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TO: ALL PRINCIPAL INVESTIGATORS/NURSES/DATA MANAGERS

FROM: MEG COLAHAN
PROTOCOL SECTION

DATE: AUGUST 15, 2016

RE: GOG-0279 – AMENDMENT #4

Protocol Title: “A PHASE II TRIAL EVALUATING CISPLATIN (NSC #119875) AND GEMCITABINE (NSC # 613327) CONCURRENT WITH INTENSITY-MODULATED RADIATION THERAPY (IMRT) IN THE TREATMENT OF LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE VULVA *NCI Version Date: 07/21/2016*

Study Chair: Neil S. Horowitz, M.D.; (617) 724-8843; E-mail: nhorowitz@partners.org

IRB Recommendations

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

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

The following changes have been made and become effective August 15, 2016:

SUMMARY OF CHANGES

For Protocol Amendment #4 to: GOG-0279

NCI Protocol #: GOG-0279
Local Protocol #: GOG-0279

NCI Version Date: 07/21/2016
Protocol Date: 08/15/2016

#	Section	Page(s)	Change
1	<i>Title Pages</i>	1 and 2	<ul style="list-style-type: none"> • NCI Version Date is now 07/21/2016 • Includes Amendments #1-4 • to reflect date of revision.
2	<i>Schema</i>	3	Consent should be obtained prior to surgery; registration should occur within 2 weeks of surgery.
3	4.3511	15	In the first sentence, “64 Gy in 34 fractions” has been corrected to “64 Gy in 32 fractions.”
4	4.39	20, 21	The second sentence now reads: “It is anticipated that radiation therapy will start as soon as clinically feasible at the discretion of the treating physician, but within 6 weeks of enrollment.”
5	5.4	28, 29	<ul style="list-style-type: none"> • “Although it is preferable to have patients registered for the trial prior to the lymph node surgical evaluation, patients may be registered/enrolled postoperatively. If patients do not register/enroll until postoperative from the groin node assessment, the treating physician should determine if patients meet eligibility requirements (requirement 3.13 can be determined as part of standard practice in preoperative lab work) and confirm that they and the patient agree the treatment protocol is appropriate and acceptable therapy” has been added to the first paragraph. • “As time to recover from a sentinel lymph node biopsy is different from an inguinal femoral dissection, commencement of radiation post-operatively will be at the discretion of the treatment physician, however, patients must be registered/enrolled in the trial within 2 weeks of surgery and IMRT must start no later than 6 weeks after surgery” has been added to the “Radiation” paragraph. • The second to the last paragraph now reads: “Chemotherapy should start on the same day as the start of radiation. There is no required timeframe for chemotherapy (i.e., before or after radiation) on the day of radiation.”
6	6.0	30	<ul style="list-style-type: none"> • A “Dose Delay” table has been added for clarity. • The dose reduction table has been labeled, “Dose Modifications.”

#	Section	Page(s)	Change
7	7.1	36	<ul style="list-style-type: none"> • <u>The list of blood chemistries has been replaced with “Clinical Chemistry” and a reference to note 10 which lists the required tests has been added to the Pre-treatment column.</u> • <u>“(+/- 10 day window)” has been added to the last Post-Treatment column heading.</u>
8	8.21	39	<u>This section now reads: “Overall Survival – defined as the observed length of life from start of protocol therapy to death or, for living patients, the date of last contact.”</u>
9	8.22	39	<u>This section now reads: “Progression-free interval – defined as the date from start of protocol therapy to date of reappearance of disease or date of last contact.”</u>
10	Appendix II	58	<u>The appendix has been revised to reflect the most current version: the last bullet has been deleted.</u>
	IC		Additional changes have been made to the IC.

NCI Protocol #: GOG-0279
Version Date: 07/21/2016

PROTOCOL GOG-0279

A PHASE II TRIAL EVALUATING CISPLATIN (NSC #119875) AND GEMCITABINE (NSC # 613327) CONCURRENT WITH INTENSITY-MODULATED RADIATION THERAPY (IMRT) IN THE TREATMENT OF LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE VULVA (NCT #01595061) (04/21/2014)

NCI Version Date: 07/21/2016

Includes Amendments #1 -4

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PER CAPITA - 20

MEMBERSHIP - 3

Lead Organization: NRG / NRG Oncology (04/21/2014)

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EN TO PATIENT ENTRY JULY 2, 2012; REVISED NOVEMBER 13, 2012;
REVISED AUGUST 26, 2013; REVISED APRIL 21, 2014;
TEMPORARILY CLOSED TO PATIENT ENTRY JUNE 15, 2015; REVISED AUGUST 15, 2016

PROTOCOL GOG-0279
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TREATMENT OF LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF THE VULVA
NCI Version Date: 07/21/2016

CONTACT INFORMATION (04/21/2014)		
To submit site registration documents:	For patient enrollments:	Submit study data
<p>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)</p>	<p>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.</p> <p>Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.</p>	<p>Use the SDC Electronic Data Entry System (SEDES) online application found at the GOG Web Menu page, to view and print a copy of each form along with instructions, and to submit forms electronically. All amendments to forms submitted through SEDES must also be submitted through SEDES. The original form and required copies for forms NOT submitted online must be mailed to the GOG SDC.</p> <p>GOG Statistical and Data Center Roswell Park Cancer Institute, Carlton and Elm Streets, Buffalo, New York, 14263-0001 716-845-5702 FAX: 716-845-8393</p> <p>Do <u>not</u> submit study data or forms to CTSU Data Operations. Do <u>not</u> copy the CTSU on data submissions.</p>
<p>The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.</p>		
<p><u>For clinical questions (i.e. patient eligibility or treatment-related)</u> Contact the Study PI of the Lead Protocol Organization</p>		
<p><u>For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission)</u> 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.</p>		
<p><u>For detailed information on the regulatory and monitoring procedures for CTSU sites</u> please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org > education and resources tab > CTSU Operations Information > CTSU Regulatory and Monitoring Policy</p>		
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SHEMA

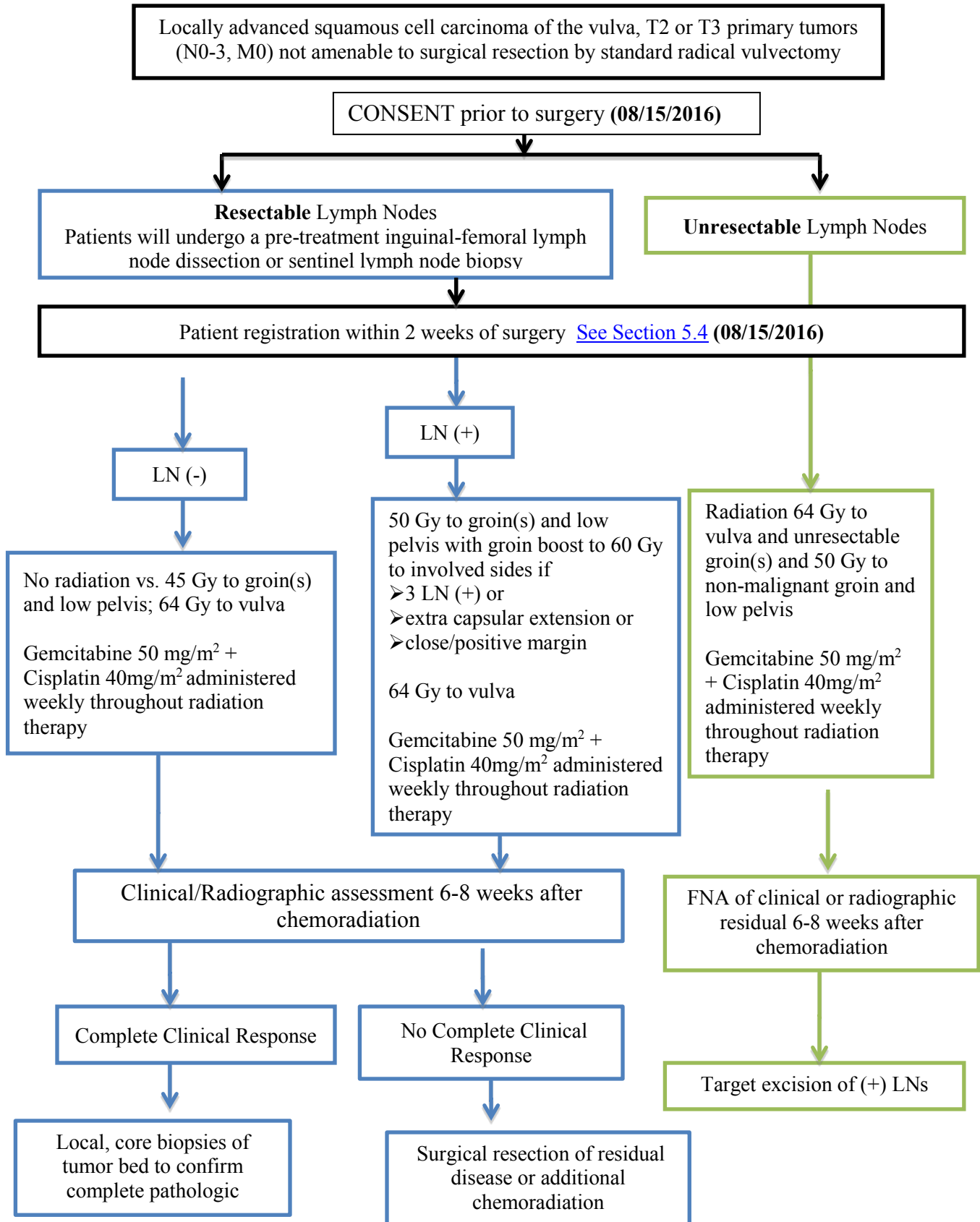


TABLE OF CONTENTS

	<u>PAGE</u>
SCHEMA	- 2 -
1.0 OBJECTIVES	- 5 -
1.1 Primary Objectives	- 5 -
1.2 Secondary Objectives	- 5 -
2.0 BACKGROUND AND RATIONALE	- 5 -
2.1 Inclusion of Women and Minorities	- 7 -
3.0 PATIENT ELIGIBILITY AND EXCLUSIONS	- 8 -
3.1 Eligible Patients	- 8 -
3.2 Ineligible Patients	- 8 -
4.0 STUDY MODALITIES	- 10 -
4.1 Cisplatin (Platinol®-AQ) (NSC #119875)	- 10 -
4.2 Gemcitabine, Gemzar® (NSC #613327)	- 11 -
4.3 Radiation Therapy	- 13 -
4.4 Pathology Requirements	- 21 -
5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE (04/21/2014)	- 23 -
5.1 IROC HOUSTON (FORMERLY THE RADIOLOGICAL PHYSICS CENTER [RPC]) CREDENTIALING REQUIREMENTS (04/21/2014)	- 23 -
5.2 Registration Procedures (04/21/2014)	- 24 -
5.3 Patient Entry and Registration (04/21/2014)	- 27 -
5.4 Treatment Plan ()	- 28 -
6.0 TREATMENT MODIFICATIONS ()	- 30 -
6.1 Cisplatin Modifications (see Section 6.2 for Gemcitabine Modifications)	- 30 -
6.2 Gemcitabine Modifications	- 33 -
6.3 Radiation Modifications:	- 35 -
7.0 STUDY PARAMETERS	- 36 -
7.1 Observations and Tests ()	- 36 -
7.2 STAINED PATHOLOGY SLIDE REQUIREMENTS FOR CENTRAL REVIEW TO CONFIRM ELIGIBILITY (08/26/2013)	- 37 -
7.3 Translational Research	- 38 -
7.4 Quality of Life	- 38 -
8.0 EVALUATION CRITERIA	- 39 -
8.1 Objective Response	- 39 -
8.2 Other Objective Response	- 39 -
8.3 Subjective Response	- 39 -
8.4 Adverse Effects	- 39 -
9.0 DURATION OF STUDY	- 40 -
9.1 Patients will continue on study until disease progression or adverse effects prohibit further treatment. The patient can refuse the study treatment at any time.	- 40 -
9.2 All patients will be treated (with completion of all required case report forms) through the duration of the protocol treatment, until disease progression while on protocol treatment, unacceptable toxicity, or study withdrawal. Patients will then be followed (with physical exams and histories) every three months for the first two years and then every six months	

