SUMMARY OF CHANGES

For Protocol Amendment #6:

NCI Protocol #: NRG-GY006

NCI Version Date: February 17, 2021

#	Section	Comments (PA will hyperlink to copy prior to submitting)
1.	Title Page	• NCI Version date is now February 17, 2021 • Research Nurse deleted. • Duplicate listing of Protocol Administrator deleted. • Duplicate listing of Clinical Data Coordinator deleted. • CCTG added as participating organization. • Canada has been added as a participating site. • CTSU logistical language updated in Contact Information Table.
2.	5.0	Triapine filtration language was updated.
3.	5.1.2	Triapine filtration language was updated.
4.	8.0 and 8.1	CTSU logistical language was updated.
5.	8.2.1	CTSU logistical language was updated.
6.	8.2.3	DTL information for Canadian sites added.
7.	8.3.1	CTSU logistical language was updated.
8.	8.4.1	CTSU logistical language was updated.
9.	9.1	Triapine preparation and administration language was updated.
10.	12.1	CTSU logistical language was updated.
11.	ICD	NCI Version Date is now February 17, 2021. No additional changes have been made to the informed consent document.

NRG-GY006

(ClinicalTrials.gov NCT #02466971)

A Randomized Phase III Trial of Radiation Therapy and Cisplatin Alone or in Combination with Intravenous Triapine in Women with Newly Diagnosed Bulky Stage IB2, Stage II, IIIB, or IVA Cancer of the Uterine Cervix or Stage II-IVA Vaginal Cancer.

NCI Version Date: 02/17/2021

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI).

Lead Organization: NRG / NRG Oncology

Participating Organizations

ALLIANCE / Alliance for Clinical Trials in Oncology
ECOG-ACRIN / ECOG-ACRIN Cancer Research Group
SWOG / SWOG
CCTG / Canadian Cancer Trials Group **(17-FEB-2021)**

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Protocol Agents

Agent	Supply	NSC #	IND #	IND Sponsor
Triapine	CTEP	663249	68338	DCTD, NCI
Cisplatin	Commercial	119875		

Participating Sites

☒ U.S.
☒ Canada **(17-FEB-2021)**
☐ Approved International Member Sites

Document History

	Version/Update Date	Broadcast Date
Closure		
Amendment 6	**02/17/2021**	
Amendment 5	11/25/2019	
Amendment 4	02/01/2019	
Amendment 3	**03/16/2018**	
Amendment 2	**11/29/2017**	**01/16/2018**
Amendment 1	**02/24/2017**	**05/30/2017**
Activation	**12/22/2015**	**01/15/2016**

NRG-GY006

A Randomized Phase III Trial of Radiation Therapy and Cisplatin Alone or in Combination with Intravenous Triapine in Women with Newly Diagnosed Bulky Stage IB2, Stage II, IIIB, or IVA Cancer of the Uterine Cervix or Stage II-IVA Vaginal Cancer.

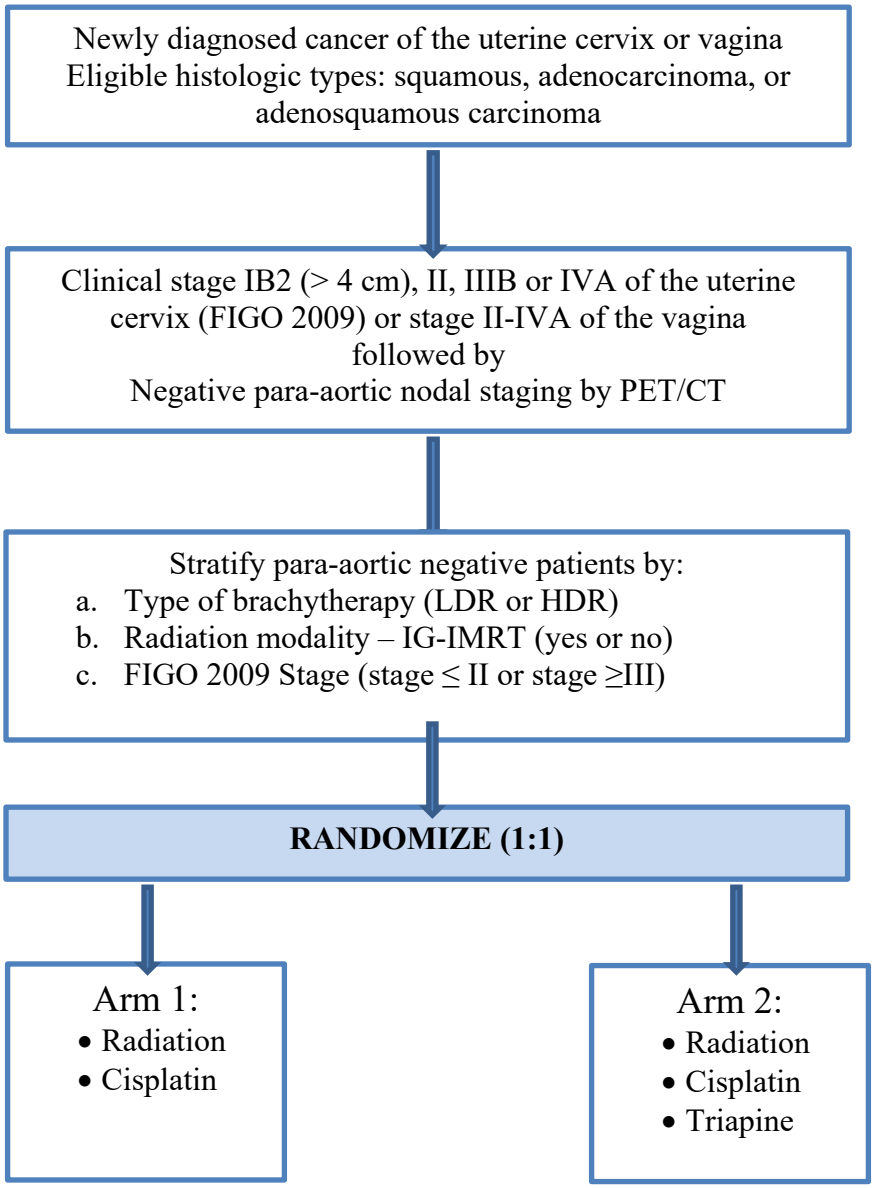
NCI Version Date: 02/17/2021

Lead Organization: NRG / NRG Oncology

CONTACT INFORMATION (17-FEB-2021)		
For regulatory requirements:	**For patient enrollments:**	**For data submission**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email : 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' web site (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 Regulatory Support System (RSS).		
For clinical questions (i.e. patient eligibility or treatment-related) *Contact the Study Principal Investigator of the Lead Protocol Organization*		

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

SCHEMA (05/30/2017)



Radiation: 45 Gy / 25 fractions of 1.8 Gy + 5.4 Gy / 3 fraction parametrium boost + 40 Gy LDR or 30 Gy HDR brachytherapy

Cisplatin: x1 weekly cisplatin 40 mg/m^2 (maximum 70 mg) days 2, 9, 16, 23, 30 of radiation (5 total infusions; a sixth administration on day 37 is permissible at the treating physician's discretion. Cisplatin may be given ± 1 day to accommodate scheduling issues for the control arm only.

Triapine: x3 weekly 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (Triapine) 25 mg/m^2 (maximum 50 mg) days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26, 29, 31, 33 of radiation (15 total infusions)

Statistics: This is a two-arm, open label randomized (1:1) phase III clinical trial.

TABLE OF CONTENTS

1.0 OBJECTIVES

Specific hypothesis:

The experimental regimen, triapine (3AP) in combination with cisplatin and radiation, will improve overall survival relative to the standard / control regimen of cisplatin and radiation in women with uterine cervix or vaginal cancer.

1.1 Primary Objective

To evaluate the efficacy of the experimental regimen of triapine (3AP), cisplatin, and radiation to increase overall survival relative to the standard / control regimen of cisplatin and radiation in women with uterine cervix or vaginal cancer.

1.2 Secondary Objectives

1.2.1 To determine the relative progression-free survival impact of triapine-cisplatin radio-chemotherapy and cisplatin radio-chemotherapy.

1.3 Tertiary Objectives

1.3.1 To evaluate incidence and severity of hematologic and gastrointestinal (GI) adverse events by radiation modality; image guided intensity modulated radiation therapy (IG-IMRT) versus conventional pelvic radiotherapy. **(05/30/2017)**

1.3.2 To summarize and compare differences in acute adverse events (CTCAE v4.0) by treatment arm and by radiation modality. **(05/30/2017)**

1.3.3 To summarize and compare differences in chronic or late (≥ 30-days from off study treatment date) adverse events (CTCAE, v4.0) by treatment arm and by radiation modality. **(05/30/2017)**

1.3.4 To determine peripheral blood methemoglobin proportion before and after triapine infusion (*optional for Arm 2 patients*).

1.3.5 To explore whether knowledge-based planning (KBP) can improve IG-IMRT plans compared to plans that would have been delivered without KBP, estimate the resulting toxicity reduction using NTCP models, and determine whether KBP should be a requirement for future IG-IMRT protocols.

1.3.6 To determine the post-therapy 3-month 18F-FDG PET/CT metabolic complete response rate by treatment arm.

1.3.7 To compare acute toxicity and chemotherapy delivery for atlas-based IG-IMRT vs. PET/CT-based IG-IMRT vs. conventional RT, and assess the impact of treatment on changes in hematopoietic compensatory response.

1.3.8 To develop and validate machine learning and radiomics techniques for dose accumulation, automated treatment planning, and prediction of treatment response.

2.0 BACKGROUND

2.1 Treatment for most solid tumors remains unsatisfactory, and new and more effective anticancer biologic agents are needed. Ideally, new anticancer biologic agents are targeted against molecular processes present or active in cancer cells and inactive in normal cells. These new agents also are expected to disrupt molecular processes that maintain malignant cell behaviors such as unchecked duplication, invasion, and metastasis. We have chosen to study, in a randomized phase III clinical trial, a molecular pathway known to act preferentially on uterine cervix cancers—ribonucleotide reductase over activity (Kunos, 2013; Kunos, Waggoner, 2010; Kunos, 2009; Kunos, Radivoyevitch, 2010; Kunos, Ferris, 2011). We focus upon women with cervical or vaginal cancer because there is an unmet therapeutic need for a biologic agent to improve overall survival and metabolic complete response (mCR) during cisplatin-based radio-chemotherapy. We meet a need to validate an early biomarker of mCR by using a 3-month post-therapy 2-[^{18}F] fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography (^{18}F-FDG PET/CT) scan as a secondary trial endpoint. Feasibility for ^{18}F-FDG PET/CT has been demonstrated in a NCI-sponsored trial for uterine cervix cancer (Kunos, 2013).

Here, we propose a randomized phase III trial of daily radiation therapy and once weekly intravenous cisplatin chemotherapy alone (arm 1), or with co-administered ribonucleotide reductase inhibition by intravenous triapine (arm 2). The study was initiated as randomized phase II study. Amendment 4 increased the sample size and converted the study from a randomized phase II to a randomized phase III. Amendment 5 converts this study to a registration trial. The primary endpoint changes to overall survival, the type I error rate decreases to 0.025 and the sample size increases to 450 patients.

2.2 There is a clinical need in women with cervical cancer for a biologic agent to improve survival after cisplatin-based radio-chemotherapy. As seen in GOG-0219, overall survival was 72% (95% CI: 65% to 78%) 36 months after enrollment, and 64% (56% to 71%) 60 months after enrollment. Estimates for cervical cancer patient progression-free survival after cisplatin-based radio-chemotherapy are 64.5% 36 months after enrollment to NRG Oncology (and legacy Gynecologic Oncology Group) trials. The combination of ribonucleotide reductase inhibitors and cisplatin-based radio-chemotherapy suggests a disease-free survival rate of 82% (Kunos, 2014).

In this trial, there is also the opportunity to consider a tertiary analysis evaluating 3-month post-therapy ^{18}F-FDG PET/CT mCR as an early "surrogate" endpoint for progression-free and overall survival. Moreover, data would determine the discriminatory usefulness of the PET/CT response surrogate for determination of treatment efficacy—a tool significantly impactful upon new cervical cancer therapy strategies to be evaluated by the United States Food and Drug Administration.

^{18}F-FDG PET/CT metabolic complete response rates are 60-85% after cisplatin-based radio-chemotherapy for women with cervical cancer (Kunos, Radivoyevitch, 2011; Schwartz, 2007). For a secondary endpoint in this protocol, mandatory standard-of-care pre-therapy (≤ 28 days from radiation start), mandatory standard-of-care post-therapy 3-month ^{18}F-FDG PET/CT scans will be obtained for mCR assessment. Feasibility for ^{18}F-FDG PET/CT as an early surrogate of response has been demonstrated in NCI-CTEP protocol #8327, as 23 (96%) of 24 eligible cervical cancer patients completed the specified imaging (Kunos, 2013). For qualitative interpretation, this study will use language as outlined by the National Cancer Institute Cancer Imaging Program (Shankar, 2006; Young, 1999). For semi-quantitative interpretation, this study will use three metrics: (a) standardized uptake value (SUV) normalized to body mass, (b) SUV normalized to lean body mass (SUL), and (c) ratio of post-therapy SUV_{max}: pre-therapy SUV_{max}. For the latter, ratios ≥ 1.25 indicate progressive metabolic disease, ratios 0.76 to 1.25 classify stable metabolic disease, ratios 0.34 to 0.75 indicate partial metabolic response, and ratios ≤ 0.33 label complete metabolic response. SUV_{max} indistinguishable from cardiac or liver blood pool activity will also indicate metabolic complete response, as before (Kunos, 2013).

2.3 Rationale for trial design

2.3.1 3-aminopyridine-2-carboxaldehyde-thiosemicarbazone (triapine, arm 2)
NCI-CTEP has sponsored a phase I trial (NCI 7336, NCT00335998) and a phase II trial (NCI 8327, NCT00941070) evaluating the safety and clinical efficacy of intravenous triapine in cervical cancer (Kunos, 2013; Kunos, Waggoner, 2010). Triapine is 500-to-1000-fold more potent inhibitor of ribonucleotide reductase M2 and M2b than hydroxyurea, which has previously shown activity in cervical cancer. Triapine has both intravenous and oral forms in clinical development, making this anticancer drug an appealing option. A Phase I trial testing of oral triapine, cisplatin, and radiation has not been completed and continues to recruit participants (NCT 02595879). The half-life of intravenous triapine is 2 hours (therapeutic window of ~6 hours), suggesting repeated dosing within a week for efficacy. In preclinical studies, triapine alone has a ~20% cytotoxic rate, triapine plus

cisplatin has a 60% cytotoxic rate, and triapine plus cisplatin plus radiation has a 90% cytotoxic rate (Kunos, Radivoyevitch, 2010). In phase I and II studies, intravenous triapine (25mg/m^2) was given three times weekly co-administered with cisplatin (40mg/m^2) and daily radiation (50.4 Gy in 28 fractions) plus brachytherapy (35-40 Gy) in 35 patients with advanced stage cervical and vaginal cancer (Kunos, 2013; Kunos, Waggoner, 2010). A total of 500 (95%) of 525 2-hour triapine infusions have been administered without complication, and so, the regimen is safe. Three-month complete clinical responses have occurred in 34 (97%) of 35 patients (1 partial response was seen in a patient not receiving brachytherapy). Three-month mCRs have occurred in 23 (96%) of 24 patients in whom the images were acquired on the phase II study (Kunos, 2013). Four (11%) of 35 patients have died from extra-pelvic disease progression.

For 24 stage II-IIIB or node-positive stage IB2 patients treated on the phase I and II trials, 3-year overall and disease-free survival estimates are 82% (95% confidence interval [CI]: 74%-90%) and 80% (95% CI: 71%-89%) (Kunos, 2014). A single (4%) loco-regional failure has been observed. Based on these impressive findings, a randomized phase II trial of triapine-cisplatin radio-chemotherapy versus cisplatin radio-chemotherapy was activated and accrued 21 patients prior to the opening of NRG-GY006. Although initially designed to be analyzed with GY006, the lack of continued follow-up has precluded the use of outcome data in these patients (NCI #9434, NCT01835171).

