrence.

H_0: $\lambda_c / \lambda_e \leq 1$ vs. H_1: $\lambda_c / \lambda_e > 1$

In this statistical representation of the primary hypothesis, λ_c represents the death hazard rate on the observation arm; λ_e represents the death hazard rate on the multi-agent adjuvant chemotherapy arm.

11.341 Effect size: A hazard ratio (HR), control to experimental, of 1.6 would be of clinical interest. This translates to an absolute difference of 15.5% at 3 years (46% vs. 61.5%) in overall survival.

11.342 Type I error for superiority: 0.05, one tail test.

11.343 Statistical power: 0.80 calculated under the alternative that $\lambda_c / \lambda_e = 1.6$

11.344 Additional assumptions: Overall and recurrence-free survival data from patients diagnosed with early stage leiomyosarcoma enrolled on GOG 40 are used as the basis for determining sample size and duration of follow-up. The death rate is initially high but dissipates somewhat over time with approximately 23% alive after 6 years and 24% alive, recurrence-free after 5 years.

Overall Survival		
	Cumulative percent of patients alive	Cumulative percent of patients alive
Months	Control Arm	Experimental Arm (HR=1.6)
6	96	97
12	84	90
24	65	76
36	46	62
48	38	55
60	31	48
72	23	40

Recurrence-free Survival		
	Cumulative percent of patients alive, recurrence free	Cumulative percent of patients alive, recurrence free
Months	Control Arm	Experimental Arm (HR=1.6)
6	83	89
12	66	77
24	45	61
36	32	49
48	26	43
60	24	41
72	23	40

11.35 Primary analysis: The intention-to-treat principle will be applied in the primary analysis comparing the distribution of time to death with censoring between assigned treatment arms. The logrank test will be used to test the null hypothesis of independence between survival and randomized treatment. Kaplan-Meier estimates will be used to graph survival distribution curves for each treatment arm. The death hazard ratio (experimental to control) will be estimated using a Cox Proportional Hazards model and a 95% Wald confidence interval will be reported.

11.351 Delta value to reject H_0 at final analysis of overall survival assuming exactly 115 events are observed: $\lambda_c / \lambda_e > 1.37$ ($\approx 0.73^{-1}$)

11.36 Secondary endpoint analysis:
Recurrence-free survival is a secondary endpoint. The intention-to-treat principle will be applied in the secondary analysis comparing the distribution of time to recurrence or death with censoring between assigned treatment arms. The recurrence or death hazard ratio (experimental to control) will be estimated using Cox's proportional hazards model and a 95% Wald confidence interval will be reported. The logrank test will be used to test the null hypothesis of independence between recurrence-free survival and randomized treatment. It is expected that this analysis will have 85% power to detect a 37.5% relative decrease in the hazard of recurrence or death (133 events) at the time that overall survival data will be mature. Kaplan-Meier estimates will be used to graph overall survival distribution curves for each treatment arm.

Additional exploratory analyses assessing the univariate and multi-variable prognostic significance of baseline clinical, pathologic or demographic factors such as patient age, tumor size, cervix involvement (yes or no), and mitotic rate will be carried out using proportional hazards models of both survival and recurrence.

11.37 Interim analysis:

An interim analysis plan is outlined below assuming the interim analyses occur exactly at 45% of the information fraction (target number of overall survival events). However the timing of the interim analysis will likely vary from this exact schedule for practical reasons. At the interim analysis, the test statistic for the primary analysis will be compared with the critical boundaries defined by the statistical design parameters described above. If a boundary is crossed, consideration will be given to terminating study accrual, if still active, and/or early release of data. Additional decisions may include recommendations on instructions for patients on study treatment.

One interim analysis of futility and superiority is planned at 45% of information time (that is, when at least 52 overall survival events have been reported). Given the rarity of this disease and the disparate treatment arms, stopping early for futility is desirable. Basing the interim futility analysis on recurrence-free survival allows for a higher degree of available information (RFS events) at the time of the interim analysis. Using RFS as the endpoint for futility analysis assumes that a lack of benefit in RFS translates to a lack of benefit in overall survival. While data for the disease under study are extremely limited, this is a likely scenario in gynecologic malignancies in general and a reasonable assumption for this study. . The boundary for futility (rejection of the alternative hypothesis, HR=0.625) will be defined by a critical region of values 0.442 or lower on the Z scale (0.90 or higher on the hazard ratio scale) provided there are exactly 74 RFS events (56% of the RFS information fraction) using linear interpolation of a spending function that has a probability of early termination under the null hypothesis of no difference of at least 65%. The actual number of RFS events will depend on the timing of the interim analysis of efficacy. Assuming equal true hazard ratios for RFS and overall survival under the alternative hypothesis, the loss in power at the final analysis of overall survival is estimated to be 0.75% or 1.9% where the correlation between RFS at the interim analysis and overall survival at the final analysis is 0.8 or 0.6, respectively. The interim superiority analysis will be based on overall survival. An O'Brien and Fleming-like spending function is used to define the boundaries for rejecting the null hypothesis. Type I error to be spent at the interim analyis is 0.0035 if exactly 52 overall survival events have been reported.

Interim and final analysis plan details for overall survival

Look #	Info Fraction	Event Size	Type I Error Spent Alpha
1	0.43	52	0.0028
2	1.000	115	0.0500

Other data to be summarized at the interim analysis will include tabulation of adverse events, deaths at least partially attributable to protocol treatment, major violations (complete refusal of protocol therapy, initiation of non-protocol therapy prior to recurrence, etc) and distribution of baseline characteristics.

The results of interim analyses are scheduled to be reviewed by the GOG Data Safety and Monitoring Board (DSMB) at its semi-annual meetings. This committee meets in January and July each year. The precise dates for these meetings are set more than one year in advance by individuals who have no knowledge of efficacy results. Approximately eight weeks prior to each of these meetings, the database is locked in order to prepare a progress report. If the prerequisite number of patients evaluated for response has been attained, an interim analysis is also prepared and presented to the DSMB at their next scheduled meeting. The decision to terminate accrual to any particular regimen includes consideration of adverse events, treatment compliance, survival data and results from external studies. Additionally, 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 the study treatment may have been a contributing cause. The SRC reports to the DSMB and may recommend study amendments pertaining to patient safety.

11.4 Safety analyses

Patients' adverse events will be captured by individual adverse event terms and grades defined by the NCI Common Terminology Criteria for Adverse Events version 4. The maximum grade of any adverse event observed during active treatment period or within 3-4 weeks of completing study treatment for each eligible patient will be tabulated. The proportion of patients with a serious adverse event or reported grade 3 or worse adverse event, regardless of attribution, will be compared between the treatment regimens using a chi-squared test. Additionally, the frequency of hospitalization while on study therapy, frequency of early study treatment discontinuation due to adverse events or refusal in the absence of disease recurrence, and the number of patients who receive non-protocol therapy prior to recurrence will be monitored in each arm. Additionally, the initial post-protocol therapy will be tabulated for each arm.