	for the next three years. Patients will be monitored for delayed toxicity and survival for this 5-year period with Q forms submitted to the GOG Statistical and Data Center, unless consent is withdrawn. (08/26/2013)	- 40 -
10.0	STUDY MONITORING AND REPORTING PROCEDURES	- 41 -
10.1	ADVERSE EVENT REPORTING FOR A COMMERCIAL AGENT (04/21/2014)	- 41 -
10.2	GOG DATA MANAGEMENT FORMS	- 44 -
11.0	STATISTICAL CONSIDERATIONS	- 46 -
11.1	Study Objectives	- 46 -
11.2	Endpoints and Data Elements	- 46 -
11.3	Accrual and Study Duration	- 47 -
11.4	Study Design and Sample Size Justification.	- 47 -
11.5	Analysis Plan	- 50 -
11.6	Study Monitoring, Data Quality Control and Semi-annual Reports	- 51 -
11.7	Planned Minority Inclusion	- 53 -
12.0	BIBLIOGRAPHY	- 54 -
	APPENDIX I	- 56 -
	APPENDIX II	- 58 -
	APPENDIX III	- 59 -
	APPENDIX IV	- 60 -
	APPENDIX V	- 61 -

SUGGESTED PATIENT INFORMATION/INFORMED CONSENT

1.0 OBJECTIVES

1.1 Primary Objectives

- 1.11 To determine the efficacy of cisplatin, gemcitabine, and Intensity-Modulated Radiation Therapy (IMRT) in achieving a complete pathologic response when used for the primary treatment of locally-advanced squamous cell carcinoma of the vulva.

1.2 Secondary Objectives

- 1.21 To determine the efficacy of cisplatin, gemcitabine, and IMRT in achieving a complete clinical response when used for the primary treatment of locally-advanced squamous cell carcinoma of the vulva.
- 1.22 To determine the vulvar progression-free survival and groin progression-free survival in women treated with cisplatin, gemcitabine and IMRT for locally advanced vulvar carcinoma.
- 1.23 To determine the toxicity and surgical morbidity of the combined modality approach of cisplatin, gemcitabine and IMRT followed by reduced-scope surgery for the treatment of locally-advanced vulvar carcinoma.

2.0 BACKGROUND AND RATIONALE

Invasive vulvar cancer is an uncommon malignancy, representing 5% of gynecologic cancers. It is estimated that 3,900 new cases and 900 deaths will be reported in the United States for 2010 with the vast majority (90%) histologically identified as squamous cell carcinoma (SCC).¹ The majority of patients present with early stage disease but for those with locally advanced vulvar cancer, disease management remains a challenge. Historically, exenterative procedures were necessary with anal, rectal, urethral or bladder involvement thus leading to significant physical and psychological morbidity. Over the last several years the GOG has improved the outcomes for these women by using multi-modality therapy of chemotherapy, radiation, and surgery. Combining cisplatin and 5 FU with radiation in GOG-0101, 93% of patients with advanced primary tumors were rendered resectable, without having to sacrifice urinary and/or gastrointestinal continence. Forty-six percent of patients had no clinical evidence of vulvar tumor following chemoradiation and 31% had no residual tumor on the pathologic specimen.² In this trial, the total radiation dose was purposefully less than what is typically used when radiation is the sole treatment and a split-course regimen was employed to diminish potential severe acute toxicity.

Building upon its experience of treating cervical squamous cell carcinoma with cisplatin, the GOG initiated protocol GOG-0205 evaluating cisplatin 40 mg/m² weekly concurrent to radiation therapy in advanced vulvar cancer. This trial eliminated a specified treatment

break and delivered a higher dose of radiation (20% dose escalation as compared to GOG-0101). There were 58 evaluable patients of whom 40 (69%) completed study treatment. Complete clinical responses were seen in 37 patients (37/58, 64%). Among the 37 patients who achieved a complete clinical response, 34 underwent surgical biopsy and 29 had confirmed complete pathologic responses, for an overall complete pathologic response rate of 50% (29/58) for all evaluable patients).³

Since the initiation of GOG-0101 and GOG-0205, significant advances have been made in radiation techniques; more specifically, the use of Intensity-Modulated Radiation Therapy (IMRT). Unlike traditional radiation utilizing external beam AP-PA fields, IMRT allows for more precise delivery of radiation to malignant tumors. Using 3-D computed tomography (CT) images of the patient, in conjunction with computerized dose calculations, IMRT allows for higher radiation doses to be conformed to tumor shapes while minimizing the dose to surrounding normal critical structures. Using this modality of radiotherapy results in higher radiation doses with reduced treatment toxicity. In a small study by Beriwal et al. 15 patients with vulvar cancer, 7 preoperatively and 8 post-operative, were treated with IMRT. Compared to traditional radiation, IMRT lead to a reduction in unnecessary dose to the bladder, rectum, and small bowel and a low incidence of severe toxicity.⁴

Gemcitabine is a deoxycytidine analog anti-metabolite that is structurally related to cytosine arabinoside that inhibits DNA synthesis. Gemcitabine leads to an accumulation of dFdCP which in turn inhibits DNA polymerase and results in chain termination and apoptosis.^{5,6} Gemcitabine is a known radiosensitizer^{7,8} and has shown synergy with cisplatin.^{9,10} Although gemcitabine has not been used to treat vulvar cancer to date, its chemical and biologic properties, in addition to the short infusion and same-day administration, make it an attractive agent to combine with cisplatin for the treatment of women with locally advanced vulvar cancer.

In a phase I trial, GOG-9912, the GOG evaluated whole pelvic radiation therapy with weekly concurrent cisplatin and gemcitabine for the treatment of cervical cancers. In this trial, patients received gemcitabine intravenously over 30 minutes followed by cisplatin. The maximum tolerated dose was gemcitabine 50 mg/m² and cisplatin 40 mg/m² with dose-limiting toxicities primarily being nausea, vomiting, diarrhea and hematologic.¹¹ Interestingly, when sequenced in reverse, cisplatin followed by gemcitabine, higher doses of gemcitabine have been administered with acceptable toxicity.¹²⁻¹⁴ Based on the experience with locally advanced cervical cancer, the combination of concurrent weekly cisplatin (40 mg/m²) and gemcitabine (125 mg/m²) with whole pelvic radiation has resulted in improved complete pathologic response, 77% v 55%, and an improved progression-free and overall survival.^{14,15}

The purpose of this study therefore was to expand upon the success of study GOG-0205 by adding gemcitabine and increasing the radiation dose using the most modern radiation techniques.

2.1 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 all women with locally-advanced squamous cell carcinoma of the vulva treated by participating institutions.

3.0 PATIENT ELIGIBILITY AND EXCLUSIONS

3.1 Eligible Patients

- 3.11 Patients with locally-advanced, previously untreated squamous cell carcinoma of the vulva.
- 3.12 Patients with T2 or T3 primary tumors (N0-3, M0) not amenable to surgical resection by standard radical vulvectomy.
- 3.13 Patients must have adequate:
 - 3.131 Bone marrow function: Absolute neutrophil count (ANC) greater than or equal to 1,500/mcl Platelets greater than or equal to 100,000/mcl. **(08/26/2013)**
 - 3.132 Renal function: Creatinine ≤ 1.5 x institutional upper limit normal (ULN) or calculated creatinine clearance ≥ 60 ml/min.
 - 3.133 Hepatic function: Bilirubin ≤ 1.5 x ULN. AST and ALT ≤ 3.0 x ULN and alkaline phosphatase ≤ 3.0 x ULN.
- 3.14 Patients judged capable of tolerating a radical course of chemoradiation therapy.
- 3.15 Patients must not be eligible for a higher priority GOG protocol, if one exists. In general, this would refer to any active GOG Phase III protocol or Rare Tumor protocol for the same patient population.
- 3.16 Patients who have met the pre-entry requirements specified in [Section 7.0](#).
- 3.17 Patients must have signed an approved informed consent and authorization permitting release of personal health information.
- 3.18 Patients must be 18 years or older.
- 3.19 Patients with a GOG Performance Status of 0, 1 or 2

3.2 Ineligible Patients

- 3.21 Patients with recurrent carcinoma of the vulva regardless of previous treatment.
- 3.22 Patients who have received prior pelvic radiation or cytotoxic chemotherapy.

- 3.23 Patients with vulvar melanomas or sarcomas.
- 3.24 Patients with circumstances that will not permit completion of the study or the required follow-up.
- 3.25 Patients with evidence of active septicemia, severe infection, gastrointestinal bleeding or severe gastrointestinal symptoms requiring medical or surgical therapy.
- 3.26 Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer, are excluded if there is any evidence of other malignancy being present within the last five years. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.

4.0 STUDY MODALITIES

4.1 Cisplatin (Platinol[®]-AQ) (NSC #119875)

- 4.11 Formulation: Cisplatin is available as an aqueous solution in 50 mg and 100 mg vials where each mL contains 1 mg of cisplatin and 9 mg of sodium chloride.
- 4.12 Preparation: Aluminum reacts with Platinol causing precipitation formation and loss of potency, therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of Platinol.
- 4.13 Storage: The aqueous solution should be stored at room temperature and protected from light.
- 4.14 Administration: [See Section 5.4](#)
- 4.15 Adverse effects: Leukopenia, thrombocytopenia, anemia nausea, vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy, electrolyte imbalance, hypocalcemia, hypomagnesemia, aminoglycoside, ototoxicity, ocular toxicity and allergic reactions. Infrequent: Cardiac abnormalities, anorexia, elevated SGOT, rash and alopecia.

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

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

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

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

Allergic reactions are rare. If accompanied by respiratory symptoms, allergic reactions require discontinuation of treatment. Patch or skin tests are recommended for patients with suspected allergy to cisplatin. Platinum desensitization protocols can be employed if it does not lead to

delayed radiation. An emergency set for the treatment of allergic reactions should be available in the treatment area.

Local necrosis and thrombophlebitis can be avoided by careful administration.

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

Ototoxicity may occur.

NOTE: Eighth (VIII) nerve toxicity resulting in hearing loss and (less commonly) vestibular symptoms is a well documented complication of cisplatin treatment and is usually related to total cumulative dose. It is advised that patients placed on cisplatin be questioned about hearing loss. Patients with a history of hearing loss should be considered for pre-treatment audiometry with follow up audimetry as clinically indicated. It is recommended that patients be queried concerning hearing loss before each cycle of cisplatin.

4.16 Supplier: Commercially available. Bristol-Myers Oncology

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

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 from Eli Lilly and Co. 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 30 minutes ([See Section 5.4](#)).