2.3.2 Rationale for intensity modulated radiation therapy (IMRT) stratification at randomization

IMRT has emerged as an effective radiation delivery approach to treat cancer while simultaneously minimizing radiation exposure to adjacent healthy tissues. Furthermore, a potential barrier to accruing to the ongoing ANZGOG OUTBACK protocol #902 has been the prohibition of IMRT use on that protocol. It is believed that allowing IMRT treatment on this protocol would facilitate patient accrual in the United States and Canada (NRG Radiation Oncology Committee, February 2014).

Multiple published studies indicate that IMRT can reduce both hematologic and gastrointestinal (GI) toxicities, and can provide excellent long-term outcomes (Klopp, 2010; Kidd, 2010). While IMRT has been used for more than a decade, few prospective trials have incorporated IMRT for definitive treatment of uterine cervical cancer. Several studies and educational videos regarding IMRT techniques have also been produced to facilitate quality control, since IMRT planning and delivery is more technical than conventional RT techniques (Lim, 2011; Small, 2008).

The phase II portion of the NCI-supported INTERTECC multi-center trial (NCT01554397/ ISRCTN54531450) enrolled 83 women with stage IB-IVA

cervix cancer (86% were IIB-IVA). The primary endpoint was the occurrence of either acute grade ≥ 3 neutropenia or clinically significant GI toxicity (grade ≥ 2 diarrhea requiring intravenous fluids and/or combination opiate/anticholinergic antidiarrheal medication) within 30 days of completing chemoradiotherapy. A pre-planned subgroup analysis was designed to test the hypothesis that positron emission tomography (PET) image-guided bone marrow-sparing IMRT (IG-BMS-IMRT) lowers the risk of acute neutropenia. Toxicity grading was according to NCI CTCAE v4. The incidence of any primary event was significantly lower than historical data (2-sided chi-square p=0.012). Compared to patients treated without IG-BMS-IMRT (N=48), patients treated with IG-BMS-IMRT (N=35) had significantly lower grade ≥ 3 neutropenia (p=0.035). These data were recently submitted to the ESTRO 35 2016 Meeting (Abstract # E35-0024).

Multiple published studies also support the use of ^{18}F -FDG-PET for defining "active" or "functional" bone marrow (Figure 1). For example, Rose et al. reported that increased radiation dose to metabolically active bone marrow defined by ^{18}F -FDG-PET was correlated with increased acute hematologic toxicity, in contrast to radiation dose to relatively less active marrow (Rose, 2012). Liang et al. reported the first use of ^{18}F -FDG-PET/CT in combination with quantitative IDEAL MRI to define active marrow regions for use as an avoidance structure in IMRT planning, showing this technique is feasible clinically (Liang, 2013). Recently, Elicin et al. associated loss of active bone marrow defined by ^{18}F -FDG-PET/CT with subacute hematologic toxicity following chemoradiotherapy for cervical cancer (Elicin, 2014).

The optimal method for delineating active bone marrow is not known. An important question is whether commonly available techniques that are paid for by patient's insurers, such as ^{18}F -FDG-PET/CT, are better than alternative methods, such as ^{18}F-FLT-PET/CT, which are rarer and more expensive. Furthermore, the precise location of a hematopoietic stem cell niche within the bone marrow remains elusive, with evidence supporting the existence of both a vascular niche and an endosteal niche (Spencer, 2014). The rationale for the approach using ^{18}F -FDG-PET/CT is to avoid metabolically active tissue within bone, which we hypothesize is mostly hematopoietically functional bone marrow. Some hematopoietic stem cells may also lie in the endosteal region. Although there can be some misspecification of cortical bone and adjacent soft tissue due to "blooming" or registration errors, this component appears to be negligible compared to the large region within the bone designated as metabolically active (Figure 1).

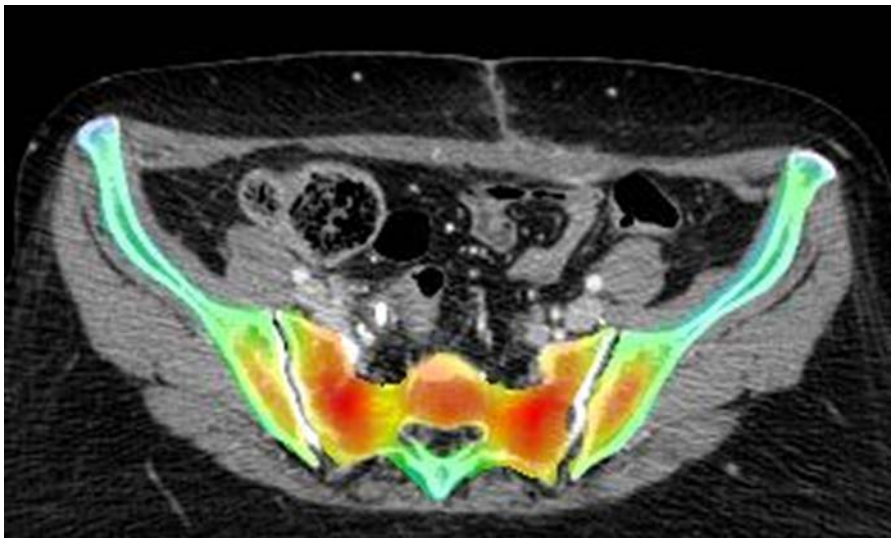


Figure 1. Heat map of metabolically active bone marrow defined by ^{18}F-FDG-PET in 32 patients with cervical cancer, rendered using deformable image registration.

Another relevant clinical trial is the American Cancer Society-sponsored Phase I trial of concurrent cisplatin/gemcitabine with IMRT designed to reduce bowel and bone marrow dose (NCT01554410), which varies the order of administration for cisplatin and gemcitabine. Gemcitabine, another ribonucleotide reductase inhibitor, has been found to improve pathologic response and overall survival in randomized trials (Duenas-Gonzalez, 2011; Duenas-Gonzalez, 2005). However, a gemcitabine-based regimen is highly toxic, and previous multicenter phase I trials have found that the maximum tolerated dose (MTD) of gemcitabine is lower (≤ 50 mg/m2) when delivered with conventional RT techniques (Swisher, 2006; Rose, 2007). In contrast, this ongoing Phase I trial has enrolled 21 patients with stage IB2-IVA cervical cancer. The MTD of gemcitabine has not yet been reached, but has been observed to be higher (≥ 100 mg/m^2) in the setting of IMRT planning, consistent with validated normal tissue complication models (Rose, 2011; Simpson, 2012). Although the trial remains ongoing, sequential administration of cisplatin 40mg/m^2 followed by gemcitabine 125mg/m^2 and pelvic IMRT as well as sequential gemcitabine 75mg/m^2 followed by cisplatin 40mg/m^2 and pelvic IMRT appear to be tolerable with manageable toxicity. More generally, these findings suggest the tolerability of concurrent doublet chemotherapy could be higher with IMRT than with conventional RT techniques.

2.3.3 Rationale for research on effectiveness and quality of IG-IMRT **(05/30/2017)**

IG-IMRT is more complex to deliver and is therefore prone to greater variation in quality compared to standard radiation techniques. Variation in imaging quality and resolution across centers is also possible, and studies to validate and gauge the quality of IG-IMRT are needed.

Although IMRT has become the radiotherapy standard-of-care for many cancers, there exist few quantitative metrics to evaluate IMRT treatment planning quality. IMRT quality assessments currently rely primarily on individual subjective evaluation, while commercial treatment planning systems employ user-specified cost functions that have few (if any) limitations on the use of conflicting and/or inappropriate planning objectives. Variation in IMRT plan quality can be attributed to a number of factors: the anatomic variations between patients, the complexity of clinical goals, the paucity of quantitative metrics to judge the optimality of a given IMRT plan, and, of course, the subjectivity and relative experience of the dosimetrists, medical physicists, and physicians involved in the planning process. Perhaps the most difficult part of IMRT quality assessment is judging the adequacy of normal tissue sparing which is the principal rationale for employing IMRT over 3D conformal radiotherapy (3DCRT).

Our research group has developed mathematical models to detect sub-optimal IMRT plans with high sensitivity and specificity, using a process termed Knowledge-Based Planning (KBP) (Moore, 2011). This system is built to identify optimal plans amongst prior training cohorts, and use the resulting model to develop predictive dose-volume histograms (pDVH) for organs-at-risk (OARs) that give precise quantitative information on plan quality deficiencies. This approach will allow us to identify, quantify, and ultimately correct sub-optimal treatment plans, a process that is ideally suited for application to quality control in the multi-center clinical trial setting, particularly when new technologies or implementations are being introduced.

Recently, studies have shown that atlas-based IG-IMRT methods are feasible and likely to achieve similar outcomes to PET/CT-guided IG-IMRT, while obviating the need for expensive PET/CT imaging (Li, 2017). This would greatly increase the access of patients to bone marrow sparing IMRT in sections of the world where PET/CT imaging is unavailable or unaffordable. Secondly, little is known about the effect of varying chemoradiotherapy regimens on the hematopoietic compensatory response. Noticewala et al. (2017) developed a technique to quantify the compensatory response on serial PET/CT imaging that can be implemented in this trial. Finally, machine learning and radiomics approaches are novel branches of applied radiation medicine and radiation physics, but little is known about their application to the gynecologic population, particularly when combining external beam radiotherapy and brachytherapy. Further work in this trial will lead to better methods of dose accumulation, automated brachytherapy planning, and the use of radiomic classifiers to predict treatment response.

2.4 Inclusion of Women and Minorities

NRG Oncology and its participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives

in a patient population representative of the entire population treated by participating institutions.

3.0 PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILTY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and to exclusion criteria are not permitted. For questions concerning eligibility, please contact the NRG Statistical and Data Management Center-Pittsburgh Office (via the contact list, NRG web site).

3.1 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.1.1 Patient has a new, untreated histologic diagnosis of stage IB2 (> 4 cm), II, IIIB or IVA squamous, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix (FIGO 2009) or stage II-IVA squamous, adenocarcinoma, or adenosquamous carcinoma of the vagina not amenable to curative surgical resection alone. The presence or absence of para-aortic lymph node metastasis will be based on pre-therapy ^{18}F-FDG PET/CT. NOTE: If the baseline ^{18}F-FDG PET/CT identifies hypermetabolic para-aortic disease, such patients will NOT be eligible. The patient must be able to tolerate imaging requirements of an ^{18}F-FDG PET/CT scan.

3.1.2 Patient must provide study specific informed consent prior to study entry.

3.1.3 Patient must have a GOG performance status of 0, 1, or 2 or equivalent (Appendix II).

3.1.4 Patient must have adequate organ and marrow function as defined below:

absolute neutrophil count	> 1,500/µL
platelets	> 100,000/µL
hemoglobin	> 10 g/dL
total bilirubin	< 2.0 mg/dL
AST (SGOT)/ALT(SGPT)	< 2.5 X institutional upper limit of normal
PT/aPTT	< 1.5 X institutional upper limit of normal
Creatinine	≤ 1.5 mg/dL to receive weekly cisplatin*

*Patients whose serum creatinine is between 1.5 and 1.9 mg/dL are eligible for cisplatin if there is no hydronephrosis and the estimated creatinine clearance (CCr) is ≥ 30 ml/min. For the purpose of estimating the CCr, the formula of Cockcroft and Gault for females should be used:

CCr = 0.85 x (140-age) x IBW / (Scr x72)
where age is the patient's age in years (from 20 to 80 years), Scr is the serum creatinine in mg/dL, and IBW is the ideal body weight in kg (according to the calculation IBW = 45.5 kg + 2.3 kg for each inch over 5 feet).

3.1.5 Patient does not have uncontrolled diabetes mellitus (i.e., fasting blood glucose >200 mg/dL).

3.1.6 Patient has a life expectancy of greater than 20 weeks.

3.1.7 Age is ≥ 18 years.

3.1.8 Patient does not have known brain metastases (testing *optional*).

3.1.9 Patient does not have known human immunodeficiency virus syndrome

(HIV, testing *optional*). Known HIV-positive patients receiving combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with triapine.

3.1.10 Patient does not have a known allergy to compounds of similar or biologic composition as triapine.

3.1.11 Patient does not have known glucose-6-phosphate dehydrogenase (G6PD) deficiency as the condition interferes with triapine antidote metabolism (G6PD testing *optional*).

3.1.12 Patient is not *actively* breastfeeding (or has agreed to discontinue breastfeeding before the initiation of protocol therapy).

3.2 Ineligibility Criteria

Patients with one or more of the following conditions are NOT eligible for this study.

3.2.1 Patient has another concurrent *active* invasive malignancy.

3.2.2 Patient has had a prior invasive malignancy diagnosed within the last three years (except [1] non-melanoma skin cancer or [2] prior *in situ* carcinoma of the cervix). Patients are excluded if they have received prior pelvic radiotherapy for any reason that would contribute radiation dose that would exceed tolerance of normal tissues at the discretion of the treating physician.

3.2.3 Patient has uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction within six months of protocol initiation, cardiac arrhythmia within six months of protocol initiation; known inadequately controlled hypertension; clinically significant pulmonary disease including dyspnea at rest, or patients requiring supplemental

oxygen, or poor pulmonary reserve; or clinically significant renal function impairment (baseline serum creatinine >2 mg/dL); or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.4 Patient is receiving another investigational agent for the treatment of cancer.

3.2.5 Patient is *currently* pregnant.

3.2.6 Patient does not agree to use two forms of birth control if they are of child-bearing potential.

3.2.7 Patients who have had a hysterectomy or are planning to have an adjuvant hysterectomy following radiation as part of their cervical cancer treatment are ineligible. **(05/30/2017)**

3.2.8 Patients scheduled to be treated with adjuvant consolidation chemotherapy or other anti-neoplastic therapy at the conclusion of their standard chemoradiation. **(05/30/2017)**

3.2.9 Patients with self-reported or known diagnosis of G6PD deficiency. **(05/30/2017)**

3.2.10 Patients with vaginal cancer may have previously undergone a hysterectomy for various indications. Patients with vaginal cancer who underwent a hysterectomy for treatment of cervical cancer less than five years prior to their diagnosis of vaginal cancer are ineligible[MC1].

4.0 REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

ASSESSMENTS FOR PRE-TREATMENT STUDY ENTRY* (05/30/2017)

Assessments	Prior to Registration (calendar days)	Prior to 1st Radiation Treatment
Informed Consent	X	
History and Physical examination (including initial clinical tumor measurement in centimeters)	≤ 28 days	
Vital Signs (heart rate, blood pressure, respiratory rate, temperature, pain scale)	≤ 28 days	
Height	≤ 28 days	
Weight	≤ 28 days	
GOG Performance Status	≤ 28 days	
Toxicity Assessment	≤ 14 days	
Concurrent Medications	≤ 14 days	
Complete Blood Count (CBC) / Differential / Platelets / PT/aPTT	≤ 14 days	
Chemistries (including sodium, potassium, chloride, bicarbonate, calcium, glucose, magnesium, BUN/creatinine, total bilirubin, total protein, ALT, AST, alkaline phosphatase, albumin)	≤ 14 days	
Pregnancy Test (for patients of child bearing potential)	≤ 7 days	≤ 7 days
Electrocardiogram (EKG)	≤ 28 days	
PET/CT scan	≤ 28 days	

*** Study treatment must begin within 4 weeks of randomization**

ASSESSMENTS DURING TREATMENT (05/30/2017)

Assessment	**Day 1**
Methemoglobinemia Sampling (optional)	Refer to Section 6.1.1 Patients on Triapine arm only (Arm 2).
Pulse Oximetry	Patients on Triapine arm only (Arm 2).
Assessments	**Day 9, 16, 23, 30, 37***
History and Physical examination	≤ 3 days
Vital Signs (heart rate, blood pressure, respiratory rate, temperature)	≤ 3 days
Weight	≤ 3 days
Toxicity Assessment	≤ 3 days
CBC / Differential / Platelets	≤ 3 days
BUN/Creatinine, Magnesium	≤ 3 days

*Assessments must be completed even if optional cisplatin on day 37 is not given.