11.5 Anticipated distribution of patients' race and ethnicity (all are female) for GOG credited enrollment **(10/28/2013)**

Ethnic Category		**Percent**
Hispanic or Latino	19	9.0
Not Hispanic or Latino	197	91.0
Ethnic Category: Total of all subjects	216	100.0
Racial Category		
American Indian or Alaskan Native	2	1.0
Asian	4	1.8
Black or African American	37	17.0
Native Hawaiian or other Pacific Islander	1	0.2
White	172	80.0
Racial Category: Total of all subjects	216	100.0

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APPENDIX I
Uterine Sarcomas FIGO Classification 2009

(1) LEIOMYOSARCOMAS AND ENDOMETRIAL STROMAL SARCOMAS (ESS)*

Stage	Definition
I	Tumor limited to uterus
IA	≤5 cm
IB	>5 cm
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Involvement of other pelvic tissues
III	Tumor invades abdominal tissues (not just protruding into the abdomen).
IIIA	One site
IIIB	>one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV IVA	Tumor invades bladder and/or rectum
IVB	Distant metastases

(2) ADENOSARCOMAS

Stage	Definition
I	Tumor limited to uterus
IA	Tumor limited to endometrium/endocervix with no myometrial invasion
IB	Less than or equal to half myometrial invasion
IC	More than half myometrial invasion
II	Tumor extends beyond the uterus, within the pelvis
IIA	Adnexal involvement
IIB	Involvement of other pelvic tissues
III	Tumor invades abdominal tissues (not just protruding into the abdomen).
IIIA	One site
IIIB	>one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV IVA	Tumor invades bladder and/or rectum
IVB	Distant metastases

(3) CARCINOSARCOMAS

Carcinosarcomas should be staged as carcinomas of the endometrium.

*Note:
Simultaneous endometrial stromal sarcomas of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors.

APPENDIX II

General Chemotherapy Guidelines

- For 21 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 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.
- 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 doses 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).

APPENDIX III **(10/28/2013)**

EORTC Group-Specific Appendix to GOG Protocol GOG-0277

Intergroup Trial

EORTC Gynecological Cancer Group EORTC Soft Tissue and Bone Sarcoma Group

EORTC protocol 55116-62114
EORTC Group Specific Appendix to GOG-0277 protocol

(EudraCT number 2012-002852-17) (NCT01533207)

A Phase III Randomized Trial of Gemcitabine plus Docetaxel followed by Doxorubicin v. observation for uterus-limited, High Grade Uterine Leiomyosarcoma.

EORTC Study Coordinators: Petronella Beatrix Ottevanger Phone: +31243610353 Fax: +31243540788 E-mail: p.ottevanger@onco.umcn.nl

Anders Krarup-Hansen Phone: +45 44 53 53 30 Fax: +45 44 53 30 77 E-mail: ankha@heh.regionh.dk

GSA version	Date of PRC approval/notification	Amendment reference		Applicable for Protocol
		N°	Category	
1.0	04 December 2012	----	----	GOG-0277-April 25, 2012 and subsequent versions

Warning:
The enclosed protocol has not been initiated and written by the EORTC and it does not follow the usual sequence of chapters of EORTC protocols.

All practical and administrative aspects of the protocol specific to the EORTC (Randomization, data flow, responsibilities, insurance, safety reporting ….) are included under this EORTC Group Specific Appendix of the protocol.

Contact addresses for the coordinating group

Study Coordinator: Martee L. Hensley (GOG)
E-mail: hensleym@mskcc.org

Coordinating Clinical Trial Office: CANCER TRIALS SUPPORT UNIT
Phone: +1-888-823-5923
E-mail: ctsucontact@westat.com

Contact addresses for EORTC

EORTC Study Coordinators: Petronella Beatrix Ottevanger
Phone: +31243610353
Fax: +31243540788
E-mail: p.ottevanger@onco.umcn.nl

Anders Krarup-Hansen
Phone: +45 44 53 53 30
Fax: +45 44 53 30 77
E-mail: ankha@heh.regionh.dk

Clinical Research Physician: Emad Shash
Phone: +32 2 774 10 59
Fax: +32 2 774 16 36
E-mail: emad.shash@eortc.be

Project Manager: Liesbeth Knaepen
Phone: +32 2 774 10 28
Fax: +32 2 772 35 45
E-mail: Liesbeth.kneaepen@eortc.be

IRCI Project Manager: Hilde Breyssens
Phone: +32 2 774 10 04
Fax: +32 2 772 35 45
E-mail: hilde.breyssens@eortc.be

Data Manager: Maarten De Rouck
Phone: +32 2 774 16 60
Fax: +32 2 771 38 10
E-mail: maarten.derouck@eortc.be

Statistician: Corneel Coens
Phone: +32 2 774 16 32
Fax: +32 2 771 38 10
E-mail: corneel.coens@eortc.be

Pharmacovigilance Unit: Phone :+ 32 2 774 16 76
Fax : + 32 2 772 80 27
E-mail: pharmacovigilance@eortc.be

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1 Trial organization

This trial is an Intergroup Trial, jointly conducted by the Gynecology Oncology Group (GOG) from USA, the EORTC Gynecology Cancer Group, EORTC Soft Tissue Bone Sarcoma Group and the National Cancer Research Network (NCRN) from United Kingdom.
♦ The GOG is the Coordinating Group in this Intergroup trial and therefore is responsible for the trial design and activation, data management (including the quality control of data), statistical analysis and publication.

♦ The EORTC is Collaborating Group in this trial.

♦ The protocol developed by the Coordinating Group is compliant with specific EORTC guidelines for Intergroup trials and will be used by EORTC. The present EORTC specific Appendix details the participation of the EORTC institutions in the trial. **The content of this appendix is therefore applicable only to the EORTC**

investigators, for whom it supersedes entirely or partially the corresponding chapters in the protocol.

- EORTC is the legal sponsor for all EORTC and NCRN participants.
  - EORTC will use the standard EORTC SAE definition. EORTC investigators will use standard EORTC SAE forms.
  - **Only the Coordinating Data Center of GOG will code the data, perform consistency checks on data and modify them. Only the Coordinating Data Center will do the analysis**.
  - All study drugs will have to be taken from the shelf and should be stored, prepared and administered in line with study protocol, normal hospital procedures and information contained within the current summary of product characteristics for each product.
  - This trial is an academic trial without any financial support from the industry.

2 Forms and procedures for collecting data

- EORTC Investigators/ Authorized personnel will enter study data in electronic CRFs via GOG Statistical and Data Centre (SDC) Electronic Data Entry System (SEDES) online application.
- All queries will be sent from GOG Statistical and Data Centre (SDC) to the participating sites via SDC Electronic Data Entry System (SEDES) online application.
- The GOG SDC is responsible for raising validation checks and for overall quality control of trial data.

3 Translational research

The translational research program is optional.

- All patients included in the clinical study will be offered to participate to the translational research project, at the time they are offered participation to the clinical study. Patients will have the possibility to accept or refuse the participation. A written informed consent should be given by the patient for inclusion in the translational research project.
- For patients who have consented, tumor material sent to the reference pathologist for histopathological diagnosis will not be returned to the local pathologists but kept for future translational research, unless specifically required otherwise.
- Further practical details will be provided through separate site guidelines.

3.1 General principles for human biological material (HBM) collection

Human biological material (HBM) collection involves the collection and storage of biological material, residual biological material or derivatives in compliance with ethical and technical requirements.

In this study, biological material will be centralized and stored at the site of the reference pathologist. From here, the biological material will be used or distributed to the other research laboratories involved in the translational research (TR) projects defined in the future.

The following principles apply to storage of HBM:

- ♦ The collected HBM should be documented, i.e. the amount remaining and its location.

The EORTC Gynecology Cancer Group (GCG) and Soft Tissue and Bone Sarcoma Group (STBSG) Committees will be responsible for TR project review and prioritization, including the consideration of newly proposed TR projects not specified in the protocol. In the absence of Group Committees, responsibilities of the GCG and STBSG Committees are transferred to the EORTC HQ as applicable.

Final decisions on the use of HBM will be determined by a majority vote of the GCG and STBSG Group committees. Additional expertise may be sought through advisory non GCG and STBSG Group committees members.

