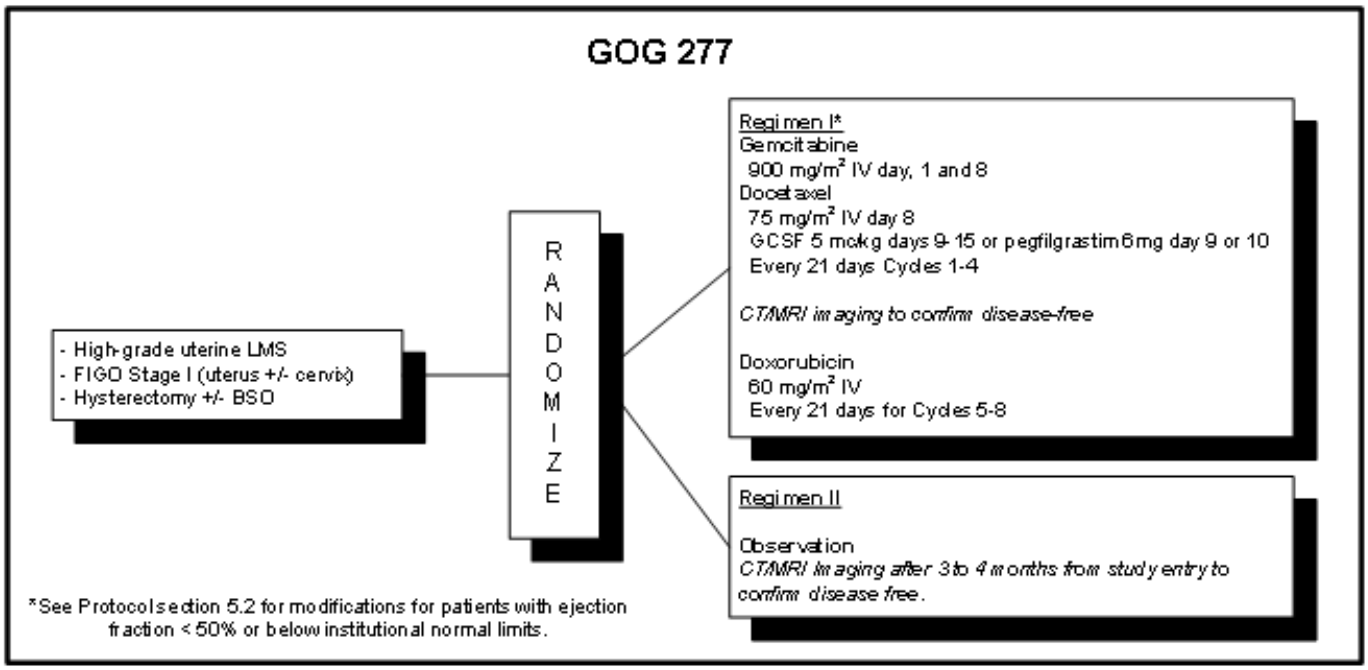
NRG ONCOLOGY

Advancing Research. Improving Lives.

GOG-0277

Report Based on Data Through 10/31/2016

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



Study Chairs: GOG: Martee Hensley, MD; NCRN: Helen Hatcher, MD; EORTC: Isabelle Ray-Coquard, MD, PhD, James Hoffman, MD, Helen Michael, MD

Protocol Statisticians: Virginia Filiaci, PhD

Data Coordinator: Bette Stonebraker, CCRA

Activated: 6/4/2012

Closed to Accrual: 9/20/2016

Status: Closed to Accrual, in follow-up for adverse events

- **Study Description**

  The study is designed as a two arm open label international 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 was to provide a direct assessment of the null hypothesis that multi-agent adjuvant chemotherapy offers no increase in survival when compared with observation until recurrence. This study is the first study opened in collaboration with the International Rare Cancer Initiative (IRCI) and has significant international support through EORTC and CRUK.

  Adult women with high risk uterine leiomyosarcoma, FIGO stage I (confined to corpus +/- cervix) are eligible. The primary endpoint is survival; the interim futility endpoint is recurrence-free survival. Secondary endpoints include the frequency and severity of adverse events in each arm and evaluation of potential predictors of recurrence or death such as patient age, and institution reported tumor size, cervix involvement (yes or no), and mitotic rate.