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/m²: 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 Radiation Therapy

4.31 Pelvic, Inguinal and Vulvar Radiation: IMRT (04/21/2014)

IMRT is **required** for this study. All patients will be treated using IMRT. Before **ANY** patient is enrolled on this study the treating radiation oncologist must complete an online Knowledge Assessment Questionnaire for this study found on the IROC Houston (formerly the Radiologic Physics Center) website (<http://irochouston.mdanderson.org> under credentialing GOG).

All institutions **MUST** be credentialed by IROC Houston at M.D. Anderson Cancer before entering any patient on this study ([See Section 5.1](#)). Institutions that have been previously credentialed for IMRT by GOG or any other NCI-funded Study Group via the head and neck phantom or pelvic phantom can determine what additional requirements must be completed by filling out the “Credentialing Status Inquiry” form on the IROC Houston website (<http://irochouston.mdanderson.org>). IROC Houston will issue credentials for this protocol to the institution and notify the GOG Statistical and Data Center (SDC).

The treatment plan for all patients treated on this protocol must be submitted via TRIAD.) After the data has been submitted via TRIAD, complete a DDSI information form found at <http://www.rtog.org/CoreLab/TRIAD.aspx>. The case will be processed in preparation for rapid review. A rapid review will be performed for each patient **PRIOR TO DELIVERING ANY PROTOCOL TREATMENT.** The rapid review will be initiated and conducted by IROC Houston in collaboration with a GOG-designated radiation oncologist, and suggestions regarding protocol compliance will be forwarded to the participating institution’s radiation oncologist. In addition, to help delineate the extent of vulvar involvement and to help ensure adequate volume definition for the boost, an electronic photograph will be submitted with the treatment plan. **(08/26/2013)**

All patients who have undergone surgical resection of the groin lymph nodes will initiate radiation within 6 weeks of surgery.

4.32 Technical Factors

4.321 Megavoltage equipment capable of delivering static intensity modulation with a multi-leaf collimator or a dynamic intensity modulation (using a multi-leaf collimator or tomotherapy) is required. Forward-planned IMRT (field in field) treatment planning methods are required.

4.322 Recognizing that higher photon energies with higher monitor units increase the neutron contamination, a 6-10 MV photon beam energy is preferable. Beam energies greater than 10 MV photons are still permissible.

4.33 Patient Immobilization

Patient must be placed in an appropriate immobilization device to ensure stability of the treatment position. The preferred position is supine with frog leg position to avoid dose to the upper thigh skin, but straight leg position is acceptable. Bolus material must be used to cover the entire vulva to ensure adequate surface dose. This may be accomplished with either bolus material or with the patient's thigh tissue acting as self bolus as per [section 4.3631](#). Because of the required use of low pelvic nodal treatment, it is recommended that simulation and treatment be done with a full bladder.

4.34 Simulation (04/21/2014)

CT simulation is required to define the gross tumor volume (GTV), clinical tumor volume (CTV), and planning tumor volume (PTV). The CT scan must be acquired in the same position and immobilization device as for treatment. The use of IV contrast and bowel prep-contrast is encourage for better delineation of the contrast-enhanced pelvic vessels used as a surrogate for regional nodal delineation as well as small bowel contouring, respectively. Skin markers must be placed on the vulva to circumscribe the extent of visible gross disease to ensure that all gross disease is delineated on the planning CT scan.

For submission to TRIAD the structure names MUST match exactly with this list or resubmission may be required.

Structure Name	Description
GTVp	Vulvar GTV is defined as the gross tumor as seen on radiographic imaging or as visible on clinical exam. Required
GTVn	Inguinal GTV is defined as unresected or residual gross disease in the inguinal-femoral region as defined on any radiographic imaging. Required
CTVp	Vulvar CTV is defined as the vulvar GTV with a 2 cm margin that includes the surrounding skin and subcutaneous tissue. Required

CTVn	Inguinal CTV is defined dependent on the presence of inguinal GTV. Both inguinal regions will be treated in all patients regardless of laterality of the tumor. Required
PTVp_6400*	Vulvar PTV, PTV expanded to encompass CTVp by a 7 mm to 10 mm margin. Required when applicable
PTVn_6400*	Inguinal PTV, PTV expanded to encompass CTVn by a 7 mm to 10 mm margin. Required when applicable
PTVp_6000*	Vulvar PTV, PTV expanded to encompass CTVp by a 7 mm to 10 mm margin. Required when applicable
PTVn_6000*	Inguinal PTV, PTV expanded to encompass CTVn by a 7 mm to 10 mm margin. Required when applicable
PTVp_4500*	Vulvar PTV, PTV expanded to encompass CTVp by a 7 mm to 10 mm margin. Required when applicable
PTVn_4500*	Inguinal PTV, PTV expanded to encompass CTVn by a 7 mm to 10 mm margin. Required when applicable
Bladder	Bladder Required
Rectum	Rectum Required
BowelSpace	Small Bowel Required
Femurs	Femurs Required
NonPTV	External minus the PTVs Required
External	External Skin Required

Required When Applicable.

4.35 Dose Specifications

4.351 Dose to Designated PTVs

- 4.3511 The vulvar PTV and the groin PTV when inguinal nodes are unresectable will receive 64 Gy in 32 fractions. Treatment will be delivered once daily, 5 days per week for 7 weeks. Breaks from treatment should be minimized and reasons for breaks must be documented. **(08/15/2016)**

4.3512 The groin PTV when high-risk positive nodal features are present (as defined in [Section 5.4](#)) will receive 60 Gy in 30 fractions. Treatment will be delivered once daily, 5 days per week for 6 weeks.

4.3513 The groin PTV and the pelvic PTV after resection of pathologically negative inguinal lymph nodes, or resected positive nodes that have low-risk features will receive 45 Gy in 25 fractions. Radiation of the pelvis and groins after dissection with negative lymph nodes on final pathology is at the discretion of the investigator.

4.352 IMRT Dose Designation to Designated PTV

The dose is prescribed to cover 97% of the vulvar PTV and the inguinal PTV and pelvic PTV. A volume of at least 0.03 cc within any PTV should not exceed >110% of the prescribed dose to each PTV. No volume within each of the PTVs that is 0.03 cc or greater shall receive less than 93% of its prescribed dose.

4.36 Contouring the Target Volumes

4.361 Please refer to the RTOG Gynecologic Atlas for volume specifications.

4.362 Gross Tumor Volume (GTV)

4.3621 Vulvar GTV is defined as the gross tumor as seen on radiographic imaging or as visible on clinical examination, radiographic imaging and delineated with surface markers on the planning CT scan. Skin markers must be placed on the vulva to demarcate the extent of gross visible disease on the vulva to ensure that all gross disease is delineated on the planning CT. An electronic photo will be submitted as well to define the extent of vulvar tumor involvement. **(08/26/2013)**

4.3622 Inguinal GTV is defined as unresected or residual gross disease in the inguinal-femoral region as defined on any radiographic imaging.

4.363 Clinical Tumor Volume (CTV)

- 4.3631 Vulvar CTV is defined as the vulvar GTV with a 2 cm margin that includes the surrounding skin and subcutaneous tissue.
CTV shall not extend outside the skin and shall exclude bony tissue unless there is documented gross bony involvement. To ensure adequate dose to the skin, bolus material or self-bolus with the patient's tissue (thigh) will be utilized.
- 4.36311 Vaginal involvement: When the vulvar GTV involves/extends into the vagina, then a minimum of 2 cm of normal vagina will be included in the vulvar CTV. It is acceptable to include the entire vagina in the CTV.
- 4.36312 Perianal skin/anorectum: When the GTV involves or extends to within 1 cm of the anal verge, then a minimum of 2 cm of normal anorectum will be included in the vulvar CTV.
- 4.36313 Periurethral/urethra: When the GTV involves the urethra or periurethral tissue then a minimum of 2 cm along the urethra will be included in the vulvar CTV.
- 4.3632 Inguinal CTV is defined dependent on the presence of inguinal GTV. Both inguinal regions will be treated in all patients regardless of laterality of the tumor. Only exception is in the case of bilateral lymph node dissection that yields negative lymph nodes, in which case radiation of the inguinal areas and low pelvis are at the discretion of the treating radiation oncologist.
- 4.36321 Inguinal CTV in the absence of an inguinal GTV will extend 2.5 cm lateral and 3 cm medial to the nearest inguinal vessel as well as 2 cm anterior and 1 cm posterior to the vessels. The cephalad border of the inguinal nodes is at the top of superior pubic rami. The caudal extent of the inguinal nodal CTV is at the level of the bottom of the lesser trochanter. Any postoperative changes from the inguinal-femoral dissection should be included in the CTV. The inguinal CTV should not include any of

the musculature of the proximal thigh. This volume will not extend outside the skin but will exclude the skin and surface by at least 3 mm.¹⁸

4.36322 Inguinal CTV in the presence of inguinal GTV will include the same volume as defined in [Section 4.36321](#) but also extend (if needed) to include the inguinal GTV with a minimum 7 mm margin beyond the GTV. If there is evidence of skin involvement the CTV will extend to include the skin and bolus material will be used to ensure adequate dose to the skin.

4.36323 Pelvic nodal CTV is defined as the nodal regions at risk for the presence of microscopic disease. Each volume will include the vasculature of each nodal region with a minimum 7 mm expansion but excludes muscle and bone. Pelvic nodal CTV for all patients shall include bilateral external iliac, obturator and internal iliac nodal regions. Treating radiation oncologists should consider treatment of pelvic nodal regions if extensive vagina, anorectum or urethral involvement is seen even in the absence of inguinal nodes on initial dissection.

4.36324 Planning tumor volume should provide a 7-10 mm margin in all directions around the vulvar, inguinal and pelvic CTVs. Involved vulvar skin should have appropriate bolus material (or self-bolus) to ensure adequate dose to the skin. The PTV in this situation shall NOT be pulled back from the skin in the planning process.

4.364 Clinical Normal Structures

4.3641 Bladder will be contoured in each slice in which it appears.

4.3642 Ano-rectum will be contoured in each slice in which it appears.

The radiation oncologist should consider the maximum caudal extent of the rectum to extend to the perineum but for calculating constraints the anorectum within the PTV will be subtracted from the total anorectal volume. The superior extent of the rectum where the sigmoid begins should be marked by the increased curvature/tortuosity of the bowel.

4.3643 Small bowel will be contoured on each slice in which it appears, extending 2 cm above the most cephalad PTV. The small bowel volume should consider all the bowel loops and any place within the peritoneal cavity small bowel could lie such as the mesentery and adipose tissue.

4.3644 Femoral head/neck will be contoured to include the entire femoral head and extend down to the top of the lesser trochanter.

4.37 Constraints

Participants are strongly encouraged to respect the following limits but the appropriate treatment of the tumor volumes is the first and primary objective:

4.371 Small bowel: < 30% to receive \geq 40%; Dmax \leq 51 Gy

4.372 Anorectum (this constraint should exclude any PTV that overlaps this volume): < 80% to receive \geq 40 Gy; Dmax < 65 Gy

4.373 Bladder: < 50% to receive \geq 45 Gy; Dmax \leq 65 Gy

4.374 Femoral heads/neck: < 50% to receive \geq 45 Gy; Dmax \leq 55 Gy

4.375 Unspecified tissue (tissue contained within the skin or any other normal structure not delineated above and outside the PTV, not included within any other structure): No more than 1% or 1 cc (whichever is smaller) of the tissue outside the PTV will receive > 110% of the prescribed vulvar PTV. However, with respect to this last constraint it is recognized that there may be patients in which, due to obesity or other factors, this constraint may not be obtainable if other constraints, e.g. rectum, are met. In these cases it is recommended that the OAR constraints be favored to the extent possible that is consistent with good radiotherapeutic practice.