Access to HBM (see EORTC Biobanking Policy POL020): HBM may be used for another purpose for which it was originally collected, subject to meeting ethical principles/and is covered by informed consent/ethics approval. In the case of secondary use of HBM, (i.e. for new TR projects that are not specified in the clinical study protocol and that were not foreseen at the time of protocol writing) interested parties may apply for the use of HBM and will follow the next steps:

- ♦ A short description of the new TR projects will be written and submitted to EORTC HQ for coordination with GCG and STBSG Group committees.
- ♦ The GCG and STBSG Group committees will prioritize the TR projects. Access procedures defined by the Groups committees will build on the following key points:
- ♦ Project prioritization
- ♦ should be strongly based on scientific merit,
- ♦ should consider the contribution of the different investigators to the trial and TR project,
- ♦ will take into consideration if the applicant is an EORTC member or not (whilst maintaining the principle of access to the wider scientific community and commitments owed to study participants and ethical committees).

- Protection of confidentiality must be respected.
- An EORTC HQ feasibility check, including recommendations for regulatory and ethical matters and other restrictions on the use of the HBM, will take place. If in the event the HBM collections are still retained at individual clinical sites, the TR project leader and the involved EORTC Group are responsible for collecting and providing information on availability of HBM for the feasibility assessment.
- Prioritized TR projects will then be reviewed by the Translational Research Advisory Committee (TRAC).
- Once GCG and STBSG Group committees prioritization, the EORTC HQ feasibility assessment, and TRAC review are complete and when all applicable competent Ethics Committees approvals are in place and ethical principles are met, the TR project can be activated and HBM release and analysis can commence.
- The EORTC Executive Committee will mediate any disagreements of opinion between TRAC, the EORTC HQ feasibility assessment, the GCG and STBSG Group committees and the TR project leader(s), as needed.

4 Investigator authorization procedure

Investigators will be authorized to register and/or randomize patients in this trial only once they have returned the following documents to the EORTC Headquarters:

- The updated signed and dated Curriculum Vitae of the Principal Investigator
- The (updated) list of the normal ranges, for the investigator's institution signed and dated by the head of the laboratory. Please make sure normal ranges are provided also for those tests required by the protocol but not routinely done at the investigator's institution.
- A Commitment Statement and Study Agreement between EORTC and Principal Investigator, stating that they will fully comply with the protocol. This must include an estimate of yearly accrual and a statement on any conflict of interest that may arise due to trial participation.

NB: A signed conflict of interest disclosure form will be required only if a possible conflict is declared on the Commitment Statement and Study Agreement.

- A copy of the favorable opinion of their local or national (whichever is applicable) ethics committee mentioning the documents that were reviewed (including the version numbers and version dates of all documents). A list of all members of the ethics committee is also requested.
- A copy of the translated and adapted (according to all national requirements) Patient Information / Informed Consent sheet. Version numbers and dates must be clearly

stated on each page.

- ♦ The signature log-list of the staff members with a sample of each authorized signature and the indication of the level of delegations.
- ♦ The full name, address, phone numbers and e-mail address of the local pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).
- ♦ An accreditation, a certification, an established quality control / external quality assessment or another validation should be provided for the own laboratory.
- ♦ The center specific applicable list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol and / or the applicable national law.

The new investigator will be added to the "authorization list", and will be allowed to register/randomize patients in the trial as soon as

♦ All the above mentioned documents are available at the EORTC Headquarters.

♦ All applicable national legal and regulatory requirements are fulfilled.

Patient registration/randomization from centers not (yet) included on the authorization list will not be accepted.

The Coordinating Data Center will be immediately informed about each investigator included on the authorization list by EORTC indicating the name of the principal investigator, the name of the institution and the EORTC institution number.

5 Treatment plan and registration/randomization procedure

5.1 Patient registration & randomization procedure

EORTC investigators will register and/or randomize patients through the leading group's online registration system "OPEN" (cfr. leading protocol Chapter 5.1).
After authorization of the individual site, EORTC HQ will take the necessary steps to request a username and password for each individual EORTC site and communicate this to the site. Any further requirements for this process relevant to EORTC investigators will be provided in a separate document with proper instructions.

5.2 Treatment plan

Patients randomly assigned to one of the two protocol regimens will be treated as per protocol (cfr. leading protocol Chapter 5.2).

Patients with cardiac ejection fraction less than 50 % will not be allowed to receive Doxorubicin, but still can receive the rest of protocol treatment.

6 Reporting of Serious Adverse Events

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/reactions in clinical trials. These procedures are described in this section of the protocol.

6.1 Definitions

These definitions reflect the minimal regulatory obligations; specific protocol requirements might apply in addition.

AE: An **Adverse Event** is defined as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment”. An adverse event can therefore be any unfavorable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including results of blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

AR: An **Adverse reaction of an investigational medicinal product** is defined as “any noxious and unintended response to a medicinal product related to any dose administered”. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

UAR: An **Unexpected Adverse Reaction** is “any adverse reaction, the nature, or severity of which is not consistent with the applicable product information" (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for a marketed product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as “serious,” which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient’s life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE: A **Serious Adverse Event** is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:

- ♦ results in death
- ♦ is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe)

- ♦ requires inpatient hospitalization or prolongation of existing patient hospitalization
- ♦ results in persistent or significant disability or incapacity
- ♦ is a congenital anomaly or birth defect
- ♦ is a medically important event or reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

! Grade 4 anaphylaxis reactions, regardless of whether a hospitalization is required also need to be reported as an SAE

SAR: A **Serious Adverse Reaction** is defined as any SAE which is considered related to the protocol treatment.

SUSAR: Suspected Unexpected Serious Adverse Reaction.
SUSARs occurring in clinical investigations qualify for expedited reporting to the appropriate Regulatory Authorities within the following timeframes:

- ♦ Fatal or life-threatening SUSARs within 7 calendar days
- ♦ Non-fatal or non-life-threatening SUSARs within 15 calendar days

Inpatient hospitalization: a hospital stay equal to, or greater than, 24 hours.
Second primary malignancy is one unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

Secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

6.2 Exceptions

The following situations do not need to be reported as SAEs:

- ♦ Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment.
- ♦ A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.
- ♦ A hospitalization planned for protocol related treatment or protocol related procedure as per institutional standard timelines.
- ♦ Social and/or convenience admission to a hospital
- ♦ Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE.
- ♦ Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, overdose without occurrence of an adverse event).
- ♦ Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

By EORTC convention, clinical events related to the primary cancer being studied or to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, **unless** the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

6.3 Severity assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v4.0 www.eortc.org\investigators-area\ctc

6.4 Causality assessment

The investigator is obligated to assess the relationship between protocol treatment and the occurrence of each SAE following the definitions in this table:

Relationship to the protocol treatment	**Description**
Definite	The adverse event is clearly related to the agent(s).
Probable	The adverse event is likely related to the agent(s).

Possible	The adverse event may be related to the agent(s).
Unlilkely	The adverse event is doubtfully related to the agent(s).
Unrelated	The adverse event is clearly NOT related to the agent(s).

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.

The decision will be recorded on the SAE form and if necessary the reason for the decision will also be recorded.

6.5 Expectedness assessment

The expectedness assessment is the responsibility of the sponsor of the study. The expectedness assessment will be performed against the following reference documents:

♦ *For Gemcitabine: Summary of Product Characteristics (SmPC)*

♦ *For Docetaxel: Summary of Product Characteristics (SmPC)*

♦ *For Doxorubicin: Summary of Product Characteristics (SmPC)*

6.6 Reporting procedure for investigators

This procedure applies to all Serious Adverse Events (SAEs) occurring from the time a subject is registered until

For investigational arm: 30 days after last protocol treatment administration and to any SAE that occurs outside of the SAE detection period (after the 30-days period), if it is considered to have a reasonable possibility to be related to the protocol treatment or study participation.
For the observation arm: end of week 24

Registration till 30 days after last protocol treatment administration/end of week 24 (in Observation arm):	All SAEs
From day 31 after last protocol treatment administration:	Only related SAEs

Any secondary malignancy should also be reported in expedited way on a SAE form with the appropriate seriousness criteria!