- **Patient Accrual**

  The study was open to accrual on 6/4/2012 (Table 1). The first participant was enrolled on May 3, 2013. The study prematurely closed on 9/20/2016 due to slow accrual despite the international effort. A total of 38 patients (18%) have been enrolled and received a random treatment assignment.

  As of May 2, 2016, the median follow-up time for 38 eligible patients is 7 months. Significant time and effort have been devoted towards international participation which began before the study activated in 2012. With the recent reorganization of NCTN, international participation had only recently begun to pick up speed. NRG Oncology had appealed CTEP's decision to close the study to accrual in light of the initiation of international accrual and was given until July 2016 to increase accrual. Due to the premature closure of GOG-0277 by the US sponsor because of slow accrual, the study will not meet the protocol specified statistical requirements for interim or final analysis.

- **Patient and Tumor Characteristics**

  Among the 38 participants, none have been deemed ineligible on central review (Table 2). Of all eligible patients enrolled, 3 were never treated and 2 have withdrawn consent to continued follow-up (Table 2). Patient and tumor characteristics of all enrolled patients are presented in Table 3. The majority of participants are between the ages of 40 and 69, non-Hispanic, or white.

- **Adverse Events**

  Adverse events for this study are graded and categorized using CTCAE v4. As of October 31, 2016, 35 eligible study participants have been reported to have initiated study treatment and are included in the adverse event tables. Three patients have refused to initiate study treatment. Table 4 reports the frequencies of the maximum grade of acute adverse events within each system organ class and overall adverse event terms, regardless of attribution. A grade 3 or higher adverse event has been reported in 11 participants; all but one occurred in patients on the treatment arm. No grade 5 adverse events have been reported. All reported adverse event terms belonging in a system organ class that had at least one grade 3 or higher adverse event reported are included in Table 5.

Table 1
GOG-0277 Accrual Summary as of 10/31/2016

Date activated to accrual:	06/04/2012
Target sample size:	216
Total accrual as of 10/31/2016:	38
Percent of total targeted accrual as of 10/31/2016:	18%

Table 2
GOG-0277 Accrual/Eligibility as of 10/31/2016

	Gem/Doc-->Dox	Observation	Total
Randomized	20	18	38
Never Treated	3	0	3
Withdrew Consent for Follow-up	1	1	2
Eligible and Treated	16	17	33

Table 3
Patient and Tumor Characteristics for All Enrolled Patients
in GOG-0277 - Data as of 10/31/2016

Characteristic	Regimen					
	Gem/Doc-->Dox		Observation		Total	
	N	%	N	%	N	%
Age Group						
30-39	2	10.0	0	0	2	5.3
40-49	4	20.0	4	22.2	8	21.1
50-59	10	50.0	7	38.9	17	44.7
60-69	3	15.0	5	27.8	8	21.1
70-79	1	5.0	2	11.1	3	7.9
Ethnicity						
Hispanic or Latino	2	10.0	0	0	2	5.3
Non-Hispanic	16	80.0	17	94.4	33	86.8
Not Specified	2	10.0	1	5.6	3	7.9
Race						
White	15	75.0	11	61.1	26	68.4
Black/African American	1	5.0	4	22.2	5	13.2
Am Indian/Alaskan Native	0	0	1	5.6	1	2.6
Other	1	5.0	1	5.6	2	5.3
Not Specified	3	15.0	1	5.6	4	10.5
Stage						
1	20	100.0	18	100.0	38	100.0
Total	20	52.6	18	47.4	38	100.0

Table 4
Distribution of GOG-0277 Patients by Highest Grade Adverse Event
By System Organ Class - Data as of 10/31/2016
For All Reported Adverse Events without Regard to Attribution