4.38 Documentation Requirements

- 4.381 All plans and the electronic photo must be submitted electronically via TRIAD for review, in addition to what is required from IROC Houston in [Section 5.1](#). **(08/26/2013) (04/21/2014)**
- 4.382 Dose-Volume Histograms (DVHs) are to be obtained for each one of the target volumes defined above as well as the critical surrounding structures and need to be submitted for evaluation.
- 4.383 Submission of digital data via TRIAD **(04/21/2014)**

Digital RT Data Submission to Using TRIAD

TRIAD is the American College of Radiology's (ACR) image exchange application and it is used by IROC-Houston (RPC). TRIAD provides sites participating in clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred. The following process must be completed prior to enrolling patients on the trial.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account.
- To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster, and should follow their procedures for assignment of roster roles.

TRIAD Installations:

When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the IROC- Houston web site.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

- 4.39 Treatment Schedule: All fields are treated with each fraction, treating once per day, five days per week. It is anticipated that radiation therapy

will start as soon as clinically feasible at the discretion of the treating physician but within 6 weeks of enrollment. **(08/26/2013) (08/15/2016)**

- 4.310 Therapy Interruptions: If interruption of two weeks or less occurs, radiation should be completed to the prescribed total dose. Therapy interruptions of more than two weeks will be considered a major or minor deviation from the protocol, depending on clinical circumstances, and resumption of therapy will be at the discretion of the radiation oncologist. Follow-up must continue regardless of radiation treatment received.
- 4.311 Radiation Therapy Quality Control and Documentation: IROC Houston is funded by the NCI to support clinical trials employing radiation therapy and will supervise the dosimetry quality control for this clinical trial.
- 4.312 In the first 5 days of treatment, each patient will have in-vivo dosimetry performed to evaluate the dose of radiation to the vulva. The dosimetry applicator will be provided by IROC Houston and returned to them for evaluation. The dosimeter will be placed on the vulvar surface, under bolus if used or in skin folds if positioning of patient is with legs together.

4.4 Pathology Requirements

4.41 Eligibility Criteria

Patients must have locally-advanced, previously untreated squamous cell carcinoma of the vulva. This protocol is for T2 or T3 primary tumors (N0-3, M0) that are not amenable to surgical resection by standard radical vulvectomy.

4.42 Requirements

(Correlation of pathology requirements with the flow chart at the beginning of this protocol is recommended).

One H&E stained slide to confirm the initial diagnosis of invasive squamous carcinoma of the vulva is required. Other tumor types are not eligible for this protocol.

If patients have (pretreatment) resectable lymph nodes: 1) If lymph nodes contain metastatic carcinoma, H&E stained slides of the resected lymph nodes are required in order to document metastatic carcinoma; 2) If lymph nodes are negative for metastatic tumor, a copy of the pathology report is required (slides of negative lymph nodes are not required).

In patients with (pretreatment) unresectable lymph nodes, H&E slides documenting residual squamous cancer (post-radiation resection) are

required. If there is no residual tumor (post-radiation), copies of all fine needle aspirate and surgical pathology resection reports documenting negative lymph nodes are required (slides from negative lymph nodes are not required).

After cisplatin + Gemcitabine + IMRT, the following H&E slides are required: 1) A surgical pathology report documenting absence of tumor if there is no residual neoplasm (slides are not required if there is no residual tumor); 2) At least one H&E slide documenting residual carcinoma from the surgical resection in patients whose residual disease is resected; 3) if residual disease is documented by a method other than histology, the method of determining that residual disease is present should be stated. Please see [sections 7.2](#) and [10.2](#) for additional instructions.

5.0 TREATMENT PLAN AND ENTRY/RANDOMIZATION PROCEDURE (04/21/2014)

5.1 IROC HOUSTON (FORMERLY THE RADIOLOGICAL PHYSICS CENTER [RPC]) CREDENTIALING REQUIREMENTS (04/21/2014)

5.11 Credentialing for this protocol will be handled by IROC Houston. All information regarding credentialing can be found on the IROC Houston website (<http://irochouston.mdanderson.org>) by selecting “Credentialing,” then “GOG.”

5.12 Before ANY patient is enrolled on this study, each the treating radiation oncologist must complete online a Knowledge Assessment Questionnaire for this study found on the IROC Houston website.

5.13 IMRT Credentialing requirements:

Institutions must be credentialed for IMRT by IROC Houston for this protocol prior to enrolling patients into this study. Each institution must successfully irradiate a standardized phantom available from IROC Houston. Instructions for requesting and irradiating the phantom are available at the IROC Houston web site. The treatment plan for irradiation of the phantom must be submitted electronically to TRIAD. Institutions that have been previously credentialed for IMRT or any other NCI-funded Study Group via the head and neck phantom or the pelvic phantom can determine what additional requirements must be completed by filling out the “Credentialing Status Inquiry” form on the IROC Houston’s website. IROC Houston will issue credentials for this protocol to the institution and notify the GOG Statistical and Data Center (SDC).

Each Institution must complete the IMRT Facility Questionnaire available on the IROC Houston web site by selecting “Credentialing,” then “GOG,” then the specific protocol credentialing requirements.” Each institution must submit the completed IMRT Facility Questionnaire online.

Institution and/or peer-reviewed documentation of target position reproducibility [planning treatment volume (PTV) and clinical target volume (CTV)] must be consistent with [Section 4.34](#) and [4.36](#).

5.14 **Digital RT Data Submission Using TRIAD (04/21/2014)**

Each institution must set up a TRIAD account prior to any patient enrollment

TRIAD is the American College of Radiology’s (ACR) image exchange application and it is used by IROC Houston (RPC). TRIAD provides sites participating in clinical trials a secure

method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred. The following process must be completed prior to enrolling patients on the trial.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account.
- To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster, and should follow their procedures for assignment of roster roles.

TRIAD Installations:

When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the IROC Houston web site.

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

5.2 Registration Procedures (04/21/2014)

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed **Statement of Investigator Form** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed **Supplemental Investigator Data Form** (IDF)
- a completed **Financial Disclosure Form** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm.

For questions, please contact the **CTEP Investigator Registration Help Desk** by email at <pmbregpend@ctep.nci.nih.gov>.

5.21 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the **CTEP Associate Registration Help Desk** by email at <ctepreghelp@ctep.nci.nih.gov>.

5.22 CTSU Registration Procedures

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

5.221 IRB Approval:

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 be approved to 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 members' website by entering credentials at <https://www.ctsu.org>. For sites under the CIRB initiative, IRB data will automatically load to RSS.

5.222 Downloading Site Registration Documents:

Site registration forms may be downloaded from the GOG-0279 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password
Click on the Protocols tab in the upper left of your screen
Click on the *NCTN NRG* link to expand, then select trial protocol # 0279
Click on the Site Registration Documents link

5.223 Requirements for GOG-0279 Site Registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
 - CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)
 - CTSU RT Facilities Inventory Form
- NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in IROC Houston monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility

5.224 Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval and Model Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSUSRegulatory@ctsu.cocccg.org (for regulatory document submission only)

5.225 Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the

CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

Go to <https://www.ctsu.org> and log in to the members' area using your CTEP-IAM username and password

Click on the Regulatory tab at the top of your screen

Click on the Site Registration tab

Enter your 5-character CTEP Institution Code and click on Go

5.3 Patient Entry and Registration (04/21/2014)

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < <https://eapps-ctep.nci.nih.gov/iam/index.jsp> >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. 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>.

All site staff will use OPEN to enroll patients to this study. OPEN can be accessed on the GOG web menu page by clicking on the OPEN link.

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).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

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 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.

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.

5.4 Treatment Plan (08/15/2016)

All patients who are eligible for this protocol ([See Section 3.0](#)) with T2 or T3 primary tumors (N0-3, M0) not amenable to surgical resection by standard radical vulvectomy will be treated according to this regimen. There is no randomization. Although it is preferable to have patients registered for the trial prior to the lymph node surgical evaluation, patients may be registered/enrolled postoperatively. If patients do not register/enroll until postoperative from the groin node assessment, the treating physicians should determine if patients meet eligibility requirements (requirement 3.13 can be determined as part of standard practice in preoperative lab work) and confirm that they and the patient agree the treatment protocol is appropriate and acceptable therapy.

Surgery: Patients with clinically negative or resectable groin nodes will undergo pretreatment inguinal – femoral lymph node dissection or sentinel lymph node biopsy at the discretion of the treating surgeon and prior to registration. Six to 8 weeks following completion of chemoradiation patients will undergo local core biopsy of the tumor bed to confirm complete pathologic response or surgical excision of gross residual disease in the vulva and/or inguinal-femoral lymph nodes. If the inguinal – femoral lymph nodes were initially deemed unresectable, an FNA of persistent clinical or radiographic suspicious lymph nodes 6-8 weeks after completion of radiation is acceptable. If the FNA is positive, a targeted excision of the groin should be done. A radical vulvectomy is not necessary. If there has been complete clinical response, an excisional biopsy of the primary tumor site to confirm pathologic response should be performed.

Radiation: Radiation therapy will be delivered by IMRT to the vulva, inguinal-femoral lymph nodes, and lower pelvic lymph nodes. As time to recover from a sentinel lymph node biopsy is different from a inguinal femoral dissection, commencement of radiation operatively will be at the discretion of the treating physician however, patients must be registered/enrolled in the trial within 2 weeks of surgery and IMRT must start no later than 6 weeks after surgery or determination of unresectable nodes.

- The vulvar CTV will receive 64 Gy regardless of the groin node dose.

- Patients with negative groin nodes as determined by pretreatment inguinal-femoral lymph node dissection will receive radiation therapy to the vulva and may receive radiation therapy to the inguinal-femoral and lower pelvic lymph nodes at the discretion of the treating physician. If treatment to the groins/low pelvis is elected, the total dose will be 45 Gy.
- For those with positive lymph nodes by inguinal-femoral lymph node dissection, radiation will be delivered to a dose of 50 Gy and with a boost to 60 Gy on any/both sides that have high risk nodal features. These features include those inguinal nodes affected by $\geq 3(+)$ LN, extracapsular extension, or close/positive margin. For those patients with unresectable lymph nodes, patients will receive radiation to a dose of 64 Gy.

Post-Radiation evaluation: An FNA of any clinical or radiographic residual disease in the groin or vulva will be performed 6-8 weeks after completing radiation. Those that have a positive FNA will undergo a targeted excision.

Chemotherapy: Patients will receive concurrent Cisplatin 40 mg/m² and Gemcitabine 50 mg/m² administered weekly throughout radiation therapy. Gemcitabine will be infused prior to cisplatin and given over approximately 30 minutes while the cisplatin will be delivered over approximately 60 minutes. The maximum dose of cisplatin is stated in [Section 6.0](#), and applies to those with a BSA >1.75m².

Chemotherapy should start on the same day as the start of radiation. There is no required timeframe for chemotherapy (i.e. before or after radiation) for on the day of radiation.