All reporting must be done by the principal investigator or authorized staff member (i.e. on the signature list) to confirm the accuracy of the report.

All SAE data must be collected on the study-specific SAE form.

All SAEs must be reported immediately and no later than 24 hours from the time the investigator or staff became aware of the event.

All SAE-related information needs to be provided in English.

All additional documents in local language must be accompanied by a translation in English, or the relevant information must be summarized in a follow-up SAE report form.

All SAE-related information must be faxed to:

EORTC Pharmacovigilance Unit:
Fax No. +32 2 772 8027

To enable the Sponsor to comply with regulatory reporting requirements, all initial SAE reports should always include the following minimal information: an identifiable patient (SeqID), a suspect medicinal product if applicable, an identifiable reporting source, the description of the medical event and seriousness criteria, as well as the causality assessment by the investigator. Complete information requested on the SAE form of any reported serious adverse event must be returned within 7 calendar days of the initial report. If the completed form is not received within this deadline, the Pharmacovigilance Unit will make a written request to the investigator.

Queries sent out by the EORTC Pharmacovigilance Unit need to be answered within 7 calendar days.

All forms need to be dated and signed by the principal investigator or any authorized staff member (i.e. on the signature list).

6.7 Reporting responsibilities for EORTC

The EORTC Pharmacovigilance Unit will forward all EORTC SAE reports to the appropriate persons within the EORTC Headquarters and enter them into AdEERs.

The EORTC Pharmacovigilance Unit will take in charge the reporting of SUSARs to the Competent Authorities, Ethics committees, EudraVigilance Clinical Trial Module (EVCTM) and all EORTC participating investigators, whenever applicable.

6.8 Pregnancy reporting

Pregnancy occurring during a patient's participation in this trial, although not considered an SAE, must be notified to the EORTC Pharmacovigilance Unit within the same timelines as an SAE (within 24 hours) on a Pregnancy Notification Form. The outcome of a pregnancy should be followed up carefully and any adverse outcome to the mother or the child should be reported.

- Any pregnancy in a female subject diagnosed during the treatment period or within 30 days after last protocol treatment administration must be reported to the EORTC

Pharmacovigilance Unit

- This must be reported within 24 hours of first becoming aware of the event by fax, to the Pharmacovigilance Unit on a Pregnancy Notification Form
- If an SAE occurs in conjunction with the pregnancy, please also complete an SAE form as explained in the SAE reporting chapter

6.9 Audits

The EORTC Quality Assurance and Control Unit (QA&C) regularly conducts audits of institutions participating in EORTC protocols. These audits are performed to provide assurance that the rights, safety and wellbeing of subjects are properly protected, to assess compliance with the protocol, processes and agreements, ICH GCP standards and applicable regulatory requirements, and to assess the quality of data.

The investigator, by accepting to participate in this protocol, agrees that EORTC, any third party (e.g. a CRO) acting on behalf of the EORTC, or any domestic or foreign regulatory agency, may come at anytime to audit or inspect their site and all subsites, if applicable.

This audit consists of interviews with the principal investigator and study team, review of documentation and practices, review of facilities, equipment and source data verification.

The investigator will grant direct access to paper and/or electronic documentation pertaining to the clinical study (e.g. CRFs, source documents such as hospital patient charts and investigator study files) to these authorized individuals. All site facilities related to the study conduct could be visited during an audit (e.g. pharmacy, laboratory, archives …). The investigator agrees to co-operate and provide assistance at reasonable times and places with respect to any auditing activity.

When site visits are performed for this study, the Coordinating Data Center provides all CRFs and related queries to the EORTC Quality Assurance and Control Unit (QA&C).

A site visit will be organized in each recruiting institution within 18 months after the first patient has been entered and these visits will be repeated on a regular basis (approximately every 3 years).

If a regulatory authority inspection is announced, the investigator must inform the EORTC Headquarters QA&C Unit immediately (contact at: QualityAssuranceandControlUnit@eortc.be). In this way EORTC can provide help in preparing and/or facilitating the inspection. EORTC representatives/ delegates may also attend the inspection.

6.10 External review of histology

6.10.1 Local pathologist

- The local pathologist shall send stained pathology slides for central review by the reference pathologist to confirm eligibility. At least one representative H&E

(haematoxylin/eosin) stained slide demonstrating the primary high grade uterine leiomyosarcoma with adequate mitotic rate, nuclear atypia and tumor necrosis (if present).

For patients who consent to participate in the translational research, the local pathologist shall also include blocks, or if no blocks are available, at least 10 unstained slides for translational research (see Chapter 3).

Submitted pathology material shall be labeled with the patient seqID and patient code.

The local pathologist shall also send the completed Pathology Form (Form F) and a copy of his/her pathology report to the reference pathologist. Personal data of the patient must be anonymized (black out patient name) and replaced by the seqID allocated to this patient at the time of randomization.

Please include also the patient code and protocol number (GOG-0277) on all pages of the pathology report.

The slides, copies of the Pathology Form and official pathology report shall be sent by mail to the reference pathologist, being:

Cyril Fisher Dept of Histopathology ROYAL MARSDEN HOSPITAL - CHELSEA, LONDON Fulham Road 203 GB London SW3 6JJ United Kingdom
Phone: +44 20 78082631 Fax: +44 20 78082578
e-mail: cyril.fisher@rmh.nhs.uk

6.10.2 Reference pathologist

- The reference pathologist will complete the Pathology Review Form
- For patients who did not take part in future research: the reference pathologist will return tumor material to the sites after review.
- For patients consenting to future research the reference pathologist will retain the stained and unstained slides for future translational research, unless specifically required otherwise.

7 Ethical considerations

7.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net)) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH

Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at http://www.ema.europa.eu/pdfs/human/ich/013595en.pdf).

The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

7.2 Subject identification

The name of the patient will neither be asked for nor recorded at the EORTC Headquarters. A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and will be included on all case report forms. In order to avoid identification errors, the patient's code (maximum of 4 alphanumerics) and date of birth will also be reported on the case report forms.

7.3 Informed consent

All patients will be informed about

- ♦ the aims of the study
- ♦ the possible adverse events
- ♦ the procedures and possible hazards to which the patient will be exposed
- ♦ the mechanism of treatment allocation
- ♦ strict confidentiality of any patient data
- ♦ medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician

The template of the patient's informed consent statement is given as a separate document dated and version controlled to this protocol.

An adapted translation of the PIS/PIC will be provided by EORTC Headquarters and it is the responsibility of the Coordinating investigators for this trial (sometimes called National Coordinators) to adapt it to national/local requirements where necessary.

The bold sections of the informed consent document must be reflected in any translation. The content of these bold sections can either be translated literally or translated in any way that best captures the information given.

The translated informed consent documents are to be submitted to ethics committees for approval. The competent ethics committee for each institution must approve the informed consent documents before the center can join the study. It is the responsibility of the competent ethics committee to ensure that the translated informed documents comply with ICH-GCP guidelines and all applicable national legislation.

It is emphasized in the patient information sheet that participation is voluntary and that the

patient is free to refuse further participation in the protocol whenever he/she wants to. This will not have any impact on the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered and/or randomized at the EORTC Headquarters. The written informed consent form must be signed and personally dated by the patient or by the patient's legally acceptable representative.

All of the above must be done in accordance with the applicable national legislation and local regulatory requirements.

8 Administrative responsibilities

8.1 The study coordinator

The EORTC Study Coordinators (in cooperation with the EORTC Headquarters) will be responsible for reviewing and discussing all the amendments to the protocol with the coordinating group.