ASSESSMENTS DURING FOLLOW UP (05/30/2017)-Per Section 5.5

Assessments	**From end of treatment: 1 mo. and 3 mos.** Follow-up forms (Q forms) are collected.
Medical history, physical examination, GOG performance status, vital signs (heart rate, blood pressure, respiratory rate, temperature), and vital status (including any recurrence)	X
Toxicity Assessment	X
CBC / Differential / Platelets	1 mo. visit only
Chemistries (including sodium, potassium, chloride, bicarbonate, calcium, glucose, magnesium, BUN/creatinine, total bilirubin, total protein, ALT, AST, alkaline phosphatase, albumin)	1 mo. visit only
PET/CT, pre-scan glucose, BUN/creatinine	3 mos. visit only

Assessments	**From end of 3 mos. post therapy visit: q3 mos. years 1 and 2; then q6 mos. years 3, 4, and 5.** Follow-up forms (Q forms) are collected for the 5-year follow-up period or until study termination.
Medical history, physical examination, ECOG performance status, vital signs (heart rate, blood pressure, respiratory rate, temperature), and vital status (including any recurrence)	X
Toxicity Assessment	X

5.0 TREATMENT PLAN (05/30/2017) (01/16/2018) (17-FEB-2021)

This study has two study groups.

- Group 1 will get the usual cisplatin chemotherapy and radiation therapy used for this type of cancer.
- Group 2 will get the usual cisplatin chemotherapy and radiation therapy used for this type of cancer plus the investigational study drug triapine three times per week.

Chemotherapy and Radiation Regimen Description					
Agent	***Pre-medications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Triapine	All patients will receive dexamethasone 4 mg IV prior to each triapine (3-AP) infusion. Pre-medicate with antiemetic as needed for patients developing nausea or vomiting with a previous dose of triapine.	25mg/m^2 (50 mg maximum) diluted in 500 ml NS or 500 ml 5% dextrose in water	IV infusion over 2 hours using DEHP-free low sorbing infusion set..	Days 1, 3, 5, 8, 10, 12, 15,17, 19, 22, 24, 26, 29, 31, 33	Three times weekly (**preferably <u>after</u>** pelvic radiation treatment)
*Cisplatin**	Increased oral intake of fluid should be encouraged 24 hours prior to infusion; 1000 ml of ½ normal saline infused IV one hour before cisplatin. Antiemetic prophylaxis with a serotonin antagonist and/or dexamethasone 10-20 mg IV is allowed as a pre-medication.	40 mg/m^2 (70 mg maximum) diluted in 250-1000 ml normal saline, reconstitution results in a colorless solution. Mixing and administration should follow local standards	IV infusion at a rate of 1mg/min, usually infusing over 1 ½ hours (90 minutes), using non-aluminum administration sets; after is an additional 1000 ml of ½ normal saline infused over one hour	Days 2, 9, 16, 23, 30 (day 36 or 37 optional)	One time weekly (**<u>preferably before</u>**, *but allowed to be after* pelvic radiation treatment)
Pelvic external beam radiation therapy	Skin, antiemetic, or anti-diarrheal medications may be administered as needed.	1.8 Gy/ day (1.7 Gy/ day for IMRT, see Section 5.2)	See Section 5.2	Daily (excludes weekends and holidays)	Daily (Start on a Monday is preferred)
Pelvic brachytherapy	Antiemetic and anti-diarrheal medication may be administered as needed.	27.5 to 40 Gy in one or multiple fractions using LDR or HDR techniques	See Section 5.2	See Section 5.2	See Section 5.2

*Cisplatin preparation, administration and supportive hydration, antiemetics and supportive medications can be per altered per institutional standards.

5.1 Chemotherapy

5.1.1 Cisplatin chemotherapy (05/30/2017)
All patients will receive five one-time weekly intravenous infusions of cisplatin 40 mg/m^2 (70mg maximum) diluted in 250-1000 mL normal saline. The cisplatin infusions occur on day 2, 9, 16, 23, and 30. To accommodate scheduling issues, cisplatin dosing on the control arm only may be given ± 1 day. At the treating physician's discretion, a sixth infusion of cisplatin may occur on day 37 per institutional protocol. Increased oral intake of fluid should be encouraged 24 hours prior to cisplatin infusion. It is recommended that 1000 ml of ½ normal saline be infused intravenously one hour before cisplatin infusion, but other institutional protocols are accepted. Antiemetic prophylaxis with a serotonin antagonist is allowed as a pre-medication. It is recommended that the cisplatin intravenous infusion proceed at a rate of 1mg/minute, usually infusing over 90 minutes. Other infusion rates are acceptable per institutional routine. Infusion may occur before or after radiation treatment. Non-aluminum intravenous administration sets are required. An additional 1000 ml of ½ normal saline should be infused intravenously over one hour after cisplatin infusion, but other institutional protocols are accepted.

5.1.2 Triapine chemotherapy (05/30/2017) (01/16/2018) (17-FEB-2021)
Patients randomized to receive triapine will receive five three-times weekly intravenous infusions of triapine 25 mg/m^2 (50mg maximum) diluted in 500 mL normal saline or 500 mL 5% dextrose in water. The triapine infusions occur on day 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26, 29, 31, and 33. Triapine infusions should not occur on days of no radiation. Triapine infusions preferably should not occur on days of cisplatin infusion, but same day triapine-cisplatin infusions are allowed. Any missed triapine infusion may be made up during a sixth week of radiation (e.g. day 36 or 38), if the sixth week of radiation is done. It is recommended that dexamethasone 4mg be given intravenously before triapine infusion. Antiemetic prophylaxis with a serotonin antagonist for example is allowed as a pre-medication. It is recommended that triapine intravenous infusion proceed over two hours, approximately 90 minutes following radiation treatment. Other infusion rates are acceptable per institutional routine. DEHP-free low sorbing infusion set.

Methemoglobinemia is a known toxicity of triapine (21). Normal human blood levels are 1-3%. Triapine 25 mg/m^2 may elevate methemoglobin levels to 3-5% after infusion (21). It is recommended that the methemoglobinemia antidotes be available for the patient on the days of triapine infusion. The antidotes include either intravenous methylene blue given 1-2 mg/kg over five minutes (contraindicated G6PD-known patients), or intravenous ascorbic acid

1000 mg given per institutional standard every six hours until methemoglobinemia resolved.

5.2 Radiation Therapy

5.2.1 General

This protocol requires photon external beam radiation therapy (EBRT), either conventional radiation therapy (RT) or intensity modulated radiation therapy (IMRT) techniques followed by low dose rate (LDR) or high dose rate (HDR) brachytherapy. Radiation therapy must be completed within 60 days of initiation. Four-field box RT and IMRT are pretreatment stratification variables.

For EBRT, the prescription dose is 45 Gy in 25 fractions at 1.8 Gy/fraction with an optional parametrial boost of 4-9 Gy in 3-5 fractions at 1.8-2.0 Gy/fraction. EBRT should be given once daily Monday-Friday, 5 fractions per week. For instructions on nodal boosts for patients treated with 3D EBRT, see section 5.8.

For IMRT, the prescription dose is 45 Gy in 25 fractions at 1.8 Gy/fraction, unless a simultaneous integrated boost (SIB) is required for gross nodal disease. For SIB cases, the primary target will receive 47.6 Gy in 1.7 Gy/fraction and the gross nodal PTV (PTV_Boost) will receive 1.93-2.12 Gy per fraction, depending on bowel tolerance. IMRT should be given once daily Monday-Friday, 5 fractions per week.

For brachytherapy, the prescription doses are 27.5 - 30 Gy for HDR and 35 - 40 Gy for LDR, following institutional protocol. Please see section **5.2.5** for dose prescription.

5.2.2 Treatment Technology

Conventional RT (4-field box)

Conventional RT plans will consist of a 4-field box arrangement using AP/PA and Right/Left lateral fields. Conventional RT must use 4-18 MV photons. It is permissible i) to use bone landmarks to draw field borders as described below or ii) to use 3D planning with explicit targets as outlined in section **5.2.3**. Custom cerrobend blocks or MLCs are acceptable for field shaping.

If bone landmarks are used, use the following portals:

- Superior border: L4-L5 interspace, or higher to encompass known disease with at least a 3 cm margin
- Lateral border: 1-2 cm lateral to the border of the true pelvis
- Inferior border: Obturator foramen or 3 cm inferior to the lowest extent of disease, whichever is lower
- Anterior border: line from pubic symphysis to 1.5 cm anterior to common iliac nodes at L4-5. At least 0.5 cm anterior of the L4-L5

vertebral bodies should be included in the field in order to adequately encompass the low para-aortic region.
- Posterior border: draw border 1.0 cm posterior to the sacrum from S1-S4
- Custom blocking to shield femoral heads. Do not block the obturator foramen or within 1 cm of the common iliac nodes

Opposed lateral pelvic fields are used using the same isocenter as the anterior and posterior pelvic fields. The superior and inferior borders will be the same as for the anterior and posterior fields.

The inferior extent or vaginal extension of disease should be marked so that the inferior border of disease can be documented. Uninvolved normal tissues may be blocked although the position of the uterus should be contoured to ensure adequate coverage.

If clips are present from the lymph node dissection to document the position of the lymph nodes, then these should be used as a guide when anterior blocks are designed to shield small bowel. When shielding bowel, at least 3 cm should not be blocked anterior to the L4 and L5 vertebral bodies in order to adequately encompass the low para-aortic region.

IMRT

IMRT plans may include static field arrangements (e.g. 5-9 fields), modulated arc therapy, or Tomotherapy. Pseudo-step-wedge intensity modulation (PSWIM) and volumetric modulated arc therapy (VMAT) techniques are permitted. IMRT should use 6-15 MV photons.

Parametrial Boost

After conventional RT or IMRT delivery, a parametrial boost can be delivered at the treating physician's discretion. The parametrial boost will use an AP/PA field arrangement. The superior border should be reduced to include only the true pelvis and the upper border of the true pelvis is defined as 1 cm above the inferior aspect of the sacroiliac joint. The inferior border remains the same as in the pelvis fields. A parametrial central field block is a minimum of 4 cm wide.

Brachytherapy (05/30/2017)

Either HDR or LDR brachytherapy is permitted according to each institution's standard. Either standard (point-directed) or volume-directed brachytherapy techniques are permitted according to each institution's standard. Tandem and ring or tandem and ovoids will be used for intact cervix brachytherapy. Interstitial brachytherapy such as with a Vienna applicator is allowed if it is felt to be clinically imperative to change the plan after treatment start because of poor response of the tumor to external beam therapy. A tandem and cylinder or tandem alone is allowed for patients where tandem and ring or ovoid application is not possible due to extent of disease or poor anatomy (e.g., obliterated fornices). Use of IMRT or other external beam techniques in place of brachytherapy to boost

gross cervical disease is expressly discouraged. If deemed necessary or essential for the patient's care (e.g., if a patient refuses brachytherapy), reasons for not performing brachytherapy should be documented and the study PI should be notified.

5.2.3 Immobilization and Simulation

Conventional RT (4-field box)

CT simulation is required. Field outlines should be drawn electronically on Digitally Reconstructed Radiographs (DRRs) produced from the CT simulation information. Localization or block-check-images of simulated fields are to be obtained in a simulator and/or treatment machine. Digital pictures of all treatment portals with the patient in the treatment position are to be submitted for quality assurance review. All treatment fields, whether formed by cerrobend blocks or multi-leaf collimation, should be independently checked against the corresponding DRRs. Prone positioning with bowel exclusion devices (e.g. belly boards) is allowed.

3D planning is at the physician's discretion. If 3D planning is being done, a CT simulation scan is required with a slice thickness ≤ 3.0 mm for the regions extending at least 4cm above and below target volumes. Patients can be simulated supine or prone. All subjects will have a customized immobilization device (e.g., Alpha Cradle or Vac-Loc) fabricated at the time of simulation. A full bladder is required at the time of simulation and treatment. Intravenous contrast is recommended to visualize vessels better. Oral or rectal contrast is not recommended for treatment planning.

IMRT

All subjects will undergo a CT (or PET/CT) simulation scan in the supine position using a slice thickness ≤ 3.0 mm and large field-of-view pelvic protocol. A customized immobilization device fabricated at the time of simulation is required. It is recommended that CT scans be obtained from the T12 vertebral body to 5 cm below the ischial tuberosities. For patients undergoing CBCT with each fraction, it is recommended that the isocenter be placed along the patient's midline 1.5 cm caudal to the inferior border of the sacroiliac joint. Otherwise, isocenter placement is left to the discretion of the treating physician. It is recommended to use a consistent bladder filling state (e.g. always full or always empty) for simulation and treatment. It is recommended for patients not to be simulated or treated with a full rectum as this may result in poor setup reproducibility. Bowel preparatory agents (enema, stool softeners, etc.) may be applied at the discretion of the physician. If an internal target volume (ITV) will be used (see section **5.2.**4), it is recommended that the patient undergo both a full and empty bladder CT simulation. Intravenous contrast is recommended unless medically contraindicated. Oral contrast is optional. Radio-opaque cervical markers or implanted fiducials are optional.

Brachytherapy

For 3D brachytherapy planning, all subjects will undergo a CT simulation scan using a slice thickness ≤ 3.0 mm with brachytherapy applicators and dummy sources in. It is recommended that CT scans contain the entire brachytherapy applicators and the critical structures such as bladder and rectum. Maintaining applicator position is required from the time of applicator insertion to simulation and treatment. Before a CT scan, a Foley catheter is inserted into the bladder and the balloon should be filled with radio-opaque fluid to define the bladder reference point in treatment planning.

For volume-directed brachytherapy, pelvic MRI (≤ 3 mm slice thickness) is recommended with either the first or second insertion. An MRI-compatible applicator is strongly recommended to perform volume-directed brachytherapy. Subsequent insertions may use CT or MRI for planning.

5.2.4 Definition of Target Volumes and Margins

All structures must be named for digital RT data submission as listed in the tables below. Capital letters, spacing and use of underscores must be applied exactly as indicated. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed.
The structures marked as "Required" in the table must be contoured and submitted with the treatment plan.

Conventional RT (4-field box)

For a 4-field box treatment without 3D planning, contouring target volumes is not required. For 3D plans, target volumes and margins will be the same as for IMRT described below. The only difference between 3D plans and IMRT contours is that patients treated with 3D planning will not have an ITV option.

IMRT

Pelvic MRI and/or PET fusion with the CT simulation scan is recommended to aid target delineation. Fusion should be optimized to match the MRI/PET scans to the treatment position. The Gross Tumor Volume (GTV), Clinical Target Volume (CTV) and Planning Target Volume (PTV) will be contoured on all CT slices in which the structures exist. The definition of all volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy and with the 1999 ICRU Report #62: Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report #50).

It is strongly recommended that, prior to IMRT planning, investigators read guidelines for contouring target volumes for both postoperative and intact cervical cancer (14, 15).