Please follow institutional standards for antiemetics and hydration pre- and post-cisplatin. Please follow institutional standards for the preparation of cisplatin and gemcitabine. **(08/26/2013)**

5.41 [See Appendix II](#), GOG General Chemotherapy Guidelines

6.0 TREATMENT MODIFICATIONS (08/15/2016)

Dose Delay (08/15/2016)			
	ANC <500 Platelets <50,000*	ANC 500-1,000 Platelets 50,000-100,000	ANC >1,000 Platelets >100,000
Cisplatin	Hold ^a	Treat normally	Treat normally
Gemcitabine	Hold	Treat normally	Treat normally
XRT	Hold	Treat normally	Treat normally
^a Dose reduction			
*For the second episode ANC <500 and platelets <50,000 see sections 6.141 and 6.211 .			

Dose Modifications (08/15/2016)			
Study Drug	<u>2 Level reduction</u>	<u>1 Level reduction</u>	<u>Initial dose level</u>
Cisplatin	20 mg/m ² (max=35mg*) (11/13/2012)	30 mg/m ² (max=52.5mg*) (11/13/2012)	40 mg/m ² (max=70mg*)
Gemcitabine	25 mg/m ²	37.5 mg/m ²	50 mg/m ²

* For cisplatin, the max doses apply to those with BSA > 1.75 m²
(08/26/2013)

NOTE: There will be no dose re-escalations after dose reduction. Only 2 dose reductions are allowed. **(08/26/2013)**

NOTE: If radiation is held for any reason, then chemotherapy should also be held. If one of the chemotherapy drugs is held or discontinued for toxicity, but the other is tolerated, that drug may be continued.
(08/26/2013)

Please note all CTCAE grading below refers to version 4.0.

6.1 Cisplatin Modifications ([see Section 6.2](#) for Gemcitabine Modifications)

6.11 Gastrointestinal Adverse Effects

6.111 Nausea: Prior to infusion of cisplatin, the use ondansetron, granisetron, dolasetron and/or Aprepitant is strongly recommended. Lorazepam may also be given if desired.

6.1111 For protracted grade 3 toxicity with nausea and vomiting

lasting two or more days or requiring hospitalization or TPN > 24 hours, cisplatin will be reduced by one dose level.

6.1112 For protracted Grade 4 toxicity despite maximal medical therapy, a two level dose reduction should be made. If a participant was previously reduced by one dose level, and then experiences protracted grade 4 nausea, the lowest dose is 20mg/m², per the table above. **(08/26/2013)**

6.112 Diarrhea: Usually can be controlled with low-fiber, low-fat, bland diets and anti-diarrheal medications. Should GI toxicity become severe, hospitalization may be required at which time the treatment may be interrupted temporarily until the patient's condition improves. If the patient does not recover to baseline within 2 weeks of last treatment, the patient will be removed from study treatment.

6.12 Renal/Genitourinary Adverse Effects

6.121 If creatinine rises to greater than 1.5 mg/dL, obtain creatinine clearance (CrCl). Creatinine clearance should be obtained via the Crockcroft Gault calculation. Cisplatin dosing will be managed based on creatinine clearance as follows: **(08/26/2013)**

6.1211 If CrCl is 50 ml/min or greater, continue cisplatin at current dose level. **(08/26/2013)**

6.1212 If the CrCl is less than 50 ml/min, hold cisplatin. The CrCl should be checked weekly. If the CrCl returns to or surpasses 50 ml/min, resume cisplatin chemotherapy with a one dose level reduction. **(11/13/2012) (08/26/2013)**

6.1213 If the CrCl remains under 50 ml/min for more than 4 weeks, the patient will be removed from study treatment and we recommend that cisplatin should be discontinued. NOTE: follow-up of patient is still required. **(08/26/2013)**

6.1214 Selective renal tubular defects are sometimes observed: hypocalcemia with hypomagnesemia and hypokalemia are common and potentially severe. The aggressive replacement of magnesium, calcium and potassium is required. Severe tubular effects, although rare, may require chronic replacement therapy. Diagnostic tests for alternative mechanisms of hypocalcemia (e.g. GI or metabolic) should be considered.

6.13 Neurologic Adverse Effects

6.131 CTCAE Grade 1 - No change

6.132 CTCAE Grade 2 - Reduce cisplatin by one dose level

6.133 CTCAE Grade 3 or 4 - Hold cisplatin until recovered to \leq grade 2 and then resume at one dose level reduction

6.14 Blood/Bone Marrow (Hematologic) Adverse Effects

NOTE: If chemotherapy is delayed but blood counts are sufficient to continue or re-start radiation, then radiation should be resumed even without chemotherapy ([see Section 6.3](#))

6.141 Neutropenia

Patients will be followed by the absolute neutrophil count (ANC), not the white blood cell count (WBC). Cisplatin should be administered as long as $ANC \geq 500/mcl$ and platelet count is $\geq 50,000/mcL$.

For $ANC < 500/mcl$, hold the cisplatin. Repeat the complete blood count three times a week until the patient recovers to or exceeds $500/mcL$. The maximum delay allowed is four weeks. Patients who do not recover within this time will be removed from study treatment. **(08/26/2013)**

Gemcitabine alone will be dose reduced for hematologic toxicity ([See Section 6.211](#)). Should patients require reduction to dose-level -2 due to recurrent febrile neutropenia (and/or documented grade 4 neutropenia lasting ≥ 7 days), then cisplatin will be dose reduced by one dose level. Patients who experience repeat febrile neutropenia and/or documented grade 4 neutropenia lasting ≥ 7 days despite Gemcitabine administered at Dose Level -2 (plus cisplatin administered at Dose Level -1) will be removed from study treatment.

6.142 Platelets

There are no planned dose reductions for cisplatin due to thrombocytopenia. Platelets $\geq 50,000/mcL$ is required for treatment. If platelet counts do not meet this threshold they should be repeated three times a week until recovery. The maximum delay allowed is four weeks. Patients who do not recover within this time

will be removed from study treatment.

6.15 Non-Hematologic Adverse Effects: **(08/26/2013)**

6.151 All other non-hematologic toxicities with an impact on organ function \geq grade 2 require reduction of one dose level in cisplatin and gemcitabine and delay in subsequent therapy for a maximum of 2 weeks until recovery to grade 1.

6.2 Gemcitabine Modifications

6.21 Hematologic Adverse Effects.

NOTE: If chemotherapy is delayed but blood counts are sufficient to continue or re-start radiation, then radiation should be resumed even without chemotherapy ([see Section 6.3](#)).

6.211 Neutropenia **(08/26/2013)**

Gemcitabine treatment requires ANC \geq 500/mcl. For patients who do not meet this criteria, blood counts should be repeated three times a week until recovery.

The first time a patient has an ANC $<$ 500 lasting greater than 1 week, a dose reduction will occur. If a second ANC $<$ 500 occurs, they will have 2 weeks to recover before another dose reduction is required.

If treatment is delayed \geq 2 weeks, subsequent doses should be reduced one dose level ([see Section 6.15](#)). The maximum delay allowed is four weeks. Patients who do not recover within this time will be removed from study treatment.

Febrile neutropenia. For first occurrence of febrile neutropenia and/or documented grade 4 neutropenia persisting \geq 7 days, gemcitabine will be reduced by one dose level in subsequent cycles.

For second occurrence of febrile neutropenia and /or recurrent documented grade 4 neutropenia persisting \geq 7 days (after initial dose reduction), add prophylactic G-CSF. Gemcitabine dose will not be further reduced. It is recommend that G-CSF be dosed at 5 mcg/kg/day and be administered subcutaneously starting the day after the last chemotherapy and continuing through hematopoietic recovery. It should not be given within 72 hours of a subsequent dose of chemotherapy. **(11/13/2012)**

Patients with a third recurrence of febrile neutropenia and or documented grade 4 neutropenia lasting ≥ 7 days (despite initial dose reduction and addition of G-CSF) will undergo further dose reduction of gemcitabine to dose level -2.

Patients who experience recurrent febrile neutropenia and or documented grade 4 neutropenia lasting ≥ 7 days despite the above interventions will undergo a dose reduction of Cisplatin as described above ([See Section 6.141](#)).

If any additional episodes of febrile neutropenia and or documented grade 4 neutropenia lasting ≥ 7 days occur, the patient should be removed from study treatment.

- 6.212 Thrombocytopenia. Gemcitabine treatment requires platelet count $\geq 50,000/\text{mcL}$. For patients who do not meet this criteria, blood counts should be repeated three times a week until recovery.

Patients with grade 4 thrombocytopenia will have a 1 level dose reduction of gemcitabine. No dose reductions are required for grade 3 or less thrombocytopenia.

If treatment is delayed ≥ 2 weeks, subsequent doses should be reduced one dose level.

If therapy has been delayed for 4 weeks or more from scheduled administration, the Study Chair will be notified and patient removed from study treatment, but follow up will continue. If chemotherapy is delayed but blood counts are sufficient to continue or re-start radiation, then radiation should be resumed even without chemotherapy.

6.22 Non-Hematologic Adverse Effects: **(11/13/2012) (08/26/2013)**

For Grade 3 or greater elevations of AST, ALT, alkaline phosphatase or Bilirubin, both cisplatin and gemcitabine should be delayed for a maximum of 2 weeks until recovery to grade 1. The patient will then restart the cisplatin at the current dose, and the gemcitabine at a one dose level reduction for all subsequent cycles.

- 6.221 All other non-hematologic toxicities with an impact on organ function \geq grade 2 require a delay in subsequent therapy for a maximum of 2 weeks until recovery to grade 1 and then a reduction of one dose level in cisplatin and gemcitabine for subsequent cycles.

6.3 Radiation Modifications:

Every attempt should be made to avoid radiation treatment interruptions. There are no scheduled radiation breaks. However, cutaneous reactions (as well as GI and GU symptomatology) may be expected with this treatment regimen. All symptoms should be managed aggressively with medications and skin care measures. Treatment breaks may be needed for confluent moist desquamation (cutaneous ulceration) or severe GI or GU toxicity, but interruptions should be kept to an absolute minimum. Also radiation should be withheld for a granulocyte count < 1000/uL or a platelet count < 40,000/uL. Patients on study should be given PRBC (packed red blood cell) transfusions as needed to keep weekly hemoglobin levels > 10 g/L. The prescribed course of therapy without breaks lasts 6.5 weeks. All composite radiation therapy breaks greater than 14 days (2 weeks) should be discussed with the Radiation Therapy Study Chair.

6.31 Cutaneous Adverse Effects:

Grade 0-2: No dose modifications. Skin hygiene and precautions should be emphasized. The use of cornstarch and non-perfumed aloe vera lotions or aquaphor may be helpful

Grade 3: Hold radiotherapy and chemotherapy. Treat patients with Silvadene cream, sitz/therapeutic whirlpool baths, Domboro soaks, Nastatin/Tetracycline/Benadryl/Hydrocortisone elixir, analgesic and antibiotics as appropriate and necessary. Re-evaluate twice weekly for recovery.

Grade 4: Hold radiotherapy and chemotherapy. Treat same as grade 3 above. Notify Radiation Therapy Study Chair.