At the time of publication, the EORTC study coordinator's responsibility is to assure, along with the EORTC Headquarters Team, that the results are used and analyzed following the EORTC policy and quality.

Study coordinator (GCG):
Petronella Beatrix Ottevanger
Radboud University Nijmegen Medical Centre
P.O. Box 9101 – Geert Grooteplein 10
6500 HB Nijmegen
The Netherlands
Phone: +31243610353
Fax: +31243540788
e-mail: p.ottevanger@onco.umcn.nl

Study coordinator (STBSG):

Anders Krarup-Hansen
HERLEV HOSPITAL - UNIVERSITY COPENHAGEN
Herlev Ringvej
2730 Herlev 2730
Denmark
Phone: +45 44 53 53 30
Fax: +45 44 53 30 77
e-mail: ankha@heh.regionh.dk

8.2 The EORTC Headquarters

The EORTC Headquarters is responsible for handling investigator authorization procedure. All methodological questions should be addressed to the EORTC Headquarters that will address them to the person competent for this trial.

EORTC HEADQUARTERS

Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Fax: +32 2 7723545

8.3 The EORTC group

All questions concerning ongoing membership in the group should be addressed to the chairman and/or secretary of the group.

For new membership contact Membership Committee at membership@eortc.be

Gynecology EORTC group

Chairman:

Antonio Casado Herraez
HOSPITAL UNIVERSITARIO SAN CARLOS
C/ Profesor Martin Lagos, s/n
28040 Madrid
Spain
Phone: +34 91 3303666
Fax: +34 91 3303546
e-mail: acasado.hcsc@salud.madrid.org

Secretary:

Petronella Beatrix Ottevanger
RADBOUD UNIVERSITY NIJMEGEN MEDICAL CENTRE
P.O. Box 9101 - Geert Grooteplein 10
6500 HB Nijmegen
The Netherlands
Phone: +31 24 3610353
Fax: +31 24 3540788
e-mail: p.ottevanger@onco.umcn.nl

Soft Tissue Bone Sarcoma Group

Chairman:

Winette Van Der Graaf
RADBOUD UNIVERSITY NIJMEGEN MEDICAL CENTRE

P.O. Box 9101 - Geert Grooteplein 10
6500 HB Nijmegen
The Netherlands
Phone: +31 24 3610353
Fax: +31 24 3540788
e-mail: w.vandergraaf@onco.umcn.nl

Secretary:

Alessandro Gronchi
FONDAZIONE IRCCS ISTITUTO NAZIONALE DEI TUMORI
Via Venezian, 1
20133 Milano
Italy
Phone: +39 02 23903234
Fax: +39 02 23902404
e-mail: alessandro.gronchi@istitutotumori.mi.it

9 Trial sponsorship and financing

EORTC is the legal Sponsor for all EORTC and NCRN participants.

The contact details of the EORTC are:

EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxelles
België - Belgique
Phone: +32 2 7741611
Fax: +32 2 7723545
e-mail: eortc@eortc.be

This trial is an academic trial without any financial support from the industry.

10 Trial insurance

A clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

Clinical trial insurance is only valid in centers authorized by the EORTC Headquarters. For details please refer to the chapter on investigator authorization.

APPENDIX IV **(10/28/2013)**

NCRN Group-Specific Appendix to GOG Protocol GOG-0277

A Phase III Randomized Trial of Gemcitabine plus Docetaxel followed by Doxorubicin v observation for uterus-limited, high grade uterine leiomyosarcoma
(GOG-0277)

(EudraCT Number: 2012-002852-17)
(NCT01533207)

UK Group Specific Appendix: Version 2, 04th July 2013

The study is being co-ordinated in UK by Cancer Research UK Clinical Trials Unit, Glasgowon behalf of the National Cancer Research Network (NCRN) and National Cancer Research Institute (NCRI) Sarcoma and Gynaecology Clinical Study Groups

UK Study Co-ordinator/:
Chief Investigator
Dr Helen Hatcher
Email: hh321@medschl.cam.ac.uk

IMPORTANT INFORMATION
The protocol to which this appendix refers to has been initiated and written by the Gynecologic Oncology Group (GOG)

All technical and administrative aspects of the protocol specific to the UK (registration, responsibilities, safety reporting, etc.) are covered by this UK Group Specific Appendix.

Contact addresses for UK study co-ordinating centre

UK Study Co-ordinator/: Chief Investigator	Dr Helen Hatcher University of Cambridge Oncology Department Box 193 (R4) Addenbrooke's Hospital Hills Road Cambridge CB2 0QQ. Tel no: +44 01223 769309 Email: hh321@medschl.cam.ac.uk
Project Manager:	Karen Carty Cancer Research UK Clinical Trials Unit, Level 0 The Beatson West of Scotland Cancer Centre 1053 Great Western Road Glasgow, G12 0YN Tel no:+44 (0) 141 301 7197 Fax no:++44 (0) 0141 301 7946 Email: karen.carty@glasgow.ac.uk
Clinical Trial Co-ordinator:	Clinical Trial Co-ordinator (GOG-0277:LMS Trial) Cancer Research UK Clinical Trials Unit, Level 0 The Beatson West of Scotland Cancer Centre 1053 Great Western Road Glasgow, G12 0YN Tel no:++44 (0)141 301 Fax no:++(0)141 301
Clinical Trial Monitor:	To be confirmed Cancer Research UK Clinical Trials Unit, 44 Shelley Court Gartnavel General Hospital Complex Glasgow, G12 0YN Tel no:++ 44(0) 141 301 Fax no: ++ 44 (0) 141 301
EORTC Pharmacovigilance Unit	Tel no:++32 2 774 16 76 Fax no:++32 2 772 80 27 Email: pharmacovigilance@eortc.be

Sponsor

The European Organisation for Research and Treatment of Cancer (EORTC) is the sole legal Sponsor for participants in the European Union.

The contact details of the EORTC are:

EORTC Headquarters
Avenue E. Mounierlaan 83/11
Brussel 1200 Bruxellles
België - Belgique
Tel no : +32 2 7741611
Fax no: +32 2 7723545
Email: 55116@eortc.be

UK Signatory Page

Sponsor:

Denis Lacombe (Date)

Director, EORTC Headquarters

EORTC

European Organisation for Research and Treatment of Cancer

AISBL-IVZW

Avenue E.Mounierlann 83/11

Brussel 1200 Bruxelles

België - Belgique

UK Study Coordinator/Chief Investigator:

Dr Helen Hatcher (Date)

University of Cambridge
Oncology Department
Box 193 (R4)
Addenbrooke's Hospital
Hills Road, Cambridge,CB2 0QQ.
England, United Kingson

Table of Contents

1. Trial Organisation

- This trial is an Intergroup Trial jointly conducted by Gynecologic Oncology Group (GOG) from USA, the EORTC Gynaecology Group, EORTC Soft Tissue Bone Sarcoma Group and National Cancer Research Network [NCRN] United Kingdom.

- GOG is the lead coordinating group in this Intergroup Trial and is therefore responsible for overall trial conduct (including trial design, protocol finalisation, trial activation, data management[including the quality control of data], statistical analysis and publication.)

- In the UK the trial is being run under the auspices of the NCRN/NCRI Sarcoma and Gynaecology Clinical Study Groups with funding from Cancer Research UK. The Cancer Research UK Clinical Trials Unit, Glasgow (CTU) is co-ordinating the UK participation in the trial on behalf of NCRI/NCRN and NHS Greater Glasgow & Clyde (NHS GG&C).

- The Cancer Research UK Clinical Trials Unit, Glasgow will be main point contact for UK sites. All questions in relation to the trial should be addressed to the Cancer Research UK Clinical Trials Unit.