	Gem/Doc-->Dox (n=17)					Observation (n=18)				
	No. and (%) of Patients by Grade					No. and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
System Organ Class										
Overall Highest Grade	0	4	7	3	0	5	5	1	0	0
	(0.0)	(23.5)	(41.2)	(17.6)	(0.0)	(27.8)	(27.8)	(5.6)	(0.0)	(0.0)
Blood and Lymphatic System Disorders	2	10	2	0	0	1	0	0	0	0
	(11.8)	(58.8)	(11.8)	(0.0)	(0.0)	(5.6)	(0.0)	(0.0)	(0.0)	(0.0)
Cardiac Disorders	2	1	0	0	0	1	0	0	0	0
	(11.8)	(5.9)	(0.0)	(0.0)	(0.0)	(5.6)	(0.0)	(0.0)	(0.0)	(0.0)
Ear and Labyrinth Disorders	1	0	0	0	0	0	0	0	0	0
	(5.9)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Eye Disorders	2	0	0	0	0	1	0	0	0	0
	(11.8)	(0.0)	(0.0)	(0.0)	(0.0)	(5.6)	(0.0)	(0.0)	(0.0)	(0.0)
Gastrointestinal Disorders	7	3	2	0	0	5	2	0	0	0
	(41.2)	(17.6)	(11.8)	(0.0)	(0.0)	(27.8)	(11.1)	(0.0)	(0.0)	(0.0)
General Disorders and Administration Site Conditions	6	5	2	0	0	8	0	0	0	0
	(35.3)	(29.4)	(11.8)	(0.0)	(0.0)	(44.4)	(0.0)	(0.0)	(0.0)	(0.0)
Infections and Infestations	0	4	2	0	0	0	1	0	0	0
	(0.0)	(23.5)	(11.8)	(0.0)	(0.0)	(0.0)	(5.6)	(0.0)	(0.0)	(0.0)
Injury, Poisoning and Procedural Complications	0	0	1	0	0	0	0	0	0	0
	(0.0)	(0.0)	(5.9)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Investigations	4	5	2	2	0	0	0	0	0	0
	(23.5)	(29.4)	(11.8)	(11.8)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Metabolism and Nutrition Disorders	3	2	1	1	0	0	1	0	0	0
	(17.6)	(11.8)	(5.9)	(5.9)	(0.0)	(0.0)	(5.6)	(0.0)	(0.0)	(0.0)
Musculoskeletal and Connective Tissue Disorders	6	0	0	0	0	5	0	0	0	0
	(35.3)	(0.0)	(0.0)	(0.0)	(0.0)	(27.8)	(0.0)	(0.0)	(0.0)	(0.0)
Nervous System Disorders	5	1	1	0	0	2	1	0	0	0
	(29.4)	(5.9)	(5.9)	(0.0)	(0.0)	(11.1)	(5.6)	(0.0)	(0.0)	(0.0)
Psychiatric Disorders	3	2	0	0	0	5	0	0	0	0

	Gem/Doc-->Dox (n=17)					Observation (n=18)				
	No. and (%) of Patients by Grade					No. and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
System Organ Class										
	(17.6)	(11.8)	(0.0)	(0.0)	(0.0)	(27.8)	(0.0)	(0.0)	(0.0)	(0.0)
Renal and Urinary Disorders	2	2	0	0	0	2	0	0	0	0
	(11.8)	(11.8)	(0.0)	(0.0)	(0.0)	(11.1)	(0.0)	(0.0)	(0.0)	(0.0)
Reproductive System and Breast Disorders	1	0	0	0	0	2	0	0	0	0
	(5.9)	(0.0)	(0.0)	(0.0)	(0.0)	(11.1)	(0.0)	(0.0)	(0.0)	(0.0)
Respiratory, Thoracic and Mediastinal Disorders	5	1	1	0	0	2	0	0	0	0
	(29.4)	(5.9)	(5.9)	(0.0)	(0.0)	(11.1)	(0.0)	(0.0)	(0.0)	(0.0)
Skin and Subcutaneous Tissue Disorders	0	11	0	0	0	2	0	0	0	0
	(0.0)	(64.7)	(0.0)	(0.0)	(0.0)	(11.1)	(0.0)	(0.0)	(0.0)	(0.0)
Surgical and Medical Procedures	1	0	0	0	0	0	0	0	0	0
	(5.9)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Vascular Disorders	2	2	1	0	0	2	3	1	0	0
	(11.8)	(11.8)	(5.9)	(0.0)	(0.0)	(11.1)	(16.7)	(5.6)	(0.0)	(0.0)

Adverse events were graded with CTCAE version 4

Table 5
Distribution of GOG-0277 Patients by Highest Grade Adverse Event
By Specific Adverse Event Term - Data as of 10/31/2016
For Selected Adverse Events without Regard to Attribution