7.0 STUDY PARAMETERS

7.1 Observations and Tests (08/15/2016)

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

PARAMETER	Pre-treatment	Weekly During Treatment	At the completion of radiation therapy	Post Operative (at the post-operative visit with the treating physician) (08/26/2013)	Post Treatment	Post Treatment Every 3 months for 2 years and every 6 months for 3 years (+/-10 day window)
History & Physical to include pelvic exam (08/26/2013)	4	5				X
Tumor Assessment by Physical Exam	4					X
Toxicity Assessment	2	5	6	9 (08/26/2013)		X
Performance Status (08/26/2013)	X (08/26/2013)	X (08/26/2013)	6 (08/26/2013)			
CBC/Diff/platelets ¹	2	5				
Clinical Chemistry	2, 10	5, 10 (08/26/2013)				
Pregnancy test	3					
Urinalysis	2					
Radiographic Tumor Measurement ¹¹ (08/26/2013)	4		7			
Chest Imaging (x-ray or CT scan of the chest)	4					
Vulva Biopsy or FNA of the Groin					8	

1. CBC is repeated three times per week for serious neutropenia (ANC<500) or thrombocytopenia (<50,000). See [Sections 6.141, 6.142, 6.211, 6.212](#).
2. Must be obtained within 14 days of the initiation of protocol therapy.

3. For women with childbearing potential; must be obtained within 7 days of initiation of protocol therapy.
4. Must be obtained within 28 days of the initiation of protocol therapy.
5. Must be obtained within 4 days of re-treatment.
6. Complete 1 week after the completion of radiation therapy.
7. Complete 6-8 weeks after completion of chemo-radiation
8. Should be performed approximately 6-8 weeks after completion of chemo-radiation treatment
9. Post-operative toxicity assessment should be conducted after the initial lymph node dissection. Post-operative toxicity assessments should also occur for patients who have a surgical resection of residual disease, or a target excision of positive lymph nodes post protocol treatment. **(08/26/2013)**
10. Weekly chemistries should include Albumin, alkaline phosphatase, total bilirubin, calcium, chloride, glucose, phosphorus, magnesium, potassium, total protein, SGOT (AST), SGPT (ALT), sodium, BUN, and creatinine. **(08/26/2013)**
11. Radiographic Tumor Measurement to include a CT Scan of the chest, abdomen, and pelvis. **(08/26/2013)**

7.2 STAINED PATHOLOGY SLIDE REQUIREMENTS FOR CENTRAL REVIEW TO CONFIRM ELIGIBILITY **(08/26/2013)**

Stained pathology slides are required for central review by the GOG Pathology Committee.

7.21 The following slides are required for all patients:

- 1) At least one representative H&E stained slide (or slides) demonstrating primary site, histologic cell type, and grade.
- 2) **One** H&E stained slide showing the most advanced stage of disease will be required if available. If the most advanced stage of disease is not documented by histology, the method of stage documentation needs to be stated (e.g. CT, MRI, etc.).

7.211 If patients have (pretreatment) resectable lymph nodes, the following additional H&E slides are required:

- 1) If lymph nodes contain metastatic carcinoma, H&E stained slides of the resected lymph nodes are required in order to document metastatic carcinoma;
- 2) If lymph nodes are negative for metastatic tumor, a copy of the pathology report is required (slides of negative lymph nodes are not required).

7.212 In patients with (pretreatment) unresectable lymph nodes, the following additional slides are required:

- 1) H&E slides documenting residual squamous cancer (post-radiation resection) are required. If there is no residual tumor (post-radiation), copies of all fine needle aspirate and surgical pathology resection reports documenting negative lymph nodes are required (slides from negative lymph nodes are not required).

7.22 The following slides are required for all patients after cisplatin + Gemcitabine + IMRT: **(04/21/2014)**

- 1) A surgical pathology report documenting absence of tumor if there is no residual neoplasm (slides are not required if there is no residual tumor);
- 2) At least one H&E slide documenting residual carcinoma from the surgical resection in patients whose residual disease is resected.

When submitting pathology material to the GOG SDC individual slides must be labeled with GOG Patient ID, patient initials and the surgical / pathology accession number (e.g., S08-2355) and block identifier (e.g., A6). Do not label the slides with disease site (e.g., right ovary) or procedure date. Pack the labeled slides into plastic slide cassette(s). Tape plastic slide cassettes shut and wrap in bubble wrap or another type of padded material prior to shipping. Please include the GOG Patient ID, patient initials, and protocol number on all pages of the pathology report and black out the patient's name. Ship pathology slides, three copies of both the Pathology Form F (if required for the protocol) and the official pathology report in your own shipping containing using postal mail at your own expense directly to the **Pathology Materials Coordinator at the GOG Statistical and Data Center, Roswell Park Cancer Institute, Research Studies Center, Carlton and Elm Streets, Buffalo, New York, 14263**; phone (716) 845-5702. The GOG Upload Application in SEDES is an alternative method for submitting stained slides, pathology reports and Form F to the GOG Statistical and Data Center. Please see [section 4.4](#) and [10.2](#) for additional requirements and instructions.

7.3 Translational Research

Not applicable for this protocol.

7.4 Quality of Life

Not applicable for this protocol.

8.0 EVALUATION CRITERIA

8.1 Objective Response

8.11 Complete clinical response--defined as no clinical/radiographic evidence of primary disease (vulva or groin) following primary chemo-radiation therapy.

8.12 Complete pathologic response (pCR) – defined among complete clinical responders with negative local core biopsy or FNA specimens. pCR is the sole primary endpoint.

8.2 Other Objective Response

8.21 Overall Survival – defined as the observed length of life from start of protocol therapy to death or, for living patients, the date of last contact.
(08/15/2016)

8.22 Progression-free interval – defined as the date from start of protocol therapy to date of reappearance of disease or date of last contact.
(08/15/2016)

8.23 Site of recurrence (or sites) to be noted regarding local (vulva, vagina) loco-regional (groin) or distant relapse.

8.3 Subjective Response

Performance Status will be recorded on the patient's record according to the standard GOG Performance Scale.

8.4 Adverse Effects

Adverse effect will be graded according to CTCAE v4 and reported on either form T (for acute effects) or form TLC (for delayed effects)

9.0 DURATION OF STUDY

9.1 Patients will continue on study until disease progression or adverse effects prohibit further treatment. The patient can refuse the study treatment at any time.

9.2 All patients will be treated (with completion of all required case report forms) through the duration of the protocol treatment, until disease progression while on protocol treatment, unacceptable toxicity, or study withdrawal. Patients will then be followed (with physical exams and histories) every three months for the first two years and then every six months for the next three years. Patients will be monitored for delayed toxicity and survival for this 5-year period with Q forms submitted to the GOG Statistical and Data Center, unless consent is withdrawn. **(08/26/2013)**

10.0 STUDY MONITORING AND REPORTING PROCEDURES

10.1 ADVERSE EVENT REPORTING FOR A COMMERCIAL AGENT (04/21/2014)

10.11 Definition of Adverse Events (AE)

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

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 Adverse Event Reporting System (CTEP-AERS). All CTEP-AERS submissions are reviewed by GOG before final submission to CTEP-AERS. Submitting a report through CTEP-AERS serves as notification to GOG, and satisfies the GOG requirements for expedited AE reporting. All adverse reactions will be immediately directed to the Study Chair for further action.

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

10.13 Phase 2 and 3 Trials Utilizing a Commercial Agent: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of Any Commercial Study Agent

Reporting Requirements for Adverse Events that occur within 30 Days¹ of the Last Dose of the Commercial Agent on Phase 2 and 3 Trials

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

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

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

- Grade 4 and Grade 5 unexpected events

CTEP-AERS 7 calendar day report:

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

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

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

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

- Expedited AE reporting timelines defined:
 - “24 hours; 3 calendar days” – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 3 calendar days of the initial 24-hour report.
 - “7 calendar days” – A complete CTEP-AERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported to GOG via CTEP-AERS if the event occurs following treatment with a commercial agent.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

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

- All Grade 2 and 3 myelosuppression (including neutropenia, anemia, and thrombocytopenia) that does not require hospitalization is exempt from expedited reporting.

10.14 Procedures for Expedited Adverse Event Reporting:

10.141 CTEP-AERS Expedited Reports: Expedited reports are to be submitted using CTEP-AERS available at <http://ctep.cancer.gov>. The 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 CTEP-AERS (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) Myelodysplastic 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 CTEP-AERS 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 forms must be completed for all patients registered and submitted according to the schedule below. Protocol forms with the exception of the BDR form and Pathology Report must be submitted via the SDC Electronic Data Entry System (SEDES) which is available through the GOG Web Menu page (www.gogstats.org). 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 Statistical and Data Center (SDC). **Note: Pathology material (Form F, path report and slides) must be submitted together via postal mail.**

Form [^]	Due within		Copies *	Comments
	Weeks	Event		
Knowledge Assessment (04/21/2014)	0	Prior to Registration	1	Available at http://irochouston.mdanderson.org under "Credentialing"
Form R (Registration Form)	2	Registration	1	Mandatory Submission via SEDES
Form OSV (Primary Vulvar Cancer – On Study Form)	2	Registration	1	Mandatory Submission via SEDES
Form DR (Pre-Treatment Summary Form)	2	Registration	1	Mandatory Submission via SEDES
Form C (Surgical Reporting Form), Operative report and Discharge Summary for each of the following procedures: - Lymph node dissection - Surgical Resection - Targeted Excision	6	Surgical Procedure	1	Available in SEDES for print only. Submit to SDC via postal mail or upload online via SEDES
Form PV (Pathology Form-Vulvar)	6	Surgical Procedure	1	Mandatory Submission via SEDES
Form F, pathology report and stained slides for each of the following procedures: - Biopsy of primary disease - Lymph node dissection - Surgical Resection - FNA - Targeted Excision	6	Surgical Procedure	2	Submit together to SDC via postal mail or upload online via SEDES**
Radiation Materials: - Daily treatment reports - CT/MRI showing relevant target volume - Simulation films or digitally reconstructed radiograph (DRR) - Portal films	4	Completion of Radiation Therapy		Form G must be submitted via SEDES. Paper copies should also be submitted with radiation materials via postal mail.

- Dosimetry calculation - Isodose distribution curves - Form G (Radiation Treatment Form) IMRT Plan electronically submitted via TRIAD (04/21/2014) - DDSI - Digital treatment planning data - Color isodose distribution - Dose Volume Histograms (DVH) -Electronic photograph to define extent of vulvar tumor involvement (08/26/2013)				Submitted electronically via TRIAD (04/21/2014)
Form D2R (Cycle Dose Drug Form) ¹	2	Completion of each cycle of therapy	1	Mandatory Submission via SEDES
Form T (Common Toxicity Reporting Form)	2	Beginning of each subsequent cycle, the completion of radiation therapy, post-op visit	1	Mandatory Submission via SEDES
Form TLC (Follow-up Period Adverse Event Reporting Form)	2	Submit every three months for two years and every six months for three years during follow-up	1	Mandatory Submission via SEDES
Form Q0 (Treatment Completion Form) ²	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	quarterly for 2 years, semi-annually for 3 more years

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

** At least one representative stained slide (or slides) documenting the primary and one representative stained slide documenting the most advanced stage are required for eligibility. See [sections 4.4](#) and [7.2](#) for additional requirements and instructions.

† Form SP must submitted via SEDES regardless of whether the specimen is submitted for research.

1. Please note: One cycle is equal to one week of chemoradiation (or one week of radiation alone if chemo is held).
2. In section 1 of Form Q0, please report the number of weeks of radiation therapy the patient received on study. In section 2 of Form Q0, please report the date of the last study directed procedure performed (e.g. biopsy, resection, excision, radiation therapy).

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

11.0 STATISTICAL CONSIDERATIONS

This is two-stage single cohort phase II clinical trial to assess efficacy and toxicity of weekly chemotherapy (CT) and radiation (RT) in patients with locally advanced vulvar cancer (T₃ or T₄, N₀ – N₃, M₀) not amenable to surgery. Consequently, randomization is not employed. The GOG Statistical and Data Center will facilitate centralized registration via a web registration tool from within the GOG's website.