Standard Name	Description	Detailed Specification
GTV_4500	GTV to receive 45 Gy **Required**	The GTV is defined as all known gross disease determined from radiographic studies, clinical information, physical

		examination, endoscopic examination, and biopsy results.
CTV_4500	CTV to receive 45 Gy **Required**	It is recommended to divide the CTV into 3 sub regions: CTV1, CTV2, CTV3. CTV1 will consist of the gross tumor, cervix, and uterus. For vaginal primary cancers, CTV1 will consist of the gross tumor and cervix only. CTV2 will consist of the parametria and superior third of the vagina (or half of the vagina, if the vagina is clinically involved). For vaginal primary cancers, CTV2 will consist of the entire vaginal length, paravaginal tissue, and parametria. CTV3 will include the common, external, and internal iliac and presacral lymph nodes. It is acceptable for CTV1, CTV2, and/or CTV3 to overlap each other. The upper border of the CTV3 should not extend above the confluence of the common iliac arteries with the aorta (i.e., aortic bifurcation), and should begin no lower than superior border of L5. The nodal CTV (CTV3) will be obtained by ensuring an approximately 7 mm margin around the vessels, plus extension to include any adjacent visible lymph nodes, lymphoceles, or pertinent surgical clips. The presacral nodes should be contoured until the superior border of the S3 vertebral body is reached; below this point the nodal volume can be separated into two structures. The external iliac nodes should be contoured to the superior aspect of the femoral head. CTV3 should be modified to exclude bone, muscle, and bowel. Patients with vaginal primary cancers or involvement of the distal third of the vagina by cervical cancer should receive inguinal nodal radiotherapy as well. The CTV should not extend inferior to the ischial tuberosities.
CTV_4760 (for SIB schemes only)	CTV to receive 47.6 Gy **Required**	Same as description of CTV_4500 above
CTV_Boost (for SIB schemes only)	CTV to receive 54.0-59.4 Gy **Required**	Gross pelvic lymph nodes
ITV_4500	ITV to receive 45 Gy **Contouring is required only when ITV approach is used.**	Patients should be simulated with both a full and empty bladder (i.e., 2 simulation scans). CTV1-CTV3 and PTV1-PTV3 should be delineated as described above on the plan

		used for treatment (either the full or empty bladder scan), and CTV1 should be delineated on both scans. The CTV1 from both scans should be fused together to generate the ITV_4500. A 7 mm margin should be applied to generate PTV4.
PTV_4500	PTV to receive 45 Gy **Required**	Around GTV and CTV1, a 15 mm uniform expansion should be used. Around CTV2, a 10 mm uniform expansion should be used. For vaginal primary cancers, the distal and radial expansion on CTV2 can be as low as 5mm. Around CTV3 (and CTV_boost, if applicable), a 5 mm uniform expansion should be used. These expansions will generate PTV1, PTV2, and PTV3, respectively. PTV1-3 will be fused to generate the PTV. If the ITV approach is used, PTV4 should be fused with PTV1-PTV3 to generate PTV_4500.
PTV_4500_m03	PTV - 3 mm from skin surface **Required when applicable**	The PTV should be manually or automatically trimmed up to 3 mm from the skin surface, if necessary, to spare skin. However, the CTV still needs to be included entirely within the PTV.
PTV_4760 (for SIB schemes only)	PTV to receive 47.6 Gy **Required**	Same as description of PTV_4500 above
PTV_4760_m03 (for SIB schemes only)	PTV - 3 mm from skin surface **Required when applicable**	The PTV should be manually or automatically trimmed up to 3 mm from the skin surface, if necessary, to spare skin.. However, the CTV still needs to be included entirely within the PTV.
PTV_Boost (for SIB schemes only)	PTV to receive 54.0-59.4 Gy **Required**	5 mm uniform expansion around CTV_Boost
PTV_Boost_m03 (for SIB schemes only)	PTV - 3 mm from skin surface **Required when applicable**	The PTV should be manually or automatically trimmed up to 3 mm from the skin surface, if necessary, to spare skin. However, the CTV still needs to be included entirely within the PTV.

Brachytherapy (Point-directed)
The definition of all points (A, B, Bladder, Rectum and Vaginal Surface) will be in accordance with the 1985 ICRU Report #38: Dose and Volume Specifications for Reporting Intracavitary Therapy in Gynecology.

Brachytherapy (Volume-directed)
Volume directed brachytherapy can be used with either CT based planning (without the aid of an MRI for any fraction), or MRI guidance. The MRI based

target delineation can be reused by superimposition in the process of contouring on CT, if for subsequent fractions of brachytherapy only CT can be used with the applicator in place. No planning margins will be added to the CTV.

Standard Name	Description	Detailed Specification
GTV	GTV to receive 27.5 - 30 Gy **Required**	Macroscopic tumor (if present) at time of brachytherapy
CTV	CTV to receive 27.5 - 30 Gy **Required**	GTV + whole cervix + presumed extra cervical tumor extension

5.2.5 Definition of Critical Structures and Margins

Note: All structures must be named for digital RT data submission as listed in the tables below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Conventional RT (4-field box)

For a 4-field box treatment without 3D planning, contouring critical structures is not required. For 3D plans, critical structures and margins will be the same as for IMRT described below.

IMRT

Standard Name	Description	Detailed Specification
External	External patient contour encompassing all patient anatomy with a single contour on each slice **Required**	Normal tissues will be contoured on the CT simulation scan. The tissue within the skin surface and outside all other critical normal structures and the PTV should be contoured on every slice and designated as "External".
NonPTV4500	All tissue excluding the PTV_4500. Generated by subtracting the PTV receiving a dose 45 Gy from External Contour **Required**	"NonPTV4500" is defined as all tissue excluding the PTV_4500, and is generated by subtracting the PTV from "External".
Bowel Space	The space that the bowel may occupy **Required**	Bowel Space will be contoured beginning from the axial slice situated 1 cm superior to the superior-most slice containing PTV (if bowel is not present at this level, the bowel

		contour will start from its most superior extent), and will continue to its most inferior extent in the pelvis. The distal descending colon and sigmoid colon should be excluded from the Bowel Space. The Bowel Space will include the outermost extent of the bowel loops plus any space within the abdominal cavity the bowel may occupy. Individual loops of bowel should not be contoured separately. Bowel Space will be outlined on each axial CT slice. Rectum should be contoured separately from bowel.
Rectum	Rectum **Required**	The outer rectal wall will be contoured and filled in, treating the organ as a solid continuous structure, and will be defined from the level of the sigmoid flexure to the anus.
Bladder	Bladder **Required**	The outer bladder wall will be contoured and filled in, treating the organ as a solid continuous structure.
Bone Marrow	Bone Marrow **Required**	The outer bone contour will be delineated and filled in, treating the bone marrow as a solid continuous structure. The regions contoured will include the os coxae, L4 and L5 vertebral bodies, entire sacrum, acetabulae, and proximal femora. The caudal-most extent of the bone marrow contour should be at the level of the ischial tuberosities.
BoneMarrow_Act	Active Bone Marrow **Required**	Active or functional BM will be a subset of the entire BM volume (delineated in Bone Marrow), as determined by ^{18}F-FDG-PET/CT. Active BM will be defined as the sub region of total BM with a standardized uptake value (SUV) greater than the mean value over the total BM volume. Automatic segmentation using commercially available software will be used to define the functional BM volume, which will be used as an avoidance structure for IMRT planning. For Phase II patients, the active bone marrow structure can be created by the treating site using a provided workflow. For Phase III patients, the active bone marrow structure will be generated at UCSD and provided to sites by IROC.
Femur_L	Left femur **Required**	The outer contours of the left femoral head will be delineated and filled in, treating each as a solid continuous structure. Do not include the femoral neck.

Femur_R	Right femur **Required**	The outer contours of the right femoral head will be delineated and filled in, treating each as a solid continuous structure. Do not include the femoral neck.

Brachytherapy

Standard Name	**Description**	**Detailed Specification**
Bladder (ICRU reference point)	Bladder **Required**	The outer bladder wall is contoured. Calculated at the center (in the superior-inferior plane on AP view) of a contrast-filled balloon of a Foley catheter and closest to the applicator system on a lateral view, as defined by ICRU 38.
Rectum (ICRU reference point)	Rectum **Required**	The outer rectal wall is contoured from above the anal sphincter to the level of transition into the sigmoid. In accordance with ICRU 38, mark the point 0.5 cm posterior to the vaginal surface (as demarcated by the opaque packing) at the midpoint of the applicator system or at the level of the flange if no ovoids are used.
Vaginal_Surf* (reference point)	**Optional**	Mark the points at surface of ovoids at mid-source position.
Sigmoid**	**Optional**	The outer sigmoid wall is to be contoured from the recto-sigmoid flexure to 2 cm superior to the parametria and the uterus.
Bowel Space	**Required**	The space that the bowel may occupy.

*Point-directed brachytherapy
**Volume-directed brachytherapy

5.2.6 Dose Prescription

Conventional RT

For Conventional RT, the prescription dose of 45 Gy at 1.8 Gy/fraction will be delivered to the isocenter which is defined as the intersection of the four beams. EBRT is preferably given once daily Monday-Friday, for 5 fractions per week. A three consecutive day parametrial boost may be optionally given in the sixth week.

IMRT

Target Standard Name	Dose (Gy)	Fraction Size (Gy)	# of Fractions	Dose Specification Technique
PTV_4500	45	1.8	25	Exactly 95% of PTV receives ≥ 45 Gy
PTV_4760 (for SIB schemes only)	47.6	1.7	28	Exactly 95% of PTV receives ≥ 47.6 Gy
PTV_boost (for SIB schemes only)	54.0-59.4	1.93-2.12	28	Exactly 95% of PTV receives ≥ 54.0-59.4 Gy

Parametrial Boost

After the delivery of 45 Gy, at the discretion of the treating physician, a parametrial boost of 5.4 Gy at 1.8 Gy/fraction may be delivered to mid-plane given by AP/PA fields and the center of the unblocked portion of the field.

Brachytherapy

In point-directed approach, the doses of 27.5 - 30 Gy and 35 - 40 Gy will be delivered to the point A for HDR and LDR, respectively as tabulated in Tables 1 and 2. The HDR brachytherapy dose can be prescribed to a high-risk clinical target volume (CTV) as volume-directed approach, but point A dose must be documented.

Table 1 HDR-Point A determined implant or volume directed approach

Total EBRT (Gy)	# HDR fractions	HDR Point A dose/fraction (Gy)	Total HDR point A dose (Gy)	Total Point A EQD2-Gy_{10}
45	4	7.0	28.0	83.9
45	5	5.5	27.5	79.8
45	5	6.0	30.0	84.3
47.6	4	7.0	28.0	86.1
47.6	5	5.5	27.5	81.9
47.6	5	6.0	30.0	86.4

Table 2 LDR-Point A determined implant

Total EBRT (Gy)	# LDR fractions	LDR Point A dose/fraction (Gy)	Total LDR point A dose (Gy)	Total Point A dose (Gy)
45	1	35-40	35-40	80-85
45	2	17.5-20	35-40	80-85
47.6	1	35-40	35-40	82.6-87.6
47.6	2	17.5-20	35-40	82.6-87.6

In general, HDR insertions should start during the fourth week and be separated by a minimum of 48 hours and no more than 2 insertions should be performed per week. Iridium-192 is the preferred source for HDR brachytherapy. In LDR point-directed brachytherapy, if 2 insertions are used they should be separated by a minimum of 7 days and maximum of 21 days. If 2 insertions are used, the second implant should be completed within three weeks of the completion of external beam irradiation. Cesium-137 is the preferred source for LDR brachytherapy. External beam radiation and brachytherapy may not be administered on the same

day. Radiation therapy must be completed within 60 days of its initiation. All brachytherapy sources must be listed on the joint AAPM/IROC Houston Registry of Brachytherapy Sources in order to be utilized on NCTN clinical trials (http://irochouston.mdanderson.org/RPC/BrachySeeds/Source_Registry.htm).

5.2.7 Compliance Criteria

Target Volume Constraints and Compliance Criteria
Conventional RT (4-field box)*

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable	Deviation Unacceptable
CTV_4500	D_{Min} (Gy)	≥ 41.85	≥ 40.5	< 40.5
	D_{Max} (Gy)	≤ 48.15	≤ 51.75	> 51.75

*These criteria are applied for 3D plans.
IMRT (05/30/2017)

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable	Deviation Unacceptable
PTV_4500	$D_{95\%}$ (Gy)	≥ 45	≥ 43.65	< 43.65
	$D_{97\%}$ (Gy)	≥ 43.65	≥ 40.5	< 40.5
	$D_{99\%}$ (Gy)	≥ 40.5	≥ 39.6	< 39.6
	D_{Max} (Gy)	≤ 51.75	≤ 54	> 54
CTV_4760	D_{Min} (Gy)	≥ 44.27	≥ 41.85	< 41.85
	D_{Max} (Gy)	≤ 63.56	≤ 68.31	> 68.31
PTV_4760	$D_{95\%}$ (Gy)	≥ 47.6	≥ 45	< 45
	$D_{97\%}$ (Gy)	≥ 46.17	≥ 41.85	< 41.85
	$D_{99\%}$ (Gy)	≥ 42.84	≥ 40.5	< 40.5
	D_{Max} (Gy)	≤ 68.31	-	> 68.31
CTV_Boost*	D_{Min} (Gy)	≥ 50.22	≥ 43.65	< 43.65
	D_{Max} (Gy)	≤ 63.56	≤ 68.31	> 68.31
PTV_Boost*	$D_{95\%}$ (Gy)	≥ 54	≥ 51.75	< 51.75
	$D_{97\%}$ (Gy)	≥ 52.38	≥ 47.6	< 47.6
	$D_{99\%}$ (Gy)	≥ 48.6	≥ 45	< 45
	D_{Max} (Gy)	≤ 68.31	-	> 68.31
Dose maximum should occur within the PTV.				

*Minimum dose is applied to a 54 Gy prescription and maximum dose to a 59.4 Gy prescription.

Parametrial Boost
No criteria are applied for parametrial boost.

Note: Dose to CTV is cumulative EQD2 (EBRT + Brachytherapy).

Normal Structure Constraints and Compliance Criteria

Conventional RT

No criteria for normal structure doses are applied for the Conventional RT.

IMRT

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable	Deviation Unacceptable
Bladder	$D_{50\%}$ (Gy)	≤ 45	≤ 55	> 55
	D_{Max} (Gy)	≤ 50	≤ 57.5	> 57.5
Rectum	$D_{50\%}$ (Gy)	≤ 45	≤ 54	> 54
	$D_{60\%}$ (Gy)	≤ 30	≤ 50	> 50
	D_{Max} (Gy)	≤ 50	≤ 55	> 55
Bowel	$D_{30\%}$ (Gy)	≤ 40	≤ 50	> 50
	D_{Max} (Gy)	≤ 59.4	≤ 62.1	> 62.1
	V_{45} (cc)	≤ 200 cc	≤ 250 cc	> 250 cc (or 110% of KBP prediction, if KBP prediction is > 250 cc)
Bone Marrow	D_{Mean} (Gy)	≤ 27	≤ 29	> 29 (or 105% of KBP prediction, if KBP prediction is > 29 Gy)
	V_{10} (%)	≤ 85.5%	≤ 90%	> 90% (or 105% of KBP prediction, if KBP prediction is > 90%)
	V_{20} (%)	≤ 66%	≤ 75%	> 75% (or 105% of KBP prediction, if KBP prediction is > 75%)
Bone Marrow Act	D_{Mean} (Gy)	≤ 28.5	≤ 30	> 30 (or 105% of KBP prediction, if KBP prediction is > 30 Gy)
	V_{10} (%)	≤ 90%	≤ 90%	> 90% (or 105% of KBP prediction, if KBP prediction is > 90%)
	V_{20} (%)	≤ 70%	≤ 75%	> 75% (or 105% of KBP prediction, if KBP prediction is > 75%)
Femurs	$D_{15\%}$ (Gy)	≤ 30	≤ 50	> 50
	D_{Max} (Gy)	≤ 50	≤ 55	> 55

EBRT+ Brachytherapy

Point-Directed Brachytherapy

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable	Deviation Unacceptable
Point A (point-directed)	D_{Min} (Gy)	80-90	> 90	< 80
Bladder	ICRU Point	≤ 90	≤ 95	> 95
Rectum	ICRU Point	≤ 75	≤ 80	> 80
Vaginal Surface	ICRU Point	≤ 150	≤ 200	> 200

Volume-Directed Brachytherapy

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable	Deviation Unacceptable
CTV (Volume-Directed)	$D_{90\%}$ (Gy)	80-90	> 90	< 80
Bladder	D_{2cc} (Gy)	≤ 90	≤ 95	> 95
Rectum	D_{2cc} (Gy	≤ 75	≤ 80	> 80
Sigmoid	D_{2cc} (Gy)	≤ 75	≤ 80	> 80
Vaginal Surface	D_{2cc} (Gy)	≤ 150	≤ 200	> 200

Note: Doses to critical structures are cumulative EQD2 (EBRT + Brachytherapy). If CT is used for planning it is recommended to keep the maximum bowel dose < 25% of the brachytherapy prescription dose.