	Gem/Doc-->Dox (n=17)					Observation (n=18)				
	No. and (%) of Patients by Grade					No. and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
Organ System/Term										
Blood and Lymphatic System Disorders	**2**	**10**	**2**	**0**	**0**	**1**	**0**	**0**	**0**	**0**
	(11.8)	**(58.8)**	**(11.8)**	**(0.0)**	**(0.0)**	**(5.6)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**
Anemia	2	10	1	0	0	1	0	0	0	0
	(11.8)	(58.8)	(5.9)	(0.0)	(0.0)	(5.6)	(0.0)	(0.0)	(0.0)	(0.0)

	Gem/Doc-->Dox (n=17)					Observation (n=18)				
	No. and (%) of Patients by Grade					No. and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
Organ System/Term										
Leukocytosis	0	0	1	0	0	0	0	0	0	0
	(0.0)	(0.0)	(5.9)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Cardiac Disorders	**2**	**1**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**
	(11.8)	**(5.9)**	**(0.0)**	**(0.0)**	**(0.0)**	**(5.6)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**
Ear and Labyrinth Disorders	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	(5.9)	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**
Eye Disorders	**2**	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**
	(11.8)	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(5.6)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**
Gastrointestinal Disorders	**7**	**3**	**2**	**0**	**0**	**5**	**2**	**0**	**0**	**0**
	(41.2)	**(17.6)**	**(11.8)**	**(0.0)**	**(0.0)**	**(27.8)**	**(11.1)**	**(0.0)**	**(0.0)**	**(0.0)**
Abdominal Pain	1	0	1	0	0	4	0	0	0	0
	(5.9)	(0.0)	(5.9)	(0.0)	(0.0)	(22.2)	(0.0)	(0.0)	(0.0)	(0.0)
Diarrhea	4	0	1	0	0	1	0	0	0	0
	(23.5)	(0.0)	(5.9)	(0.0)	(0.0)	(5.6)	(0.0)	(0.0)	(0.0)	(0.0)
Nausea	8	1	1	0	0	1	0	0	0	0
	(47.1)	(5.9)	(5.9)	(0.0)	(0.0)	(5.6)	(0.0)	(0.0)	(0.0)	(0.0)
Vomiting	3	0	1	0	0	1	0	0	0	0
	(17.6)	(0.0)	(5.9)	(0.0)	(0.0)	(5.6)	(0.0)	(0.0)	(0.0)	(0.0)
General Disorders and Administration Site Conditions	**6**	**5**	**2**	**0**	**0**	**8**	**0**	**0**	**0**	**0**
	(35.3)	**(29.4)**	**(11.8)**	**(0.0)**	**(0.0)**	**(44.4)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**
Fatigue	8	3	1	0	0	5	0	0	0	0
	(47.1)	(17.6)	(5.9)	(0.0)	(0.0)	(27.8)	(0.0)	(0.0)	(0.0)	(0.0)
Pain	1	0	1	0	0	1	0	0	0	0
	(5.9)	(0.0)	(5.9)	(0.0)	(0.0)	(5.6)	(0.0)	(0.0)	(0.0)	(0.0)
Infections and Infestations	**0**	**4**	**2**	**0**	**0**	**0**	**1**	**0**	**0**	**0**
	(0.0)	**(23.5)**	**(11.8)**	**(0.0)**	**(0.0)**	**(0.0)**	**(5.6)**	**(0.0)**	**(0.0)**	**(0.0)**
Catheter Related Infection	0	0	1	0	0	0	0	0	0	0
	(0.0)	(0.0)	(5.9)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Skin Infection	0	0	1	0	0	0	0	0	0	0
	(0.0)	(0.0)	(5.9)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)