11.1 Study Objectives

This study will evaluate endpoints that are specific to clinical and translational research (TR) objectives.

11.11 Primary objective

To determine the efficacy of cisplatin, gemcitabine, and IMRT in achieving a complete pathologic response (pCR).

11.12 Secondary objectives

11.121 To determine the efficacy of cisplatin, gemcitabine, and IMRT in achieving a complete clinical response

11.122 To assess treatment toxicity in the study population

11.123 To estimate progression-free survival (PFS) in the study population

11.2 Endpoints and Data Elements

Primary endpoint is complete pathologic response (pCR), defined among patients who experienced a complete clinical response and had a negative local core biopsy or FNA. In addition, the following endpoints and data elements will be used to evaluate primary, secondary, and/or translational research objectives:

11.21 Complete clinical response (cCR) is defined as no clinical/radiographic evidence of primary disease (vulvar or groin) following chemo-radiation therapy.

11.22 Incidence and severity of adverse effects as assessed by CTCAE v4.0

11.23 Progression free survival (PFS)

11.24 Site(s) of recurrence/relapse (local, loco-regional or distant)

11.25 Regarding treatment compliance: treatment span, incidence and duration of treatment delay, reasons for delays, chemotherapy dose, radiation dose and reasons for dose level reductions

11.26 Baseline patient characteristics: age, performance status, race and ethnicity

11.27 Disease characteristics: clinical tumor size, cell type, FIGO stage, grade, TNM classification, time from primary diagnosis to study entry, location of lesion(s)

11.3 Accrual and Study Duration

Accrual estimates and study duration are based on GOG-0205 experience.

11.31 Anticipated monthly accrual is 1 to 2 patients.

11.32 Accrual objective is at most 52 evaluable patients

11.34 Anticipated active accrual period is 30 to 48 months.

11.33 Post-accrual follow-up period is 6 months.

11.4 Study Design and Sample Size Justification.

The optimal design selected for this study seeks to: a) minimize the number of patients treated and b) estimate efficacy with reasonable precision. However, in multi-center clinical trial, stopping accrual at the exact minimum sample size is logistically challenging, if not impossible. As a result it makes sense to adopt a flexible design, with nearly optimal decision rules across a range of sample sizes. In particular, this study will utilize a “flexible two-stage” design with “nearly optimal” decision rules according to Chen (1998)¹⁹

Historical data and design parameters were selected based on GOG-0205, a recently concluded phase II trial of CIS-RT in patients with previously untreated squamous cell carcinoma of the vulva. There were 61 women on GOG-0205, accrued over a period of 4 years. Three patients were later deemed ineligible due to: improper pre-protocol therapy (N=1); inadequate pathology (N=2)

At the conclusion of primary chemo-radiation, the estimated complete clinical and pathologic response rates (on GOG 0205) were 64% and 50% respectively. In follow-up, 35 women are alive (4 with evidence of recurrent/persistent vulva cancer) and 23 have died as a result of: cancer (N=18); treatment-related complications (N=1), other causes (N=3), undetermined (N=1). The 12 month PFS is estimated at 70% (Figure 11.4.1)

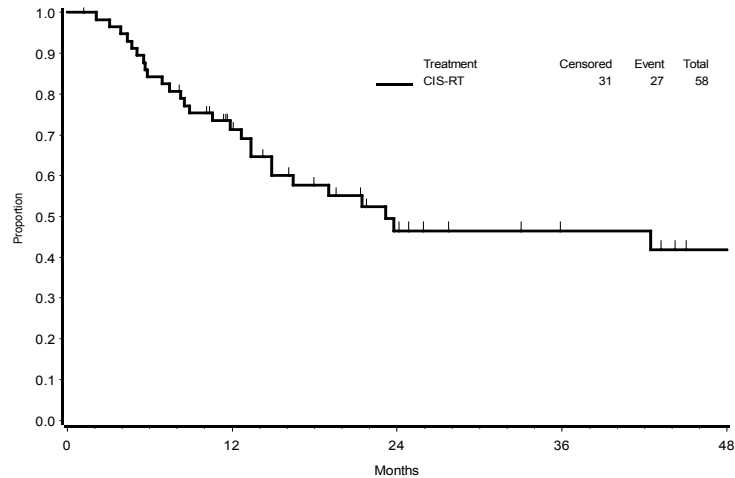


Figure 11.4.1 Progression free survival among GOG-0205 cohort

This current study seeks to improve on the results of GOG -0205. Treatment efficacy will be access based on the relative frequency of complete pathologic response (pCR). The null hypothesis provides the range of pCR probability associated with an insufficiently active treatment and the alternative hypothesis provides the probability range associated with an active treatment: $H_0: pCR \leq 0.50$ versus $H_A: pCR \geq 0.70$

The target size for the first stage of accrual is 24 evaluable patients. If more than 12 (i.e. >12 out of 24) patients experienced a pCR, accrual to the second stage will be initiated. Otherwise, accrual will be stopped and the treatment regimen will be deemed as clinically uninteresting. If the study advances to the second stage, then an overall study accrual of 49 eligible and evaluable patients will be targeted. If no more than 28 (i.e. ≤ 28 out of 49) patients experienced a pCR, the regimen will be considered clinically uninteresting.

The preceding set of decision rules are based on a fixed target size. Since accruing the target size exactly is administratively challenging, especially for multi-center clinical trials, in practice the first and second (if needed) stage accrual sizes will be permitted to range from 20 to 27 and 45 to 52 eligible and evaluable patients respectively. Table 11.4.2 provides specific stopping rules across the allowed sample size range for each stage of accrual.

Accrual			* pCR (Sample size)
Stage	Target	Limits	
1	24	20 – 27	10(20 – 21), 11(22 – 23) , 12(24), 13(25 – 26), 14(27)
2	49	45 - 52	28(45 - 51), 29(52)

*Maximum number of pCR to reject H_A

Table 11.4.2: Decision / stopping rules by stage of accrual

Design characteristics: if the true probability of pCR is equal to 50% (H_O), these decision rules (table 11.4.2) limit the average probability of designating the treatment as active to 10% (i.e. probability of type I error = 0.10) and have an average probability of stopping after completing the first stage of accrual equal to 58%. On the other hand, if the true probability of pCR is 70% (H_A) then the average probability of correctly classifying the treatment as active is 93% (i.e. probability of type II error = 0.070). These statistical probabilities are average probabilities computed from individual probabilities averaged over all permitted accrual combinations and assuming each combination is equally likely. Limited investigations have indicated that the false positive and false negative errors are fairly insensitive to variations in the true probability distribution of accrual combinations²⁰. Figure 11.4.3 shows the average probability of early termination (solid line) and average total probability of rejecting the treatment (broken line) as a function of the true probability of complete pathologic response (pCR).

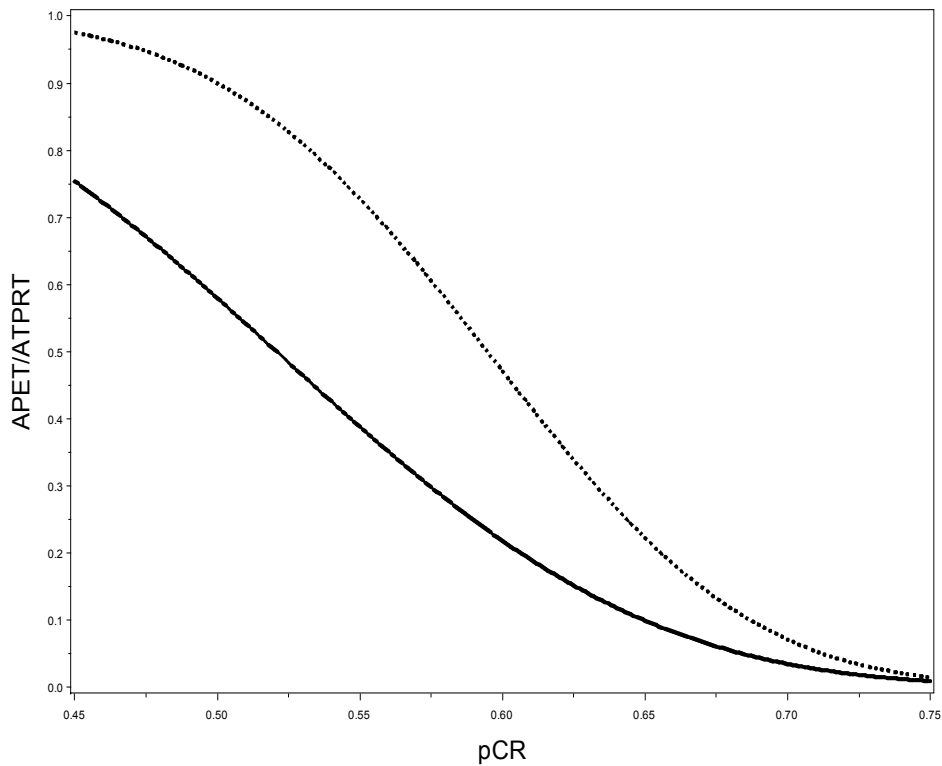


Figure 1

Figure 11.4.3

It is important to emphasize this design choice encompasses characteristics similar to an Simon's optimal two-stage design ²¹ ([see table 11.4.4](#)) and also allows for sample size flexibility.

Design	Targeted Accrual (Rejection Boundary)		APET	Error	
	Stage I	Stage II		Type I	Type II
Rigid (Simon's) ²¹	24 (≤ 13)	49 (≤ 28)	0.729	9.6%	9.2%
Flexible	24 (≤ 12)	49 (≤ 28)	0.579	10.0%	7.0%

Table 11.4.4

11.5 Analysis Plan

Only those patients who are deemed "ineligible" or who receive no therapy will be excluded from the analysis. All patients who receive any therapy will be evaluated for both treatment efficacy and toxicity.

Evaluation of Primary Endpoints

Efficacy will be evaluated as the frequency of complete clinical and pathologic response after primary therapy. Only those patients who are deemed ineligible or receive no therapy or refused all radiation therapy

without any medical contraindication will be considered inevaluable for response. All patients who receive any therapy will be evaluated for toxicity.

While on occasion, circumstances may prevent the determination of treatment efficacy, such patients will be included in the analysis and labeled as "unknown". This category will be listed and be reflected in the calculation of the response rate. The probability of attaining a complete pathologic response will be estimated.

Evaluation of PFS and OS

Product-limit estimates according to the method of Kaplan and Meier will be calculated to assess duration PFS and OS among the entire study cohort and by response status.

Evaluation of Site(s) of Recurrence

Site(s) of first disease recurrence will be classified as: local (vagina or vulva), loco-regional (within the pelvic) or distant and tabulated by response status.

Toxicity

Maximum grade of treatment related adverse effect will be tabulated based CTCAE v4.0 grading system

11.6 Study Monitoring, Data Quality Control and Semi-annual Reports

The GOG SDC will be responsible for, conducting centralized patient registration, study monitoring, data collection, storage and analysis. To assure the best possible data quality, the study statistician in collaboration the data manager/coordinator (DM) will execute regular data checks. Inconsistencies and errors will be queried and sites will notify the DM upon resolution. In turn the DM will repeat data checks to make certain queried issues were indeed resolved. Every effort will be made to resolve outstanding queries promptly. Unresolved queries will be documented and cited in a comment field of the study scientific table.