For point-directed brachytherapy, the dose to points A and B, the rectal reference point dose, bladder reference point dose, and vaginal surface reference point dose, and central axis isodose curve must be calculated and reported. Please follow the definitions in ICRU 38.

For volume-directed brachytherapy, uniform dose volume reporting according to the GEC ESTRO guidelines is required (Kunos, 2012; Balter). For each fraction the following parameters should be recorded:
• TRAK
• D100 for GTV, CTV
• D90 for GTV, CTV
• D50 for CTV
• V100 for CTV
• D2cc of the bladder, rectum and sigmoid, (converted to EQD2 doses per formula EQD2= D X [(d + α/β)/ (2 + α/β)); use α /β=3.
• ICRU bladder and ICRU rectal points

Delivery Compliance Criteria

	Per Protocol	Variation Acceptable	Deviation Unacceptable
Overall Treatment time	≤ 60 days	≤ 66 days	> 66 days

5.2.8 Treatment Planning Priorities and Instructions

Critical Structures and target priorities are listed in order of decreasing importance:

EBRT

1. Bowel
2. Bone Marrow
3. Rectum
4. Bladder
5. Femurs

If max dose constraints are exceeded, the following solution can be entertained:
For conventional RT with 3D planning, use the field in field technique to decrease hot spots and to reduce the bowel dose when MLCs are used.

Brachytherapy

1. Rectum
2. Bladder
3. Sigmoid

If dose constraints of critical structures are exceeded, the following solution can be entertained:
For volume-directed brachytherapy, if the treatment planning system provides a manual optimization option, optimize the plan manually to reduce dose to the critical structures as long as D90 of CTV meets target volume constraints.

5.2.9 Dose Calculations

The primary data set for dose calculations is CT. In the case in which contrast is present during the treatment planning CT, the density of the contrast should be overridden to a representative background electron density. Heterogeneity corrections should be applied. The dose grid size should be ≤ 3 mm in all directions, which means that the CT slice thickness should be ≤ 3 mm.

5.2.10 Patient Specific QA

For IMRT plans, patient specific QA is required (Section 5.7). QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber array or other 2D/3D device. Measured dose distribution will be compared to planned dose distribution using a Gamma criterion of 3% dose difference and 3 mm distance to agreement. The pass rate should be at least 90% measured for the entire plan.

5.2.11 Daily Treatment Localization/IGRT

Conventional RT (4-field box)

Skeletal imaging using an electronic portal imaging device (EPID) or film portal imaging should be performed at least weekly to verify setup accuracy. Image-guided radiotherapy (IGRT)) technique such as orthogonal kV or volumetric imaging such as Cone Beam CT (CBCT) can also be used for weekly setup verification. However, these systems do not directly verify patient position, and recommendations of the AAPM for periodically checking correspondence of the imaging and treatment reference points must be followed.

IMRT
Daily IGRT is required for this protocol when the IMRT treatment technique is used. Any form of online imaging is acceptable, such as MV or kV planar imaging, MVCT or MV CBCT, kV CBCT, CT on rails, etc. The AAPM recommendations stated above for verifying coincidence of the imaging and treatment beam reference points must be adhered to for daily use of IGRT. At the time of simulation, it is recommended to place the isocenter along the patient's midline 1.5 cm caudal to the inferior border of the sacroiliac joint. In general, the CT or CBCT will be used for setup verification using bone landmarks only and not for soft tissue alignment. Small soft tissue shifts (≥3 mm) are acceptable. Otherwise, the treating physician may elect to postpone treatment or re-simulate.

5.2.12 Re-planning
Re-planning (such as to account for changes in tumor volume) is allowed. If re-planning is necessary, the new treatment plan should meet the same criteria as the initial plan, as if the new plan were delivered for the entire treatment course. The new treatment plan should be submitted for central review according to the same process as the initial plan.

5.3 Expected Toxicity from Radiation Therapy
Nausea and emesis may occur after extended field irradiation, especially after the first few treatments. It is recommended but not required that patients be pre-medicated with a serotonin antagonist before each daily treatment. Intractable nausea and emesis beyond the first few days should arouse suspicion of recurrent tumor or other causes of bowel obstruction, as it is rarely seen as a result of radiation alone. Consider stool sample for *Clostridia difficile* toxin. Increased bowel activity with diarrhea can be expected fairly routinely after the first two weeks of pelvic and para-aortic radiation. It is recommended that instructions be given to patients for a low fiber, low-fat, soft diet. Most patients will require anti-diarrheal medications during therapy. Should gastrointestinal toxicity become severe enough to require hospitalization or outpatient intravenous fluid replacement, all treatment should be discontinued temporarily until the patient's condition improves. If radiation therapy is discontinued, the treating physician must notify the principal investigator within 96 hours. The expected adverse effects and the guidelines for treatment modifications are described in Section 6.3.

5.4 Duration of Protocol Treatment
In the absence of treatment delays due to adverse events, study treatment may continue uninterrupted until the completion of therapy or until one of the following criteria applies:

- Intercurrent disease progression;
- Intercurrent illness that prevents further administration of treatment;
- Unacceptable adverse event(s);
- Patient decides to withdraw from the study; or

- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the treating physician.

5.5 Duration of Protocol Follow-Up

Patients will be followed for toxicity assessments at the 1-month and 3-months follow-up visit (± 7 days) after completion of radio-chemotherapy or until death, whichever occurs first. Patients are considered "on-study" regarding the tertiary endpoint of ^{18}F-FDG PET/CT metabolic complete response until the 3-month follow-up visit (± 7 days). Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event(s). To assess the primary overall survival endpoint, long-term follow-up will consist of 3-month follow-up contacts for years 1 and 2, then every 6 months in years 3, 4, and 5. Patients will be followed for overall survival after documentation of disease progression.

5.6 General Concomitant Medication and Supportive Care Guidelines

Patients should receive full supportive care, including transfusions of blood and blood products, supplemental iron, antibiotics, anti-emetics, etc., when appropriate at the discretion of the treating physician. Because it has been observed that hemoglobin levels below 10-12 g/dL during radiotherapy are associated with decreased local control, blood transfusions should be offered to and used to treat patients at the discretion of treating physicians prior to or during radiotherapy. There should be no radiotherapy treatment delays due to a low hemoglobin levels. Trials evaluating epoeitin alpha (Procrit, Epogen) and radio-chemotherapy in cervical cancer have indicated that epoeitin alpha may be associated with an increased risk for thromboembolism, and thus, may not be used in this study.

In particular, patients should be told to be aware of their typical defecation pattern. At the first sign that their stools become softer than usual or they have any increase in stool frequency over what is normal for them, they should begin taking over-the-counter loperamide as directed by their physician(s). Patient should understand that if they do not start taking loperamide at the start of diarrhea, the diarrhea may become severe and last several days. Persistent diarrhea or any evidence of hematochezia should prompt a stool evaluation for fecal leukocytes and/or *Clostridium difficile* toxin & ova/parasite evaluation. Diphenoxylate/ atropine prescriptions are permitted. Loperamide will be recommended during the study in order to prevent diarrhea that may ultimately lead to intravenous infusion of fluids or hospitalizations.

For the administration of loperamide, it is recommended that patients take two (2) caplets (4 mg) at the first sign of diarrhea. Patients should continue taking one (1) caplet (2 mg) every two hours until they return to their normal pattern of bowel movements. They may repeat same doses and frequency if diarrhea returns. During the night, patients may take two (2) caplets every four hours

rather than one (1) every two hours. Patients should call their doctor if they have any questions about taking loperamide, if they believe they are not achieving adequate control of diarrhea, or if they are feeling extremely weak, lightheaded, or dizzy (symptoms of dehydration). Side effects of loperamide include tiredness, drowsiness, or dizziness. If they experience these side effects, they should avoid driving a motorized vehicle or operating machinery. Before using any laxative, patients should consult their physician. Patients should make an extra effort to drink lots of fluids (several glasses of water, fruit juices, soda, soup, etc.) every day while they participate in this study.

Because there is a potential for interaction of triapine with other administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The principal investigator should be alerted if the patient is taking any agent known to affect, or with the potential to affect, selected P450 isoenzymes.

5.7 Centralized Quality Assurance and Knowledge-Based Planning Analysis

Sites planning to treat with IG-IMRT on this trial will initially undergo standard IMRT credentialing on either a pelvic or head/neck phantom. Once sites are credentialed for IG-IMRT they must commit to treating all patients they enroll on the protocol with this technique. All IG-IMRT cases will undergo a Pre-Treatment Review process to validate the contouring of target and critical normal tissues and approve the treatment plan. Anonymized DICOM data for the simulation CT and baseline FDG-PET/CT will be transmitted electronically via TRIAD to IROC-Philadelphia for central review and processing. The active bone marrow structure will be created using a commercial planning system and transmitted back to the enrolling site's treatment planning team as an avoidance structure. For Phase II patients, the active bone marrow structure can be created by the treating site using a provided workflow. For Phase III patients, the active bone marrow structure will be generated at UCSD and provided to sites by IROC. The reference IG-IMRT plan will then be transmitted centrally and IROC-Philadelphia will run the KBP algorithm on the resulting plans to measure potential planning improvements. Feedback from the KBP model will be provided to the enrolling site's treatment planning team. We will assess the following metrics: bowel V45, total and functional bone marrow V10 and V20 (See section 8.3 for specific requirements).

5.8 Pelvic nodal boost for 3D Radiotherapy

A pelvic nodal boost is allowed for patients receiving 3D radiotherapy, at the discretion of the treating radiation oncologist. Nodal involvement is defined as any pelvic or common iliac nodes if they are either PET positive or their short axis diameter is > 15mm on CT and/or MRI or if nodes are found to be histologically positive on surgical sampling. Dose to the nodal boost volume should not exceed 10 Gy, with a total dose to the sidewall not to exceed 65 Gy at midplane. Fractions of 1.8-2 Gy can be used. If nodal involvement is documented,

fields with up to 2.0 cm margin around the gross nodal disease as seen on the CT scan, MRI or PET is recommended. Nodal boost fields can be delivered via conformal fields. The nodal boost can occur after completion of EBRT and in between the brachytherapy insertions.

6.0 TREATMENT MODIFICATIONS/MANAGEMENT (05/30/2017)

Treatment modifications will consist of either cycle delay and/or dose reduction as noted below. Hematologic treatment decisions will be based on the absolute neutrophil count (ANC) on day of treatment or no greater than 72 hours prior to planned treatment. No cisplatin will be administered unless pre-treatment counts demonstrate an ANC ≥ 1,500/ μL and platelet count is ≥ 75,000 / μL. Chemotherapy will be held until these values are exceeded. External radiation should continue while chemotherapy us being held. Please refer below to specific toxicities and dose modifications.

Chemotherapeutic	Starting Dose Level	25% Reduction Dose Level
Cisplatin	40 mg/m^2	30 mg/m^2

6.1 Triapine (3-AP) Dose Modifications **(05/30/2017)**

Patients may receive dexamethasone 4 mg IV prior to each triapine infusion. Patients may pre-medicate with antiemetic as needed for nausea or vomiting with any previous dose of triapine. Acute reactions to triapine, occurring either during the infusion or soon after the infusion is completed, have been observed primarily at doses ≥ 140 mg/m^2 infused IV over 2-4 hours, which dose is not given in this protocol. At lower doses, the incidence of symptomatic reactions is estimated to be < 10%. The reactions include hypoxia (with or without dyspnea and with or without associated cough) and hypotension. The cause of hypoxia and dyspnea is thought to be an increase in methemoglobin levels, which usually resolves quickly (within hours) after the completion of the infusion. Isolated hypoxia without symptoms (usually noticed only as cyanosis) may be managed with supplemental oxygen at 2-4 liters/minute by nasal cannula. Chemotherapy will not be administered during a radiation therapy delay.

While acute infusion reactions are not anticipated, the reactions include hypoxia (with or without dyspnea and with or without associated cough) and hypotension (See Table 1 in section 6.1.2 below).

- Patients developing dyspnea at rest should undergo pulse oximetry throughout the rest of the triapine infusion. Isolated hypoxia (<92%) may be managed with supplemental oxygen, 2 liters/minute by nasal cannula. If pulse oxygen saturation does not return to > 92% with oxygen supplementation, triapine should be stopped and the patient should not receive additional triapine treatment on study.
- Patients developing dyspnea at rest or hypotension (systolic blood pressure <85 mm Hg) should have the triapine administration stopped and should not receive additional triapine treatment on study.
- EKG changes consisting of ST-T wave changes and mild prolongation of the QT interval have been observed immediately post-treatment with

triapine, and are not an indication to stop treatment unless associated with hypoxia or hypotension during triapine infusion. Patients remaining on study following these changes should be undergo repeat EKG testing if they develop hypoxia or hypotension.

Should any patient enrolled on the study miss a scheduled triapine dose for whatever reason (e.g., as a result of facility closure due to a holiday), the patient will be allowed to take the scheduled dose up to a maximum of 24 hours after that scheduled dose time (preferably not on a day of cisplatin infusion). If greater than 24 hours after the scheduled dose time, the missed dose may be scheduled as a 'make-up' dose during any day of radiation in the optional sixth week of radiation.

6.1.1 Schedule for Research Monitoring of Triapine Infusion, Day 1 (*optional for study participants*) (05/30/2017)

Methemoglobinemia is a known side effect of triapine administration (21). This clinical trial includes an *optional* set of peripheral venous blood samples to be collected (2 ml [<1 teaspoon]) in heparinized arterial blood gas syringes and put on ice for methemoglobin determination per institutional guideline (e.g., blood bank guidelines) as a possible surrogate biomarker for therapeutic effect of triapine. Sampling will occur on day 1 of the first cycle, before triapine dosing (t=0-) and 1, 3, 5 and 24 hours after triapine administration. Methemoglobin will be reported as a percentage of total hemoglobin as before (2). Pulse and respiratory rate monitoring is recommended. It is recommended that the methemoglobinemia antidotes, methylene blue or ascorbic acid, be available during the time of triapine infusion (21). If the hour 5 methemoglobinemia level results at greater than 6%, the subsequent hourly methemoglobin assays should be obtained and resulted until a decline in methemoglobin percentage is documented AND the methemoglobin percentage is < or = 6%.

Frequency	
Prior to infusion	After infusion
Once predose (t = 0-)	1, 3, 5, and 24 hours

6.1.2 Schedule for Clinical Monitoring of Triapine Infusion, other than Day 1

If the patient is symptomatic or has hypoxia (< 92%) requiring oxygen, obtain a "spot" methemoglobin level and repeat the level prior to next triapine dose to determine whether dose modification or further treatment is indicated. Supportive care should be provided as clinically indicated (See Table 1).

If no changes in O2 saturation are seen during triapine treatments, on subsequent days the patient may be discharged after radiation per the treatment schedule. If patients had prolonged methemoglobinemia or hypoxia requiring dose adjustment on day 1, please follow the monitoring schema (see Table 1) until stable.

Table 1 – Clinical Management of hypoxia or prolonged methemoglobinemia **(05/30/2017)**

Prolonged Methemoglobinemia / Hypoxia Monitoring	
Pulse, respiratory rate, O2 saturation (pulse oximeter)	All patients
EKG	Only if patient is hypotensive or hypoxic

Please note that it is the trend in the O2 saturation that is of importance. Since pulse oximetry is known to be unreliable in the presence of significant methemoglobinemia, clinical importance should not be given to a single pulse oximetry value alone. In any case where there is significant doubt, arterial blood gases to assess O2 saturation should be obtained.