	Gem/Doc-->Dox (n=17)					Observation (n=18)				
	No. and (%) of Patients by Grade					No. and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
Organ System/Term										
Wound Infection	0	0	1	0	0	0	0	0	0	0
	(0.0)	(0.0)	(5.9)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Injury, Poisoning and Procedural Complications	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	(0.0)	**(0.0)**	**(5.9)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**
Vascular Access Complication	0	0	1	0	0	0	0	0	0	0
	(0.0)	(0.0)	(5.9)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Investigations	**4**	**5**	**2**	**2**	**0**	**0**	**0**	**0**	**0**	**0**
	(23.5)	**(29.4)**	**(11.8)**	**(11.8)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**
Alanine Aminotransferase Increased	3	1	1	0	0	0	0	0	0	0
	(17.6)	(5.9)	(5.9)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Neutrophil Count Decreased	1	3	1	2	0	0	0	0	0	0
	(5.9)	(17.6)	(5.9)	(11.8)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
White Blood Cell Decreased	3	1	2	0	0	0	0	0	0	0
	(17.6)	(5.9)	(11.8)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Metabolism and Nutrition Disorders	**3**	**2**	**1**	**1**	**0**	**0**	**1**	**0**	**0**	**0**
	(17.6)	**(11.8)**	**(5.9)**	**(5.9)**	**(0.0)**	**(0.0)**	**(5.6)**	**(0.0)**	**(0.0)**	**(0.0)**
Hyperglycemia	0	1	1	1	0	0	1	0	0	0
	(0.0)	(5.9)	(5.9)	(5.9)	(0.0)	(0.0)	(5.6)	(0.0)	(0.0)	(0.0)
Musculoskeletal and Connective Tissue Disorders	**6**	**0**	**0**	**0**	**0**	**5**	**0**	**0**	**0**	**0**
	(35.3)	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(27.8)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**
Nervous System Disorders	**5**	**1**	**1**	**0**	**0**	**2**	**1**	**0**	**0**	**0**
	(29.4)	**(5.9)**	**(5.9)**	**(0.0)**	**(0.0)**	**(11.1)**	**(5.6)**	**(0.0)**	**(0.0)**	**(0.0)**
Syncope	0	0	1	0	0	0	0	0	0	0
	(0.0)	(0.0)	(5.9)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Psychiatric Disorders	**3**	**2**	**0**	**0**	**0**	**5**	**0**	**0**	**0**	**0**
	(17.6)	**(11.8)**	**(0.0)**	**(0.0)**	**(0.0)**	**(27.8)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**
Renal and Urinary Disorders	**2**	**2**	**0**	**0**	**0**	**2**	**0**	**0**	**0**	**0**
	(11.8)	**(11.8)**	**(0.0)**	**(0.0)**	**(0.0)**	**(11.1)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**

	Gem/Doc-->Dox (n=17)					Observation (n=18)				
	No. and (%) of Patients by Grade					No. and (%) of Patients by Grade				
	1	2	3	4	5	1	2	3	4	5
Organ System/Term										
Reproductive System and Breast Disorders	**1**	**0**	**0**	**0**	**0**	**2**	**0**	**0**	**0**	**0**
	(5.9)	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(11.1)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**
Respiratory, Thoracic and Mediastinal Disorders	**5**	**1**	**1**	**0**	**0**	**2**	**0**	**0**	**0**	**0**
	(29.4)	**(5.9)**	**(5.9)**	**(0.0)**	**(0.0)**	**(11.1)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**
Dyspnea	2	1	1	0	0	0	0	0	0	0
	(11.8)	(5.9)	(5.9)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
Skin and Subcutaneous Tissue Disorders	**0**	**11**	**0**	**0**	**0**	**2**	**0**	**0**	**0**	**0**
	(0.0)	**(64.7)**	**(0.0)**	**(0.0)**	**(0.0)**	**(11.1)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**
Surgical and Medical Procedures	**1**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	(5.9)	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**	**(0.0)**
Vascular Disorders	**2**	**2**	**1**	**0**	**0**	**2**	**3**	**1**	**0**	**0**
	(11.8)	**(11.8)**	**(5.9)**	**(0.0)**	**(0.0)**	**(11.1)**	**(16.7)**	**(5.6)**	**(0.0)**	**(0.0)**
Hypertension	0	1	1	0	0	0	1	1	0	0
	(0.0)	(5.9)	(5.9)	(0.0)	(0.0)	(0.0)	(5.6)	(5.6)	(0.0)	(0.0)
Thromboembolic Event	0	1	1	0	0	0	0	0	0	0
	(0.0)	(5.9)	(5.9)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)

Adverse events were graded with CTCAE version 4