Case report forms (CRFs) will be reviewed before each semi-annual meeting and will also be reviewed by the Study Chairperson in conjunction with the Statistical and Data Center. The purpose of these reviews is to access protocol compliance and possibly make recommendations aimed at improving study compliance. In some instances, because of unexpectedly severe toxicity, the Statistical and Data Center may elect, after consultation with the Study Chairperson and the Medical Oncology Committee, to recommend early closure of a study.

After data checks, study chair (co-chair) reviews and data updates, a locked dataset void of protected patient information will be saved using standard GOG SDC dataset achieving convention.

Reports will be generated from the most recent locked information by the study statistician for inclusion into the GOG's Semi-annual Statistical Report (GOG

SR). The study SR will comprise of accrual (and patient accession) information, distribution of baseline traits, treatment compliance, and patient safety (adverse events) data, thus providing a mechanism for reviewing and monitoring study progress and for conducting a study with optimal efficiency.

All serious (SAE) and unexpected adverse events regardless of attribution will be communicated promptly to the study chair, and any regulatory agencies as mandated in the protocol. These reports are reviewed within two working days for consideration of investigator notification, amendment, or immediate study suspension.

Toxicity information will also be reviewed by the GOG Safety Review Committee (SRC) at each semi-annual meeting during the period for which patients are on study (being treated). The goal of the SRC is to review the AE data, including all new SAE reports (from ongoing GOG studies) submitted between consecutive GOG business meetings held in January and July each year. **(04/21/2014)**

In addition, in the event of more than one treatment-related death that occur on-study, or more than TWO identical unexpected treatment-related non-hematologic grade 4 toxicities, centralized registration and accrual will be suspended pending further review. All participating institutions will then receive notification of the toxicities and reason for study suspension. Under these circumstances, accrual cannot be re-activated until the study is reviewed by the GOG Data and Safety Monitoring Board. However, patients currently receiving treatment may continue to receive treatment in accordance protocol guidelines at the discretion of their physicians, unless directed otherwise.

As this is a two-stage group-wide phase II protocol, the initial overall review of toxicity is usually performed after completion of the first stage of accrual, at which point accrual is generally suspended pending formal analysis of response and toxicity.

11.7 Planned Minority Inclusion

The following table provides race and ethnicity distribution anticipated for this trial (based on GOG-0205).

Accrual Targets (N = 49)				
Ethnic Category	Sex/Gender			
	Females		Males	Total
Hispanic or Latino	2	+	0	= 2
Not Hispanic or Latino	47	+	0	= 47
Ethnic Category: Total of all subjects	49	+	0	= 49
	(A1)		(B1)	(C1)
Racial Category				
American Indian or Alaskan Native	2	+	0	= 2
Asian	1	+	0	= 1
Black or African American	3	+	0	= 3
Native Hawaiian or other Pacific Islander	1	+	0	= 1
White	42	+	0	= 42
Racial Category: Total of all subjects	49	+	0	= 49
	(A2)		(B2)	(C2)
	(A1 = A2)		(B1 = B2)	(C1 = C2)

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APPENDIX I

TNM and International Federation of Gynecology and Obstetrics (FIGO)
Staging Systems for Vulvar Carcinoma

The TNM staging system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) for carcinoma of the vulva is recommended and is shown below.^{1,2} Comparison with FIGO staging is also shown.^{3,4}

According to AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically infeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

TNM and FIGO Staging Systems for Vulvar Carcinoma

Primary Tumor (T)

TNM Categories	FIGO Stages	
TX		Primary tumor cannot be assessed
TO		No evidence of primary tumor
Tis		Carcinoma in situ (preinvasive carcinoma)
T1a	IA	Lesions 2cm or less in size, confined to the vulva or perineum and with stromal invasion 1.0 mm or less
T1b	IB	Lesions more than 2 cm in size or any size with stromal invasion more than 1.0 mm, confined to the vulva or perineum
T2	II	Tumor of any size with extension to adjacent perineal structures (lower/distal 1/3 urethra, lower/distal 1/3 vagina, anal involvement)
T3	IVA	Tumor of any size with extension to any of the following: upper/proximal 2/3 of urethra, upper/proximal 2/3 vagina, bladder mucosa, rectal mucosa, or fixed to pelvic bone

Note: The depth of invasions is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

Regional Lymph Nodes (N)

NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		One or two regional lymph nodes with the following features
N1a	IIIA	One or two lymph node metastasis each 5 mm or less
N1b	IIIA	One lymph node metastasis 5 mm or greater
N2	IIIB	Regional lymph nodes metastasis with the following features
N2a	IIIB	Three or more lymph node metastases each less than 5 mm
N2b	IIIB	Two or more lymph node metastases 5 mm or greater
N2c	IIIC	Lymph node metastasis with extracapsular spread
N3	IVA	Fixed or ulcerated regional lymph node metastasis

Distant Metastasis (M)

M0		No distant metastasis
M1	IVB	Distant metastasis (including pelvic lymph node metastasis)

Anatomic Stage/prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage II	T2	N0	M0
Stage IIIA	T1, T2	N1a, N1b	M0
Stage IIIB	T1, T2	N2a, N2b	M0
Stage IIIC	T1, T2	N2c	M0
Stage IVA	T1, T2	N3	M0
	T3	Any N	M0
Stage IVB	Any T	Any N	M1

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APPENDIX II

GOG General Chemotherapy Guidelines (08/15/2016)

- For 21 or 28 day cycles, a patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.
- It will be acceptable for individual chemotherapy doses to be delivered within a “24-hour window before and after the protocol-defined date” for “Day 1” treatment of 21 or 28 day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due).
- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a “24-hour window,” for example; “Day 8 chemotherapy” can be delivered on Day 7, Day 8, or Day 9 and “Day 15 chemotherapy” can be given on Day 14, Day 15, or Day 16.
- Chemotherapy doses can be “rounded” according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).
- Chemotherapy doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for < 10% weight changes.

APPENDIX III

SENTINAL NODE BIOPSY FOR VULVAR CANCER

Purpose 1) Histologic evaluation for nodal metastasis.
2) Surgical-pathologic staging of vulvar cancer.
3) Provide guidelines for subsequent therapy.

Indications 1) Primary invasive cancer of the vulva.

Contraindications 1) Poor surgical risk
2) Grossly positive groin nodes

Content of the procedure

Prior to surgery, lymphoscintigraphy is performed by injecting radionuclide intradermally at the leading border of the primary tumor (the border closest to the groin(s) or scar site if an excisional biopsy was done). For midline tumors, inject on both sides of the tumor. Anatomic markers should be placed on the symphysis pubis and anterior superior iliac spines. The patient is immediately scanned. The skin over the SN can be marked with an indelible marker. Transmission scans, which show the outline of the body, should be performed if possible. Following induction of anesthesia, the hand-held gamma counter is used to try to identify the sentinel node transcutaneously. The skin over the sentinel node is marked. Intradermal injection of isosulfan or methylene blue is made at the leading edge of the primary tumor (the border closest to the groin(s) or scar site if an excisional biopsy was done). The skin incision is made approximately 5 minutes following the injection of isosulfan blue. The hand-held gamma counter may assist in the localization of the sentinel node. The sentinel node is identified and labeled.

ADVERSE EFFECTS THAT MAY BE ASSOCIATED WITH AN UNEVENTFUL PROCEDURE

<u>SYSTEM</u>	<u>GRADE</u> (up to and including)
Hematopoietic	2
Genitourinary	1
Gastrointestinal	1
Hepatic	1
Pulmonary	1
Cardiovascular	1
Peripheral Neurologic	1
Central Neurologic	1
Cutaneous	2
Lymphatics	1
Fever	2
Allergic	0

APPENDIX IV

DEEP INGUINAL LYMPHADENECTOMY

Purpose 1) Excisional biopsy of the deep inguinal or femoral lymph nodes for histologic evaluation and treatment in patients with invasive cancer of the vulva.

Indications 2) Primary invasive cancer of the vulva.

Contraindications 1) Evidence of distant metastases or pelvic adenopathy
2) Significant medical problems that make the patient a poor surgical risk.

Content of Procedures

A superficial lymphadenectomy (See Superficial Inguinal Lymphadenectomy) has already been performed at the same setting. Any incision adequate for exposure may be used. During the previous superficial groin node dissection, the cribriform fascia over the fossa ovalis should have been preserved. The fascia covering the sartorius muscle should be reflected to ensure total removal of the lymph nodes in the femoral triangle. The femoral artery should be identified and the dissection carried along the artery until all lymphatic tissue is removed. The femoral nerve should be preserved. The femoral vein and saphenous vein should be identified and the lymphatic dissection continued caudad until the saphenous vein can be adequately mobilized. At the discretion of the surgeon, the saphenous vein may be doubly ligated near the sapheno-femoral junction and a segment removed with the node bearing tissue or it may be spared by dividing this tissue over the saphenous vein. Dissection continues to removal of all lymphatic tissue laterally to the sartorius and medially to the adductor longus muscles. At the discretion of the surgeon, the sartorius muscle is then mobilized, transected at its insertion with electrocautery, transplanted over the femoral vessels and sutured to the inguinal ligament with permanent suture. Suction drains may be placed bilaterally followed by closure of the subcutaneous tissues and skin.

ADVERSE EFFECTS THAT MAY BE ASSOCIATED WITH AN UNEVENTFUL PROCEDURE

<u>SYSTEM</u>	<u>GRADE</u> (up to and including)
Hematopoietic	2
Genitourinary	1
Gastrointestinal	1
Hepatic	1
Pulmonary	1
Cardiovascular	1
Peripheral Neurologic	1
Central Neurologic	1
Cutaneous	2
Lymphatics	1
Fever	2
Allergic	0

APPENDIX V

SUPERFICIAL INGUINAL LYMPHADENECTOMY

Purpose 1) Excisional biopsy of the superficial inguinal lymph nodes for histologic study in patients with early, invasive squamous cell carcinoma of the vulva.

Indications 1) Primary invasive cancer of the vulva.

Contraindications 1) More advanced stages of clinical disease.
2) Suspicious or grossly positive inguinal adenopathy.

Content of Procedure

Superficial inguinal lymphadenectomy may be approached through groin incisions 1-2 cm below and parallel to Poupart's ligament or through a vertical incision. The superficial inguinal fat pad is removed by dissecting the node-bearing fatty areolar tissue which lies deep to Camper's fascia, superficial to Colles's fascia, the cribriform fascia and the fascia lata. The cephalad extent of dissection is Poupart's ligament; the medial extent is the medial surface of the adductor longus muscle; the lateral extent is the medial border of the sartorius muscle; and the distal extent is approximately 6 cms distal to Poupart's ligament. The dissection may proceed from medial to lateral at the surgeon's discretion. Care should be taken to preserve the cribriform fascia over the fossa ovalis. The operative field may be drained with suction drains. Closure of the subcutaneous tissues and skin may be accomplished at the surgeon's discretion.

ADVERSE EFFECTS THAT MAY BE ASSOCIATED WITH AN UNEVENTFUL PROCEDURE

<u>SYSTEM</u>	<u>GRADE</u> (up to and including)
Hematopoietic	2
Genitourinary	1
Gastrointestinal	1
Hepatic	1
Pulmonary	1
Cardiovascular	1
Peripheral Neurologic	1
Central Neurologic	1
Cutaneous	2
Lymphatics	1
Fever	2
Allergic	0