- The EORTC is the sole legal Sponsor for participants in the European Union.

- NHS GG&C (Legal name Greater Glasgow Health Board [GGHB]) is the Sponsor's contact (EORTC) for correspondence in the UK. GGHB and the EORTC have entered into an agreement for the study which outlines the roles and responsibilities of each party in relation to UK participation in the trial.
- The content of this appendix is applicable only for UK participating investigators; this appendix complements or supercedes the corresponding sections in the protocol.

- This trial is an academic trial without any financial support from industry.

2. Investigation Authorisation Procedure

Investigators will be authorised to register and/or randomise patients to the trial when they have returned the following documents to the Cancer Research UK Clinical Trial Unit, Glasgow and completed the site initiation process for the trial:

- Board/Trust R&D approval letter
- Fully signed Clinical Study Site Agreement.
- Completed Staff Contact and Responsibilities Sheets for all members of staff.
- Up to date, signed and dated CV's for the Principal Investigator, Co-Investigators and study team must be provided. The CV should detail the qualifications, experience and training (including GCP training) of site personnel relevant to their role in the study, and should be updated every 2 years.
- Copy of GCP certificate for Principal Investigator, Co Investigators and study team (if no formal certificate is available, some evidence should be present [i.e. register log email].If PI has had no GCP training, this should be arranged as soon as possible, and some evidence of this provided).

- Local versions of Patient Information Sheets, Consent Forms and GP Letters on hospital headed paper.
- Full contact details for all site personnel.
- Biochemistry and Haematology normal ranges and laboratory accreditation certificates

Once all of the above documentation has been received and the site initiation process for the site is complete the Cancer Research UK Clinical Trials Unit will inform the NCI Cancer Trials Support Unit (CTSU) to enable the institution to be registered on the authorisation list.

The site will be notified by email or fax when they are activated and are able to recruit patients to the trial.

3. Patient Registration & Randomisation Procedure

UK Investigators will register and/or randomise patients through the NCI Cancer Trials Support Unit (CTSU) online registration system "OPEN" (Refer to Study Protocol Chapter 5.1)

After authorisation of each site, the Cancer Research UK Clinical Trials Unit, Glasgow will take the necessary steps to request a username and password for each sites and communicate this to the site.

Any further details relevant to UK Investigators will be provided at a later time in a separate document.

3.1 Central Pathological Review (Retrospective)

3.1.1 Local Pathologist

Central pathology review will be performed retrospectively for all patients entered to the study to confirm eligibility for the study. This is **mandatory** for the study.

Following entry to the study the local pathologist will require to send stained pathology slides for central review by the reference pathologist to confirm eligibility. At least one representative H&E (haematoxylin/eosin) H&E stained slide demonstrating the primary high grade uterine leiomyosarcoma with adequate mitotic rate, nuclear atypia and tumour necrosis (if present).

For patients who have consented to take part in future translational research the local pathologist shall also include blocks or if no blocks available at least 10 unstained slides for translational research (see chapter 13)

Submitted pathology material shall be labelled with the patients sequentialID, patient initials, surgical/pathology number and block identifier.

The local pathologist shall also send the completed Pathology Form (Form F) and a copy of his/her pathology report to the reference pathologist. Personal data of the patient must be anonymised (black out the patient's name) and replaced with the sequential indentification

number allocated to the patient at time of randomisation. Please also include the patient initials and protocol number (GOG-0277) on all pages of the pathology report

The slides, copies of the Pathology Form (Form F) and official pathology report shall be sent by post to the reference pathologist for the study (Professor Cyril Fisher) at the below address:

Professor Cyril Fisher
Royal Marsden Hospital - Chelsea
Department of Histopathology
Fulham Road,
LONDON, SW3 6JJ
United Kingdom
Tel no: ++ (0) 20 78082631
Fax no: ++ (0) 20 78082578
Email: cyril.fisher@rmh.nhs.uk

UK Sites will be provided with a supply of Royal Mail Safeboxes which should be used to send pathology slides and associated paperwork to the Reference Pathologist for the study (Professor Cyril Fisher)

3.1.2 Reference Pathologist

The reference pathologist will complete the pathology review form.

For patients who have not consented to take part in future translational research , the reference pathologist will return tumour material to the sites after pathology review.

For patients who have consented to take part in the future translational research, the reference pathologist will retain the stained and unstained slides for future translational research, unless specifically required otherwise.

4. Management and Handling of Investigational Medicinal Product (IMP)

4.1 General

All the IMPs for use in the trial should be taken from usual pharmacy shelf stock, there is no provision for funding, reimbursement or discounted stock.

All IMPs should be stored prepared and administered in line with study protocol, normal hospital procedures and information contained within the current summary of product characteristics for each product.

Dose banding of IMPs is permitted where it is local policy to do so. The Cancer Research UK Clinical Trials Unit, Glasgow should be informed of this during the set-up phase of the study.

4.2 Labelling

Labelling for dispensed IMPs (Gemcitabine, Docetaxel,and Doxorubicin)
Pharmacy sites do not have to follow the template below, but should ensure that all supplies have at a minimum the following additional labelling text in addition to normal dispensing labels. (XXXX – to be completed according to local information)

LMS study (GOG-0277) **EudraCT number**: 2012-002852-17
Principal investigator: XXXX
Sponsor: European Organisation of Research and Treatment of Cancer (EORTC)
For clinical trial use only

Cycle No: XXXX **Patient Trial No:** XXXX

4.3 Storage and Accountability of IMPs

The Investigator or a delegated individual (e.g. pharmacist) must ensure that study drugs are stored and dispensed in accordance with local standard operation procedures and applicable regulatory requirements.

Each patient taking part in the study should have a log maintained of the IMP administered, the date of administration, the cycle number, the dose administered and the brand, batch number and expiry date of the product administered. Logs can be supplied by the Cancer Research UK Clinical Trials Unit, Glasgow for use for the study but local documentation can also be used after approval by the Cancer Research UK Clinical Trials Unit, Glasgow.

4.4 IMP Destruction

IMP destruction, if necessary, should be undertaken in line with local policies and procedures and a destruction log completed.

5. Drug Interactions/ Contraindications with Concomitant Medications

Please refer to the current Summary of Product Characteristics for the product for details on drug interactions and contraindications with concomitant medications.

6. Trial Management and Data Collection

6.1 Case report forms

6.2 Data Flow

- All queries will be sent from GOG Statistical and Data Centre (SDC) to the participating sites via SDC Electronic Data Entry System (SEDES) online application.

- Investigators/ Authorised personnel will submit CRFs via SDC Electronic Data Entry System (SEDES) online application.

- The GOG SDC is responsible for raising validation checks and for overall quality control of trial data.

7. Assessment of Safety/ Reporting of Serious Adverse Events

ICH GCP and the EU Directive 2001/20/EC require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events/ reactions in clinical trials. These procedures are described in this section.

7.1 Definitions

These definitions reflect the minimal regulatory obligations; specific protocol requirements might apply in addition.

AE: An **Adverse Event** is defined as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment". An adverse event can therefore be any unfavourable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including results of blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

AR: An **Adverse reaction of an investigational medicinal product** is defined as "any noxious and unintended response to a medicinal product related to any dose administered".
All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

UAR: An **Unexpected Adverse Reaction** is "any adverse reaction, the nature, or severity of which is not consistent with the applicable product information" (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for a marketed product).
When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate or severe, or as described in CTC grades); the event itself, however, may be of relative minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

SAE: A **Serious Adverse Event** is defined as any untoward medical occurrence or effect in a patient, whether or not considered related to the protocol treatment, that at any dose:
results in death

- is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- requires inpatient hospitalization or prolongation of existing patient hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is a medically important event or reaction.

  Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

  ! Grade 4 anaphylaxis reactions, regardless of whether a hospitalization is required also need to be reported as an SAE

SAR: A **Serious Adverse Reaction** is defined as any SAE which is considered related to the protocol treatment.

SUSAR: Suspected Unexpected Serious Adverse Reaction.
SUSARs occurring in clinical investigations qualify for expedited reporting to the appropriate Regulatory Authorities within the following timeframes:

- Fatal or life-threatening SUSARs within 7 calendar days
- Non-fatal or non-life-threatening SUSARs within 15 calendar days

Inpatient hospitalization: a hospital stay equal to, or greater than, 24 hours.

Second primary malignancy is one unrelated to the treatment of a previous malignancy (and is NOT a metastasis from the previous malignancy).

Secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the previous malignancy.

7.2 Exceptions

The following situations do not need to be reported as SAEs:

- Elective hospitalization for pre-existing conditions that have not been exacerbated by trial treatment.
- A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.
- A hospitalization planned for protocol related treatment or protocol related procedure as per institutional standard timelines.

- Social and/or convenience admission to a hospital
- Medical or surgical procedure (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an (S)AE.
- Situations where an untoward medical occurrence did not occur (palliative care, rehabilitation, overdose without occurrence of an adverse event).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

By EORTC convention, clinical events related to the primary cancer being studied or to the primary cancer progression are not to be reported as SAEs, even if they meet any of the seriousness criteria from the standard SAE definition, **unless** the event is more severe than expected and therefore the investigator considers that their clinical significance deserves reporting.

7.3 Severity Assessment

The severity of all AEs (serious and non-serious) in this trial should be graded using CTCAE v4.0. A copy of this can be downloaded from the following website:

www.eortc.org\investigators-area\ctc

7.4 Causality Assessment

The investigator is obligated to assess the relationship between protocol treatment and the occurrence of each SAE following the definitions in this table:

Relationship to the protocol treatment	Description
Definite	The adverse event is clearly related to the agent(s).
Probable	The adverse event is likely related to the agent(s).
Possible	The adverse event may be related to the agent(s).
Unlikely	The adverse event is doubtfully related to the agent(s).
Unrelated	The adverse event is clearly NOT related to the agent(s).

The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, medical history, concurrent conditions, concomitant therapy, other risk factors, and the temporal relationship of the event to the protocol treatment will be considered and investigated.
The decision will be recorded on the SAE form and if necessary the reason for the decision will also be recorded.

7.5 Expectedness Assessment

The expectedness assessment is the responsibility of the sponsor of the study. The expectedness assessment will be performed against the following reference documents:

- *For Gemcitabine: Summary of Product Characteristics (SmPC)*
- *For Docetaxel: Summary of Product Characteristics (SmPC)*

- *For Doxorubicin: Summary of Product Characteristics (SmPC)*

7.6 Reporting Procedure for Investigators

This procedure applies to all Serious Adverse Events (SAEs) occurring from the time a subject is registered until

For investigational arm: 30 days after last protocol treatment administration and to any SAE that occurs outside of the SAE detection period (after the 30-days period), if it is considered to have a reasonable possibility to be related to the protocol treatment or study participation.

For the observation arm: end of week 24

Registration till 30 days after last protocol treatment administration/ end of week 24 (in Observation arm):	All SAEs
From day 31 after last protocol treatment administration:	Only related SAEs

Any secondary malignancy should also be reported in expedited way on a SAE form with the appropriate seriousness criteria!

All reporting must be done by the principal investigator or authorized staff member (i.e. on the signature list) to confirm the accuracy of the report.

All SAE data must be collected on the study-specific SAE form.

All SAEs must be reported immediately and no later than 24 hours from the time the investigator or staff became aware of the event.

All SAE-related information needs to be provided in English.

All additional documents in local language must be accompanied by a translation in English, or the relevant information must be summarized in a follow-up SAE report form.

All SAE-related information must be faxed to:
EORTC Pharmacovigilance Unit:
Fax No. +32 2 772 8027

To enable the Sponsor to comply with regulatory reporting requirements, all initial SAE reports should always include the following minimal information: an identifiable patient (SeqID), a suspect medicinal product if applicable, an identifiable reporting source, the description of the medical event and seriousness criteria, as well as the causality assessment by the investigator. Complete information requested on the SAE form of any reported serious adverse event must be returned within 7 calendar days of the initial report. If the completed form is not received within this deadline, the Pharmacovigilance Unit will make a written request to the investigator.

Queries sent out by the EORTC Pharmacovigilance Unit need to be answered within 7 calendar days.

All forms need to be dated and signed by the principal investigator or any authorized staff member (i.e. on the signature list).

7.7 Reporting Responsibilities for EORTC

The EORTC Pharmacovigilance Unit will forward all EORTC/NCRN SAE reports to the appropriate persons within the EORTC Headquarters and enter them into AdEERs.
The EORTC Pharmacovigilance Unit will take in charge the reporting of SUSARs to the Competent Authorities, Ethics committees, EudraVigilance Clinical Trial Module (EVCTM) and all participating investigators, whenever applicable, or as specified in the intergroup agreement.

7.8 Pregnancy Reporting

Pregnancy occurring during a patient's participation in this trial, although not considered an SAE, must be notified to the EORTC Pharmacovigilance Unit within the same timelines as an SAE (within 24 hours) on a Pregnancy Notification Form. The outcome of a pregnancy should be followed up carefully and any adverse outcome to the mother or the child should be reported. This also applies to pregnancies in female partners of a male patient participating in this trial.

- Any pregnancy in a female subject or in a female partner of a male subject diagnosed during the treatment period or within 30 days after last protocol treatment administration must be reported to the EORTC Pharmacovigilance Unit
- This must be reported within 24 hours of first becoming aware of the event by fax, to the Pharmacovigilance Unit on a Pregnancy Notification Form
- If an SAE occurs in conjunction with the pregnancy, please also complete an SAE form as explained in the SAE reporting chapter

7.9 Development Safety Update Reports

Development Safety Update Reports (DSURs) will be prepared by GOG in the ICH E2F format. The DSUR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed, by: (1) examining whether the information obtained by the sponsor during the reporting period is in accord with previous knowledge of the investigational drug safety;(2) describing new safety issues that could have an impact on the protection of clinical trial subjects;(3) summarising the current understanding and management of identified and potential risks; and (4) providing an update on the status of the clinical investigation/development programme and study results.

8. Study Responsibilities

The European Organisation for Research and Treatment of Cancer (EORTC) is the sole legal Sponsor for participants in the European Union.

NHS Greater Glasgow and Clyde [NHS GG&C] (Legal name Greater Glasgow Health Board [GGHB]) is the Sponsor's contact (EORTC) for correspondence in the UK.

Prior to study initiation, an intergroup agreement will be put in place between the EORTC and [NHS GG&C] (Legal Name Greater Glasgow Health Board). The roles and responsibilities of each party in relation to UK participation in the trial are laid out in this agreement signed by both organisations.

A Clinical Study Agreement will be put in place between NHS Greater Glasgow and Clyde and each of the participating sites. This agreement outlines the responsibilities of each party's responsibilities in the running of the trial; the sponsor, the Chief Investigator (C.I.), the Cancer Research UK Clinical Trials Unit, Glasgow (CTU), the Principal Investigator (P.I.) at the Participating Site and the Participating Site. In summary, they are as follows:

8.1 Sponsor Responsibilities (EORTC)

The Sponsor's responsibilities will be for Authorisation and Ethics Committee opinion, GCP and Conduct and Pharmacovigilance. In the UK, the majority of the Sponsor's responsibilities have been delegated to NHS GG&C which has, in turn, delegated these to the Chief Investigator (CI) who performs these via the CTU as the co-ordinating centre for the study in the UK. As such, the main role of the Sponsor is to ensure that NHS GG&C, the CI and CTU fulfil their responsibilities as outlined in the Clinical Study Agreement and to ensure that any identified "risks" either have controls or action points put in place.