6.1.3 Treatment modifications for triapine methemoglobinemia in clinical trial protocols:

It is expected that all patients will show a transient rise in methemoglobin (up to 3-5%, maximum 15%) while on study, but unless accompanied by hypoxia, by clinical symptoms (e.g., dyspnea, tachypnea), or by failure of methemoglobin levels to drop to <5% within 24 hours, NO changes to treatment or dose are required. For patients not fitting any of these patterns, the following guidelines should be followed:

If methemoglobinemia is asymptomatic, methemoglobin levels are <15%, and unaccompanied by hypoxia, treat without change in triapine dose.

If oxygen saturation is <92%, or methemoglobin levels are >15%, or patient has moderate to severe symptoms, then monitor the patient hourly and provide appropriate supportive care. Discharge the patient when symptoms are tolerable and O2 saturation normalizes (>92%). At the next triapine infusion, reduce the triapine dose to 20 mg/m^2 and each subsequent treatment(s).

If a patient had moderate to severe, but rapidly reversible (i.e., over several hours) symptoms NOT requiring hospitalization, then reduce the triapine dose to 20 mg/m^2 for subsequent treatment(s). If methemoglobinemia (>15%) does not promptly recover (e.g., within a few hours) or symptoms do not rapidly reverse at the 20 mg/m^2 dose level, then stop subsequent triapine treatment(s) and pursue further appropriate clinical evaluations.

Treatment options for methemoglobinemia could include methylene blue, 1-2 mg/kg IV over five minutes. However, methylene blue is contraindicated in patients with glucose-6-phosphate deficiency, since its pharmacologic action as an electron carrier in the reduction of methemoglobin is itself dependent on the

generation of NADPH by G6PD through the hexose monophosphate shunt. Thus, methylene blue may be at best ineffective in such patients and may have the potential to complicate the clinical situation by provoking hemolysis, although this association is less clear. In situations where the use of methylene blue may be contraindicated (e.g., in those individuals who are in the high-risk group (patients of African, Asian or Mediterranean origin/ancestry), who may have had a false negative G6PD deficiency test), the successful use of ascorbic acid (1000 mg IV q6h) has been described.

6.1.4 Grade 3/4 toxicities thought to be attributed to triapine alone have been uncommon in previous trials. Please contact the study principal investigator if you believe the patient has a grade 3 or 4 toxicity related to triapine alone. The study principal investigator will refer to the CAEPR (section 7.3) as well as the patients other toxicities in an attempt to determine if the reported toxicity is related to triapine. If thought to be related to triapine, the investigator will hold the next dose and reevaluate the patient prior to the following scheduled dose of triapine. Patients that have had resolution of their toxicity to grade 1 or 2 should receive the next dose of triapine. **(05/30/2017)**

6.2 Cisplatin Dose Modifications **(05/30/2017)**
Cisplatin dose modifications will be made according to observed symptoms. Chemotherapy will not be administered during a radiation therapy delay.

6.2.1 Gastrointestinal Adverse Effects: (e.g., nausea and vomiting)
Prophylactic antiemetics should be used as described above in section 5.1.1. Please follow local institutional standards for patients that develop nausea and vomiting in spite of the use of prophylactic measures. For persistent grade 4 nausea and vomiting despite optimal medical management, hold cisplatin until reduced to grade 1 and reduce cisplatin by 25%. For patients with recurrence of this following dose reduction, cisplatin must be discontinued. **(05/30/2017)**

6.2.2 Renal Adverse Effects: If creatinine rises to greater than 2.0 mg/dL, discontinue cisplatin therapy. Selective renal tubular defects are sometimes observed. Documented hypomagnesemia will be treated with increased magnesium supplementation per institutional protocol. Hypocalcemia and hypokalemia are common and potentially severe. Replacement of potassium and calcium are usually effective per institutional protocol. Severe tubular effects may require chronic replacement therapy. Diagnostic tests for other etiology of hypocalcemia (GI or metabolic) should be considered per institutional protocol.

6.2.3 Neurotoxicity Adverse Effects: For grade 2, reduce cisplatin dose by 25%. For grade 3-4, discontinue cisplatin therapy.

6.2.4 Tinnitus or hearing changes: For grade 2 hold cisplatin until neuropathy resolves to grade 1 and dose reduce by 25%. Discontinue cisplatin

if tinnitus or hearing changes do not resolve within 21 days. Discontinue cisplatin for grade 3 or 4 toxicity. **(05/30/2017)**

6.2.5 Hematologic Adverse Effects: Cisplatin should be withheld from patients with an absolute neutrophil count less than 1500 / mm^3 or platelet count less than 75,000 / mm^3. Cisplatin infusions should be delayed week-by-week until these levels are exceeded. Please refer to the table below for specific hematologic toxicities and recommended modifications. **(05/30/2017)**

HEMATOLOGIC TOXICITY	**PARAMETER**	**DOSE MODIFICATION**
Anemia	Not applicable for this protocol	No dose modifications for anemia. Please refer to section 5.6 for additional details.
Febrile Neutropenia or ANC	First occurrence of febrile neutropenia (grade 3 or 4) - OR – ANC < 500 / µL lasting greater than 7 days	Hold cisplatin x 1 week and repeat CBC. If ANC has resolved to grade1 (>1500 / µL), then dose reduce by 25% and treat. If ANC has not resolved to grade 1 then discontinue cisplatin.
Febrile Neutropenia or ANC	Second occurrence	Discontinue cisplatin.
ANC alone	Uncomplicated ANC < 500 / µL lasting greater than 7 days without infection or fever	Dose reduction not indicated, but hold therapy until ANC resolves to grade 1
Platelets without bleeding	Grade 3 uncomplicated	Hold until platelets > 75,000 /µL and resume at current dose level without modification
Platelets with bleeding	First occurrence grade 4 thrombocytopenia –OR – grade 3 thrombocytopenia with bleeding	Hold cisplatin x 1 week and repeat CBC. If platelet count has resolved to > 75,000 / µL, then dose reduce by 25% and treat. If thrombocytopenia has not resolved to grade 1, then discontinue cisplatin
Platelets with bleeding		Discontinue cisplatin

6.2.6 Other non-hematologic toxicity: For any other non-specific grade 3 or 4 toxicity, other than fatigue, hold cisplatin until toxicity resolves to grade 1 and then resume at same dose. If toxicity does not resolve to grade 1 within 21 days, discontinue cisplatin. **(05/30/2017)**

6.2.7 External-beam pelvic radiation and triapine infusions should continue while any or all courses of cisplatin are withheld. For delays in cisplatin infusion greater than two weeks, cisplatin may not be continued at the joint discretion of the patient's treating physicians and the principal investigator (face sheet).

6.3 Radiation Dose Delivery Modifications

6.3.1 Radiation therapy may only be suspended secondary to a significant adverse event at the joint discretion of the patient's treating physicians and the study chair (face sheet). The study chair must be notified in writing (e.g., email) of dose modifications or treatment modality modifications for external beam radiation therapy or for brachytherapy.

6.3.2 Because it has been observed that hemoglobin levels below 10-12 g/dL during radiation therapy are associated with decreased local control, blood transfusions should be offered to patients and used to treat patients at the discretion of treating physicians prior to or during radiotherapy per institutional protocol. There should be no radiation therapy treatment delays due to a low hemoglobin levels. Published results evaluating epoeitin alpha (Procrit, Epogen) and radiochemotherapy in cervical cancer have indicated that epoeitin alpha may be associated with an increased risk for thromboembolism, and therefore, may NOT be used in this study.

6.3.3 Hematologic Adverse Events: Hematologic toxicities are seen infrequently unless pelvic radiation occurs with chemotherapy. A complete blood count should be obtained weekly during radiochemotherapy. If the absolute neutrophil count falls to less than 500 / mm^3 or platelet count falls to less than 25,000 / mm^3, radiation therapy may be temporarily withheld to allow recovery above these levels at the discretion of the treating physician.

6.3.4 Gastrointestinal Adverse Events: Nausea and vomiting are rather unusual after pelvic radiation. Antiemetics may be given when symptoms occur or may be given prophylactically prior to treatment per institutional protocol. Intractable nausea or vomiting is rarely seen with pelvic radiation alone and is usually the result of another process, i.e. bowel obstruction. Increased bowel activity with diarrhea usually can be controlled with low fiber, low fat, bland diets and antidiarrheal medications. Should gastrointestinal toxicity become severe, hospitalization may be required at which time the treatment may be interrupted temporarily until the patient's condition improves.

6.3.5 Genitourinary Adverse Events: Acute toxicity of the urinary tract is manifested by cystitis. Maintaining high fluid intake is important. Bladder antispasmodics, analgesics and antibiotics are recommended per institutional protocol. Hematuria is not usually seen with acute cystitis and suggests bladder

invasion by tumor. Acute vulvovaginitis is seen when the pelvic fields extend inferiorly to include the vulvoperineal area. Treatment of acute vulvoperineal reaction may require warm saline soaks, wearing loose clothing and keeping the area dry using a hair dryer. Topical steroids, antibiotics, creams, and treatment interruption may be necessary per institutional protocol.

6.3.6 Cutaneous Skin Toxicity Adverse Events: With the use of megavoltage external beam radiation therapy, skin reactions in the treatment field are infrequent but are more likely to develop if sites such as the inguinal area, vulva, and the perineum are extensively within the radiation fields. During radiation therapy, mild irritation and redness of the skin may occur within the radiation fields. Some patients may experience more intense skin reaction such as dry or moist desquamation depending upon the energy of the megavoltage beam, number of fields used per day, need to cover distal vagina and therefore flashing perineum and use of chemotherapy. Hair loss in the pubic area may occur which can be permanent. Late subcutaneous fibrosis, telangiectasia, and skin atrophy are uncommon sequelae. Almost all patients with vulvar/perineal skin in the treatment fields may expect to develop acute moist desquamation during the course of external beam radiation therapy.

Acute skin reactions may be treated according to institutional preferences. Aquaphor or steroid creams may be used for CTCAE v4 grade 1-2 reactions and it is not necessary to interrupt the radiation therapy. For CTCAE v4 grade 3-4 skin reactions when generalized macular, papular or vesicular eruptions have developed, or there is generalized exfoliative or ulcerative dermatitis in the treatment fields, radiation therapy may be interrupted, but this should be avoided. Treatment may require symptomatic management of pain, use of warm saline soaks, vitamin A&D ointment, wearing loose clothing, and keeping the area dry according to institutional protocol. Radiation therapy should be resumed as soon as the skin reactions have improved. The principal investigator should be notified within 96 hours of any grade 4 toxicity.

7.0 ADVERSE EVENTS REPORTING REQUIREMENTS (05/30/2017)

7.1 Protocol Agents

Investigational Agents

The investigational agent administered in NRG-GY006 is triapine, which is being made available under an IND sponsored by DCTD, NCI. For patient on Arm 2 receiving triapine and cisplatin, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in **Section 7.5.2.1** of the protocol.

Triapine: IND #_68338**; IND Sponsor: DCTD/NCI**

Commercial Agents

The commercial agent in NRG-GY006 is cisplatin. For patients on Arm 1 receiving cisplatin alone, determination of whether an adverse event meets the expedited reporting criteria, see the reporting table in **Section 7.5.2.2** of the protocol.

7.2 Adverse Events and Serious Adverse Events

7.2.1 This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

7.2.2 Definition of an Adverse Event (AE)
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Triapine® (NSC 663249)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 182 patients.* Below is the CAEPR for Triapine®.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple

investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, June 6, 2013[1]

Adverse Events with Possible Relationship to Triapine® (CTCAE 4.0 Term) [n= 182]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)** (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	Blood and lymphatic system disorders - Other (methemoglobinemia)		***Blood and lymphatic system disorders - Other (methemoglobinemia) (Gr 2)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
		Hemolysis	***Hemolysis (Gr 2)***
CARDIAC DISORDERS			
	Cardiac disorders - Other (cyanosis)		***Cardiac disorders - Other (cyanosis) (Gr 2)***
		Left ventricular systolic dysfunction	
GASTROINTESTINAL DISORDERS			
	Colitis		***Colitis (Gr 2)***
	Constipation		
	Diarrhea		***Diarrhea (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
Fever			***Fever (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Infection[2]		***Infection[2] (Gr 3)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		***Creatinine increased (Gr 2)***
	Electrocardiogram QT corrected interval prolonged		***Electrocardiogram QT corrected interval prolonged (Gr 2)***
	Investigations - Other (decreased bicarbonate)		***Investigations - Other (decreased bicarbonate) (Gr 2)***
	Investigations - Other (elevated ST and T wave changes)		***Investigations - Other (elevated ST and T wave changes) (Gr 2)***

	Lipase increased		***Lipase increased (Gr 2)***
	Lymphocyte count decreased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hypercalcemia		***Hypercalcemia (Gr 2)***
	Hyperkalemia		***Hyperkalemia (Gr 2)***
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypokalemia		***Hypokalemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Myalgia		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Hypoxia		***Hypoxia (Gr 3)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
VASCULAR DISORDERS			
	Flushing		***Flushing (Gr 2)***
	Hypertension		***Hypertension (Gr 2)***
	Hypotension		***Hypotension (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Also reported on triapine trials but with the relationship to triapine still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (monocytosis); Blood and lymphatic system disorders - Other (thrombotic microangiopathy (e.g., thrombotic thrombocytopenia purpura [TTP] or hemolytic uremic syndrome [HUS])); Disseminated intravascular coagulation; Leukocytosis; Spleen disorder
CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (cardiovascular edema); Cardiac disorders - Other (premature ventricular contraction); Myocardial infarction; Palpitations; Pericardial effusion; Restrictive cardiomyopathy; Sinus tachycardia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (ear congestion); Ear and labyrinth disorders - Other (hyperacusis); Ear pain; Hearing impaired; Middle ear inflammation; Tinnitus; Vertigo
EYE DISORDERS - Dry eye; Watering eyes

GASTROINTESTINAL DISORDERS - Abdominal pain; Ascites; Dry mouth; Dysphagia; Esophagitis; Flatulence; Gastrointestinal disorders - Other (glossitis); Gastrointestinal disorders - Other (leukoplakia of the mouth); Gastrointestinal disorders - Other (mouth ulceration); Gastrointestinal disorders - Other (salivary hypersecretion); Gastrointestinal disorders - Other (steatorrhea); Gastrointestinal disorders - Other (stool discoloration); Gastrointestinal disorders - Other (tongue discoloration); Hemorrhoids; Ileus; Oral hemorrhage; Pancreatitis; Rectal hemorrhage; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS – Death NOS; Edema face; Edema limbs; Flu like symptoms; General disorders and administration site conditions - Other (extravasation); Infusion related reaction; Malaise; Non-cardiac chest pain; Pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (hepatomegaly); Hepatobiliary disorders - Other (jaundice); Hepatobiliary disorders - Other (liver tenderness)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Cytokine release syndrome
INVESTIGATIONS - Activated partial thromboplastin time prolonged; CPK increased; Cholesterol high; GGT increased; INR increased; Investigations - Other (BUN increased); Investigations - Other (C-reactive protein increased); Investigations - Other (lactate dehydrogenase increased); Investigations - Other (NPN increased); Investigations - Other (PT decreased); Investigations - Other (sedimentation rate increased); Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Acidosis; Alkalosis; Hyperglycemia; Hypernatremia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Iron overload; Metabolism and nutrition disorders - Other (hypoproteinemia); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Arthritis; Back pain; Bone pain; Chest wall pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (hypertonia); Musculoskeletal and connective tissue disorder - Other (leg cramps); Musculoskeletal and connective tissue disorder - Other (myoglobin); Musculoskeletal and connective tissue disorder - Other (twitching); Pain in extremity
NERVOUS SYSTEM DISORDERS - Amnesia; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Nervous system disorders - Other (cerebellar toxicity); Nervous system disorders - Other (reflexed decreased); Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Syncope; Tremor
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delayed orgasm; Delirium; Depression; Insomnia; Personality change
RENAL AND URINARY DISORDERS - Acute kidney injury; Cystitis noninfective; Hematuria; Urinary frequency; Urinary tract pain; Urine discoloration
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction; Genital edema; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Apnea; Epistaxis; Hiccups; Laryngospasm; Pleural effusion; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Erythema multiforme; Hirsutism; Hyperhidrosis; Photosensitivity; Pruritus; Skin and subcutaneous tissue disorders - Other (skin nodule); Skin ulceration; Stevens-Johnson syndrome
VASCULAR DISORDERS - Hematoma; Phlebitis; Thromboembolic event; Vascular disorders - Other (pallor); Vascular disorders - Other (vasodilation)

Note: Triapine® in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.4 Adverse Events for Commercial Study Agents **(05/30/2017)**

Refer to the package insert for detailed pharmacologic and safety information

List of adverse events for cisplatin:
Adverse effects: Leukopenia, thrombocytopenia, anemia, nausea, vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy, electrolyte imbalance,

hypocalcemia, hypomagnesemia, aminoglycoside, ocular toxicity and allergic reactions.