8.2 CR-UK Clinical Trials Unit (CTU)

NHS GG&C via the CTU is responsible for the co-ordination of the clinical trial in the UK. This includes all regulatory submissions (ethics, R&D and CTA), all administration relating to the submissions and any amendments, circulation of all correspondence to participating sites, ongoing communication with participating sites, and where applicable the management of any financial arrangements (e.g. payment for pathology samples etc).

8.3 Chief Investigator (C.I.)

The Chief Investigator has delegated the majority of his/her responsibilities to the CTU. The C.I. is directly responsible for ensuring the protocol and any amendments are in place, for review of SAE forms and determination of whether they meet the criteria for a SUSAR, and to provide advice and recommendations on medical issues that arise involving the management of the patients on the study. As the Chief Investigator is external to NHS GG&C an agreement will be put in place between the Chief Investigator's employer and NHS GG&C for this study to outline the responsibilities of each party.

8.4 Participating Site

The Participating Site is responsible for the management of the trial within their site. This includes ensuring local management approval has been given, ensuring the study is conducted according to ICH GCP requirements, and ensuring the appropriate insurance or indemnity is in place. The Participating Site is also responsible for arranging access for on-site monitoring and auditing as identified in the study protocol and also for regulatory inspections.

8.5 Principal Investigator (P.I.)

The P.I. is responsible for the delegation of study activities within their unit and ensuring all personnel are adequately trained and qualified to carry out their responsibilities. The P.I will be required to provide evidence of GCP training (usually a certificate) or undergo the required GCP training. Regarding the management of patients within their site, the P.I. is responsible for the safety and well being of trial patients, reporting any deviations from the

protocol to the CTU as well as any SAEs or safety issues. Full details of the responsibilities of the P.I. are outlined in the Clinical Study Agreement. Two original copies of this will be held – one with NHS GG&C and the other at the Participating Site. A photocopy of the signed agreement will also be held within the CTU and EORTC.

9. Liability and Indemnity

The Health Board/NHS Trust at each participating site is responsible for the following:

1. Acts and omissions of its own staff and others engaged by it, including the Clinical Trials Unit and PI;
2. Ensuring the appropriate insurance administered by the National Health Service Litigation Authority is in place;
3. Ensuring any non-NHS employee involved in the clinical trial has an Honorary Contract with the Trust to cover access to patients and liability arrangements.

These responsibilities are outlined and agreed within the Clinical Study Agreement.

Clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted by the EORTC. An insurance certificate will be made available to participating sites at the time of study initiation.

Clinical trial insurance is only valid in centres in the UK which have been authorised. Please refer to the section 2 of this appendix for details of the investigator authorisation procedure for the study.

10. Regulatory Issues

10.1 Clinical Trials Authorisation (CTA)

The Cancer Research UK Clinical Trials Unit, Glasgow will apply to the MHRA for a clinical trials authorisation (CTA) to conduct the trial in the UK and will also be responsible for the maintenance of the CTA.

10.2 Ethics and Research & Development Approval

Ethics favourable opinion will be sought for the study from a Main REC prior to commencement of this trial. Further to that approval each participating site will be responsible for obtaining their own local approval by submitting an SSI to their appropriate R&D department for management approval.

10.3 Informed Consent

Consent to enter the study must be sought from each participant only after full explanation has been given, the participant has been given an information sheet and a minimum of 24 hours to consider trial participation. Signed participant consent must be obtained, the consent forms should also be signed by the person undertaking the consent procedure at site, who must be detailed on the Staff Contact and Responsibility Log as having this authorisation. The Principal Investigator is responsible for ensuring if taking consent is delegated to a

designee, the designee is suitably qualified by training or experience to take informed consent.

The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the best interests of the participant, but the reasons for doing so must be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

An original completed consent form must be retained at each site in the appropriate section of the Investigator Site File, and a copy placed in the patient's medical records. All patients must be given an original of the signed patient information sheet and consent form for their records. Consent forms must be retained on site and not submitted to the Trials Office.

10.4 Confidentiality

National Health Service Guidelines for storage, transmittal and disclosure of patient information will be followed at all times.

This study will be carried out in accordance with ICH GCP Guidelines. Following formal admission to the study, patient data will be recorded in the hospital case record in the usual way including the circumstances of their entry to the study. Additionally data will be held in study case report forms (CRF). These files will be identified by a trial number and patient initials only.

Representatives from the Study Sponsors and from the regulatory authorities will be given access to the records that relate to the study. They will have full access to the anonymous CRF for the purposes of data validation.

Results of the study may be communicated at scientific meetings and will contribute to the scientific literature. At no time will this be done in such a way that an individual patient may be identified.

10.5 Quality Assurance/Quality Control

Quality Assurance/Quality Control will be maintained by the following requirements and activities:

- All study sites taking part in the trial will be required to participate in site initiation to ensure compliance with the protocol and allow training on study procedures and data collection methods.

- Trial Investigators and site staff must ensure that the trial is conducted in compliance with the protocol, GCP and applicable regulatory requirements.

- The CR-UK CTU, Glasgow will the assist the Trial Investigators and check they are complying with protocol, GCP and regulatory requirements by monitoring trial

documentation. Trial data and documentation will be checked for completeness, accuracy and reliability at monitoring visits.

10.6 Monitoring

Central Monitoring
Study sites will be centrally monitored by checking CRFs and other study documents for protocol compliance, data accuracy and completeness.

On-Site Monitoring
All UK participating study sites will be visited by a member of the CR-UK Clinical Trials Unit monitoring team. The PI will allow the study staff access to source documents as requested. In addition, the pharmacy department responsible for the trial will be visited to allow monitoring of the pharmacy site file and review of security, storage and accountability of trial drug. Investigators and site staff will be notified in advance about forthcoming monitoring visits. On occasion, members of the CR-UK CTU monitoring team may be accompanied by other trial staff from the unit for training purposes.

10.7 Audits and Inspections

Trial Investigators must permit trial related monitoring, audits, REC review and regulatory inspections as required, by providing direct access to source data, CRFs and other documents (patients medical records, trial site file, and other pertinent data).

The study may be subject to inspection and audit by EORTC under their remit as Sponsor the CR-UK CTU and other regulatory bodies, i.e. the MHRA, to ensure adherence to GCP, the Gynaecologic Oncology Group (GOG) as the lead co-ordinating group for the trial.

If an inspection is scheduled at any participating site, the site must notify the CR-UK CTU at the earliest opportunity.

11. Patient Information Sheets and Consent Forms

The UK Main Patient Information Sheet and Consent Form and Translational Patient Information Sheet will be provided separately for this study. Please check local approval letters to ensure the most current approved Patient Information Sheets and Consent Forms are being used.

12. GP Letter

The UK GP letter will be provided separately for this study. Please check local approval letters to ensure the most current GP letter is being used.

13. Translational Research

In this trial, tissue specimens will be collected for future translational research. However, specimen submission for translational research is not mandatory for participation in the

clinical study. Specimens will be collected from enrolled patients who are willing and who have consented to the future translational research.

Please note submission of a stained pathology slide for confirming eligibility to the study is mandatory for all patients as detailed in section 3.1 for central pathological review is mandatory for all patients. The samples provided for central pathology review will be returned to sites after pathology review has taken place for patients who have not consented to participate in the future translational research .

For patients who have consented to take part in the future translational research, the reference pathologist will retain the unstained slides for future translational research, unless specifically required otherwise.