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Infrequent: Cardiac abnormalities, anorexia, elevated SGOT, rash, alopecia, and acute myeloid leukemia.

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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 diuresis before, during and after treatment.

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

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

7.5 Expedited Reporting of Adverse Events

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to NRG and satisfies NRG requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Regulatory Affairs by phone at 215-854-0770. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.5.1 Expedited Reporting Methods

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS24-hour notification must be followed by a complete report within 3 days. Supporting source documentation is requested by NRG as needed to complete adverse event review. When submitting supporting source documentation, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to the NRG Regulatory Affairs at 215-854-0716.

- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action not recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.5.2 Expedited Reporting of Requirements for Adverse Events

7.5.2.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days			24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		7 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

7.5.2.2 Phase 1, 2 and 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a non-IND/IDE within 30 Days of the Last Administration of the Commercial Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the commercial agent(s)/intervention

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to NRG via CTEP-AERS within 24 hours of learning of the AE, followed by a complete report within 3 calendar days of the initial 24-hour report.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	24-Hour 3 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.

[1]Serious adverse events that occur more than 30 days after the last administration of commercial agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

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

- All Grade 3, 4, and Grade 5 AEs
- Grade 1 and 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

[1]Serious adverse events that occur **more than** 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

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

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

7.5.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.5.4 Secondary Malignancy

Secondary Malignancy

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

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy
  Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7.5.5 Routine Adverse Event Reporting

For studies using investigational agents, the NRG Statistical and Data Management Center-Buffalo Office (SDMC) routinely reports adverse events electronically to the CTEP Clinical Data Update System (CDUS Version 3.0). The SDMC submits this data quarterly. The AEs reported through CTEP-AERS

will also be included with the quarterly CDUS data submissions.

8.0 REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES (17-FEB-2021)

8.1 Investigator Registration Requirements

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	**IVR**	**NPIVR**	**AP**	**A**	**AB**
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				

Documentation Required	IVR	NPIVR	AP	A	AB
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

8.2 Site Registration Requirements

8.2.1 Cancer Trials Support Unit Registration Procedures **(17-FEB-2021)**

This study is supported by the NCI CTSU.

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the

network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and

Protocol Specific Requirements for NRG-GY006 Site Registration

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on any roster is required to update provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU website.

IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process.

Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select NRG, and protocol number NRG-GY006;
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Site's Registration Status

You can verify your site's registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration;* and
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol

requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- 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

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

8.2.2 The following radiotherapy requirements must be followed by all participating institutions:

PET/CT Qualification is required for all institutions and must be renewed yearly.

Sites that have IMRT must utilize the IMRT modality.

IMRT credentialing is required unless the institution is utilizing 3D CRT. This requirement will be set to "complied" if IMRT approval is received from IROC. The 3D CR requirement will be set to "N/A" even if approval is received from IROC. Sites that have the IMRT protocol specific requirement (PSR) "complied" in RSS will be able to select the IMRT modality when enrolling patients in OPEN.

3D CRT credentialing is required unless institution is utilizing IMRT. This requirement will be set to "complied" if 3D CRT approval is received from IROC. Sites that have the 3D CRT PSU "complied" in RSS will be able to select the 3D RT modality when enrolling patients in OPEN.

Institutions that do not have current PET/CT qualification approval and either IMRt or 3D CRT approval on file with the CTSU will have "pending" status.

8.2.3 **Delegation of Task Log (DTL) (17-FEB-2021)**

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

Canadian sites participating under the Canadian Cancer Trials Group (CCTG), should complete the DTL in CCTG's Ripple application when CCTG holds the Clinical Trials Agreement with Health Canada. Ripple is integrated with the CTSU DTL application for this trial.

8.3 RT-Specific Pre-registration Requirements **(05/30/2017)**

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. IROC-Houston will be the entity to notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study.

NOTE: Pre-Treatment reviews are required <u>for every</u> IMRT case. Sites will initially submit their simulation CT scan and PET/CT to IROC, along with their targets and OARs for review. Sites that are able to generate the active bone marrow structure locally using deformable imaging registration software can submit this structure at this time and will receive instructions during the IMRT credentialing process. Otherwise, the active bone marrow structure will be created by IROC personnel then returned to the treating site as a DICOM structure set for use in planning (Figure 2). Sites will then submit an initial IMRT plan for review, and will receive information back following implementation of a KBP algorithm for use in re-optimization, before submitting the final IMRT used for treatment. Please allow three (3) business days for this to be completed. If a resubmission is required, the three (3)-business day timeline will restart. Treatment cannot begin until approval from NRG Oncology has been received at the site. IMRT plans for <u>all patients</u>

enrolled on the study will be centrally reviewed to determine protocol compliance.

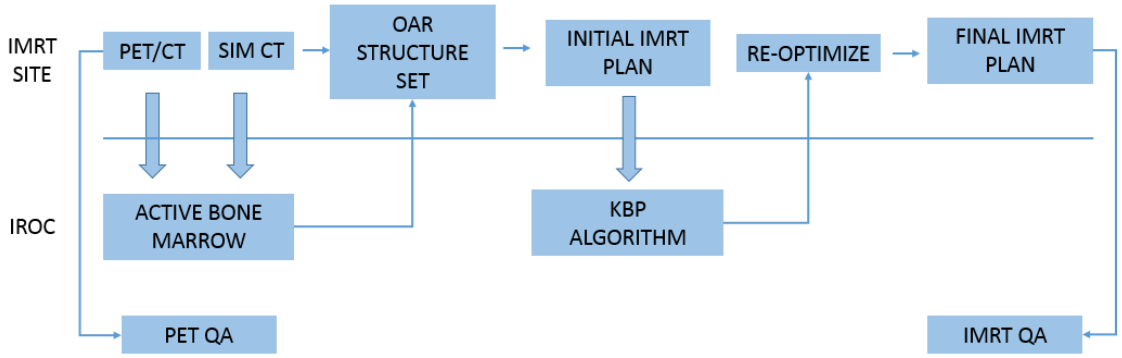

Figure 2. IMRT Pre-Treatment Workflow

RT Credentialing Requirements	Web Link for Procedures and Instructions: http://irochouston.mdanderson.org	
	Treatment Modality	
	IMRT	**Key Information**
Facility Questionnaire	X	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	X	To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org)
Phantom Irradiation	X	An IMRT H&N phantom study provided by the IROC QA Center Houston must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org). Tomotherapy treatment delivery modality must be credentialed individually.
Dry Run	X	A previous patient from the institution needs to be planned per protocol and submitted via TRIAD to go through the ABM, KBP and pre-treatment processes. (http://irochouston.mdanderson.org)
Pre-Treatment Review	X	Pre-Treatment reviews are required for each IMRT case.
Institution		IROC Houston QA Center will notify the institution and NRG Headquarters that all desired credentialing requirements have been met.

8.3.1 Digital RT Data Submission to NRG Oncology Using TRIAD (17-FEB-2021)

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- A valid CTEP - IAMaccount.
- Registration and Credential Repository (RCR) registration type of Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR) or Investigator (IVR) registration type. Refer to the CTEP

Registration Procedures section for Instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN

TRIAD Installations:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

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

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858**.**

8.4 Patient Enrollment

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.4.1 The Oncology Patient Enrollment Network (OPEN) (17-FEB-2021)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access: A valid CTEP-IAM account;

- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a

DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- 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. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website at https://www.ctsu.org or https://open.ctsu.org.. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com

8.5 ^{18}F-FDG PET CT Scanner Qualification and Evaluation **(05/30/2017)**
Please refer to section 15.0 regarding directions for pre-study qualification of an institutions PET/CT scanner.

9.0 DRUG INFORMATION (01/16/2018)

9.1 Triapine (NSC #663249) IND#: 68338 **(17-FEB-2021)**

Chemical Name: 3-aminopyridine-2-carboxaldehyde thiosemicarbazone

Other Names: 3-AP

Classification: Triapine®, an α-heterocyclic carboxaldehyde thiosemicarbazone (HCT), is a ribonucleotide reductase (RR) inhibitor that acts on the M2 (R2) subunit. The HCTs are the most potent RR inhibitors, being 65 -5,000 times more potent than hydroxyurea.

Mechanism of Action: Ribonucleotide reductase (RR) inhibitor

CAS Registry Number: 143621-35-6

Molecular Formula: $C_7H_9N_5S$ **M.W.:** 195

Approximate Solubility: Water = 0.1 mg/mL
Ethanol = 1.25 mg/mL
PEG-300 = 15 mg/mL

How Supplied: Triapine® is supplied by DCTD, NCI and distributed by the CTEP, DCTD, NCI. Triapine® Injection is supplied in 10 mL amber vials containing 10 mL of a clear yellowish slightly viscous, sterile, non-aqueous solution for IV administration. Each 10 mL vial contains 50 mg of Triapine® (5 mg/mL), 60 mg of citric acid, anhydrous, 10 mg of L-ascorbic acid, 3 mL of ethyl alcohol, and 7 mL of polyethylene glycol 300.

Preparation: Withdraw the Triapine dose volume from the vial and add to 0.9% sodium chloride or 5% dextrose in water to a final concentration of 0.01 to 2 mg/mL. Triapine infusion should be a clear, yellow solution with no discernible haziness. If haziness appears or persists after dilution, do not use the product**.**

Dilutions of Triapine® must be performed in glass bottles, or in plastic IV bags that do not contain di (ethylhexyl) phthalate (DEHP), since the nonaqueous solvents in Triapine® injection have been shown to extract DEHP.

Storage: Store Triapine® injection between 2-8°C (36-46°F). Do not freeze.

If a storage temperature excursion is identified, promptly return Triapine® injection to refrigerated temperature and quarantine the

supply. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: When diluted with 0.9% sodium chloride or 5% dextrose in water, to a final concentration of 0.01 to 2 mg/mL, Triapine® infusions have been found to be stable for 8 hours at room temperature or at 2 - 8ºC. Do not freeze. Do not expose diluted solutions of Triapine® injection to direct sunlight or temperatures above 25°C (77°F).

Shelf life stability studies of Triapine® injection vials are on-going.

Route of Administration: Intravenous

Method of Administration: Infuse intravenously over 2 hours using a DEHP-free (e.g., polyethylene) low sorbing infusion set on days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26, 29, 31, 33 of radiation (15 total infusions).

Availability: Triapine is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. **NO STARTER SUPPLIES MAY BE ORDERED.** Subjects must be enrolled and assigned to the treatment arm prior to submitting the agent request to PMB.

Agent Ordering: "NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent.

Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password and an active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management."

Phase III and increase in sample size: If a drug supply shortage occurs, the protocol may need to temporarily close to accrual.

Agent Inventory Records: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability
The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP/
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9.2 Cisplatin (NSC# 119875)

Formulation: PLATINOL®-AQ (cisplatin injection) infusion concentrate is a clear, colorless, sterile aqueous solution available in amber vials. Each 50 mL or 100 mL amber vial of infusion concentrate contains: 1 mg/mL cisplatin, 9 mg/mL sodium chloride, hydrochloric acid and sodium hydroxide to approximate pH of 4.0, and water for injection to a final volume of 50 mL or 100 mL, respectively.

Supplier: Commercially available. Refer to individual FDA-approved package insert.

Preparation: PLATINOL®-AQ (cisplatin injection) infusion concentrate (1 mg/mL) must be further diluted prior to administration. Cisplatin (40 mg/m^2, 70 mg maximum) will be diluted in 250-1000 mL of normal saline.

NOTE: Aluminum reacts with cisplatin 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 cisplatin.

Storage: Store at 15° to 25°C (59° to 77°F). Do not refrigerate. Protect unopened container from light.

Stability: The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.

Administration: Once weekly cisplatin (40 mg/m^2, 70 mg maximum) is administered intravenously on Days 2, 9, 16, 23, and 30 with an optional infusion on day 36 (sixth cycle). An infusion of 1000 ml of ½ normal saline should be given intravenously one hour before cisplatin. Increased oral intake should be encouraged starting the day before. Additional fluid may be given as needed for symptomatic support. Cisplatin should be infused at a rate of 1 mg/min, usually over a total of 90 minutes or as per institutional protocol. Immediately after completion of the cisplatin infusion, an additional 1000 ml of ½ normal saline should be given or as per institutional protocol.

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, alopecia, and acute myeloid leukemia.

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 diuresis before, during and after treatment.

Mild renal dysfunction is a common complication (10%) of chronic therapy and may require discontinuation of therapy if BUN > 30mg/dl or creatinine > 2.0 mg/dl develop.
*See FDA- approved package insert for a comprehensive list of adverse events associated with cisplatin.

10.0 PATHOLOGY

No central pathology review will be required in this trial (NRG-GY006).

11.0 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

11.1 Reimbursement

Methemoglobin level biomarker test monitors 1st dose triapine toxicity. Patients' insurer will be billed for the tests and they may or may not be reimbursed by their insurer. **(05/30/2017)**

11.2 Translational Science

Note: Testing of blood specimens will occur immediately following collection.

11.2.1 Specimen Requirements **(05/30/2017)**

This clinical trial includes an *optional* set of peripheral venous blood samples to be collected (2mL [<1 teaspoon]) in heparinized arterial blood gas syringes and put on ice for methemoglobin determination as a possible surrogate biomarker for therapeutic effect. **Sampling will occur on day 1 of the first cycle, before triapine dosing (t=0-) and 1, 3, 5, and 24 hours after start of triapine administration.**

Optional Methemoglobinemia testing	
Prior to infusion	After infusion
Once predose (t=0-)	1, 3, 5, and 24 hours

11.2.2 Specimen Procedures

Once the blood specimen is obtained, it should be sent on ice to a laboratory or blood bank for methemoglobin determination according to the institution's normal practice.

11.2.3 Laboratory Testing

Methemoglobin Peripheral Venous Blood Samples (Exploratory Biomarker)
Methemoglobin is a known side effect of triapine administration (21). Methemoglobin will be reported as a percentage of total hemoglobin as determined by routine clinical laboratory (for instance, in a blood bank).

12.0 DATA AND RECORDS (05/30/2017)

12.1 Data Submission / Data Reporting **(17-FEB-2021)**

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.
- Rave role requirements:
- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.
- Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a

separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

12.2 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. See Section 7 for information about expedited and routine reporting.

12.3 Digital Data Submission Requirements

Summary of Dosimetry Digital Data Submission

Submit Digital RT Data via TRIAD; see section 8.3.1 for TRIAD account access and installation instructions.

Item		**Due**
Arm 1		
DICOM Items	DICOM CT Image	**By 4 weeks after completion of all radiation therapy. If IMRT, then DICOM RT plan must be submitted for pre-treatment review <u>prior to RT delivery</u>. Allow at least 3 business days from the receipt of complete data for this review to be completed. Changes may be required and therefore another pre-treatment review would be needed. Allow time for this.** **Prior to treatment start.** **By 4 weeks after all therapy.**
	DICOM CT Image (Contrast)	
	PET Image	
	DICOM Structure	
	DICOM Dose	
	DICOM RT Plan	
Screen Capture of Fusion		
Completed online GYN Brachy Protocol Compliance Form (http://irochouston.mdanderson.org)		
Hardcopy Brachytherapy Treatment Plan, Brachytherapy Plan Summary		
Digital Data Submission Information Form (DDSI): http://www.rtog.org/CoreLab/RTQASubmissionInformation.aspx		
Arm 2		
DICOM Items	DICOM CT Image	**By 4 weeks after completion of all radiation therapy. If IMRT, then DICOM RT plan must be submitted for pre-treatment review <u>prior to RT delivery</u>. Allow at least 3 business days from the receipt of complete data for this review to be completed. Changes may be required and therefore another pre-treatment review would be needed. Allow time for this.** **Prior to treatment start.** **By 4 weeks after all therapy.**
	DICOM CT Image (Contrast)	
	PET Image	
	DICOM Structure	
	DICOM Dose	
	DICOM RT Plan	
Screen Capture of Fusion		
Completed online GYN Brachy Protocol Compliance Form (http://irochouston.mdanderson.org)		
Hardcopy Brachytherapy Treatment Plan, Brachytherapy Plan Summary		
Digital Data Submission Information Form (DDSI): http://www.rtog.org/CoreLab/RTQASubmissionInformation.aspx		
Brachytherapy (Arm 1 and Arm 2)		
DICOM Items: DICOM CT Image (Brachytherapy)		By 4 weeks after all therapy

PDF Items: Brachytherapy Treatment Plan and Summary	By 4 weeks after all therapy
Completed online GYN Brachy Protocol Compliance Form (http://irochouston.mdanderson.org)	

12.4 Global Reporting/Monitoring
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 of each calendar year.

12.5 Site visit audits are conducted according to CTEP audit procedures, employing source data verification of data reported in RAVE for informed consent, eligibility, treatment, disease outcome/response, adverse events and general data quality. In addition to the regularly scheduled audits, the following expanded audit program is implemented for this protocol:

12.5.1 Expedited Audits: Individual sites (identified by unique institutional CTEP ID) that have enrolled 3 or more patients and are not due for their regularly scheduled audit within 9 months of the 3rd patient enrolled will be scheduled for an off-cycle, expedited audit.

12.5.2 Additional Case Review: During both regularly scheduled and off-cycle, expedited audits, a greater number of cases will be reviewed: For sites enrolling > 50 patients, at least 30% of cases will be selected, for sites enrolling <50 and >5 patients, at least 50% of cases will be selected and for sites enrolling 5 or fewer patients, 100% of cases will be selected.

12.5.3 After initial audits for this protocol, subsequent audits will include additional cases enrolled since the prior audit.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design
This is an open label randomized (1:1 allocation ratio) phase III clinical trial to access efficacy of radiation therapy (RT) and cisplatin (CIS) alone or in combination with intravenous triapine (3AP) in women with bulky stage IB2, II, IIIB or IVA cancer of the uterine cervix or stage II-IV vagina. The study includes two interim analyses. The first interim safety analysis was conducted in July 2018 as part of the Phase II study. The second interim analysis will consider early stopping for futility.

Treatment assignments will be concealed from institutions and patients until the registration process is completed. Future randomization will be stratified by three factors: type of brachytherapy (LDR or HDR), clinical stage (≤ II or ≥III) and planned radiation therapy modality (IG-IMRT: yes or no). A dynamic allocation (minimization) randomization algorithm that tends to assign treatment with equal

probabilities to the two treatment arms within strata will be used to facilitate optimal balance between arms (Pocock, 1975).

13.2 Study Objectives

13.2.1 Primary objective

13.2.1.1 To evaluate efficacy of the experimental regimen (RT+CIS+3AP, arm 2) in improving overall survival (OS) relative to the standard, control regimen (RT+CIS, arm 1).

13.2.2 Secondary objectives

13.2.2.1 To compare progression-free survival (PFS) by treatment arm and by radiation modality.

13.2.3 Tertiary Objectives

13.2.3.1 To evaluate incidence and severity of hematologic and gastrointestinal (GI) adverse events (CTCAE version 4) by radiation treatment modality.

13.2.3.2 To summarize and compare differences in acute adverse events (CTCAE, version 4) by treatment arm and by radiation modality.

13.2.3.3 To summarize and compare differences in chronic or late (≥ 30-days from off study treatment date) adverse events (CTCAE, version 4) by treatment arm and by radiation modality.

13.2.3.4 To determine peripheral blood methemoglobin proportion before and after triapine infusion.

13.2.3.5 To explore whether knowledge-based planning (KBP) can improve IG-IMRT plans compared to plans that would have been delivered without KBP, estimate the resulting toxicity reduction using NTCP models, and determine whether KBP should be a requirement for future IG-IMRT protocols.

13.2.3.6 To determine the post-therapy 3-month ^{18}F-FDG PET/CT metabolic complete response (mCR) rate by treatment arm.

13.2.3.7 To compare hematopoietic compensatory response by treatment arm and radiation modality

13.2.3.8 To develop and validate machine learning and radiomic tools for automated brachytherapy planning, dose accumulation, and prediction of treatment response

13.3 Clinical Endpoints and Data Elements

13.3.1 Measures of Efficacy and Safety

The principal observations for evaluating the therapeutic efficacy and safety of the study regimens are:

i. Primary efficacy endpoint: Overall Survival (OS)
ii. Secondary efficacy endpoints
    1. Progression-free survival (PFS)
        a. Disease progression or recurrence will be determined from
            i. The physical examinations conducted during treatment (day 9, 16, 23, 30 and 37)
            ii. The physical examinations conducted during follow-up (1 and 3 months after completing protocol therapy, every 3 months for years 1 and 2, and every 6 months for years 3, 4 and 5)
            iii. The PET/CT scan conducted 3 months after the end of treatment.
        b. The disease assessment schedule is tabulated in Section 4.0.
    2. The ^{18}F-FDG PET/CT metabolic complete response rate 3 months after completing the protocol therapy, as defined in Section 2.2

    3. Safety endpoints: frequency and severity of adverse effects as defined by Common Terminology Criteria for Adverse Events (CTCAE).

13.3.2 OS time – is the time in months from registration (and randomization) onto the study to the date of death or last contact. OS is the primary efficacy endpoint.

13.3.3 PFS time – is the time in months from registration (and randomization) onto the study to the date of first documented recurrence/progression, death, last complete PFS assessment or last contact, whichever occurs first. Recurrence is defined as clinical, radiologic or histologic evidence of recurrent disease post study treatment. PFS is primary secondary efficacy endpoint.

The following censoring rules will apply to the primary PFS analyses:

1. Patients with no baseline tumor assessments will be censored on the date of randomization.
2. Patients with no adequate post baseline tumor assessments and no death reported within 2 assessment intervals following randomization will be censored on the date of randomization.
3. Patients who have not progressed and are alive without recurrence will be censored on the date of the last tumor assessment without documented disease progression/recurrence.

13.3.4 Safety endpoints: frequency and maximum severity of adverse events (Common Terminology Criteria for Adverse Events (CTCAE) – version 4.0).
13.3.5 Dates and Sites of recurrence – local (pelvis regions including vagina) or distant (abdomen, lung, brain, and other).
13.3.6 ^{18}F-FDG PET/CT mCR – assessed at 3 month follow-up visit.
13.3.7 Disease characteristics at study entry– clinical stage, clinical tumor size, tumor histology (grade and cell type), and pelvic and para-aortic nodal status.
13.3.8 Patient characteristics at study entry– age, performance status, race and ethnicity,
13.3.9 Proportion of peripheral blood methemoglobin before and post triapine infusion (t=0-, 1, 3, 5, 6, 7, and 24 hours).
13.3.10 Type of IG-IMRT – knowledge-based planning (KBP) vs. without KBP.

13.3.11 Treatment compliance: amount of radiation, cisplatin and triapine administered, incidence and duration of treatment delays, reason for delays, and reason why off study therapy.

13.4 Stratification Factors at Randomization

Treatment assignment will be balanced among strata defined by levels of three factors:
13.4.1 Type of brachytherapy (LDR or HDR)
13.4.2 Radiation modality – IG-IMRT (yes or no)
13.4.3 Stage (clinical stage ≤ II, or clinical stage ≥III)

13.5 Accrual and Study Duration

Accrual estimates, and study duration are based on the GOG-0219 experience and anticipated NCTN participation. GOG-0219 accrued 402 patients over 40 months, which translates to an overall rate of 10 per month (Figure 3). Thus it is reasonable to assume the accrual rate will be at least 8 - 10 patients per month when available to the entire NCTN.

Note: Due to the increase in sample size, it is possible that a drug shortage may occur. If a drug shortage occurs, the study may temporarily close to accrual.

13.5.1 Accrual rate: 8 to 10 patients per month
13.5.2 Accrual objective: 450 patients will be accrued, of which 430 are expected to eligible.
13.5.3 Post-accrual follow-up period: 42 months

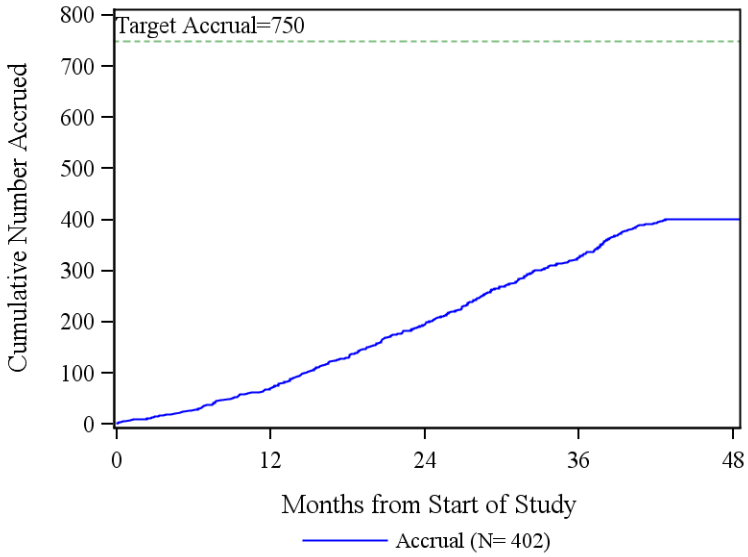

Figure 3. Accrual since activation, GOG-0219

13.6 Statistical Power and Sample Size Justification

The primary objective is to determine whether the addition of triapine increases overall survival relative cisplatin and radiation alone. The critical event of interest is death from any cause. The null hypothesis is the OS hazard ratio (HR) of the experimental regimen to the control regimen is 1.0 or higher. That is, H_0: HR $\geq$ 1.0. The alternative hypothesis is that the HR for OS of the experimental regimen to the control regimen is less than 1, i.e., H_1: HR < 1.0.

A hazard ratio (HR) of $\leq$ 0.60 is considered the upper bound on the least clinically important treatment advantage to detect, and to provide sufficient evidence to warrant further evaluation of the experimental regimen. This effect size translates to 36-month OS rates among control and experimental arm patients of $\leq$ 72% and $\geq$ 82.0%, respectively. The choice for 72% as the lower bound for the 36 month survival proportion under H_0 is based on Kaplan-Meier (KM) estimate of survival for GOG-0219 control arm (Figure 4).

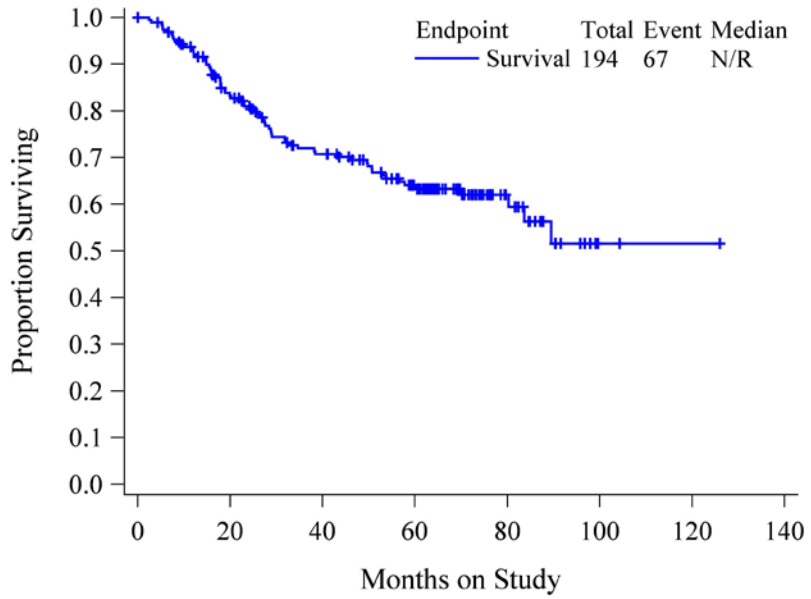

Figure 4. Kaplan-Meier estimated of overall survival among patients on the GOG-0219 control arm

The original Phase II study was designed with a one-sided log rank test and an overall sample size of 172 patients (86 per arm) to achieve at least 82% power at 10% significance level ($\alpha = 0.10$) to detect a HR of 0.5089 when the proportion surviving progression-free in the control arm is 64.5% (Lakatos, 1988; Lakatos, 2002; Hintze, 2008). An interim safety analysis that allowed early stopping for excessive toxicity was also included.

NRG-GY006 has been modified as a Phase III registration trial accruing 450 patients, 430 of which are expected to be evaluable. With 127 OS events in both arms from the sample of 430 eligible patients, this design has 80% power at 2.5% significance level ($\alpha = 0.025$) by a one-sided log-rank test to detect a HR of 0.6 or lower (Lan, 1983; East 6). A non-binding interim futility analysis is included. Table 13.1 summarizes the theoretical operating characteristics of this study.

Table 13.1: Theoretical Operating Characteristics

Hazard Ratio	PET[1]	Probability Accept Rx[2]	Theoretical Pr (Rej. Rx)[3]
0.5	0.0138	0.9659	0.0341
0.6	0.0705	0.8003	0.1997
0.7	0.1961	0.4979	0.5021
0.8	0.3739	0.2278	0.7722
0.9	0.5594	0.0803	0.9197

Hazard Ratio	PET[1]	Probability Accept Rx[2]	Theoretical Pr (Rej. Rx)[3]
1	0.716	0.0232	0.9768

[1] PET = Theoretical probability of early termination.
[2] Accept = Declaring the regimen interesting and worthy of further investigation.
[3]Theoretical calculation provided with the methods of Jennison and Turnbull.

Study duration estimates were obtained from simulations. The simulations assume OS in the GY006 control arm will follow a Gompertz distribution parameterized after the GOG-0219 control arm (cure rate = 0.34, shape parameter = 0.009291, scale = -0.00864). With a uniform accrual rate of 10 patients per month, the simulations suggest a total study duration of about 87 months (+/-7), including 45 months of accrual and 42 months of follow-up for the primary endpoint to mature. Table 13.2 shows the simulated probability of observing 127 OS events at different follow-up times, in months after accrual is complete.

Table 13.2: Proportion of simulations observing 127 OS events by follow-up time

Hazard Ratio	Monthly accrual rate	Follow-up time (months)	Proportion of simulations with 127 OS events
0.6	10	24	<5%
0.6	10	36	25%
0.6	10	38	36%
0.6	10	42	58%
0.6	10	48	83%
0.6	10	54	95%

On the assumptions above, the GY006 OS endpoint is expected to mature in early 2025.

13.7 Interim Safety Monitoring

All serious adverse events (SAE) and any unexpected AEs will be communicated to the study chair and regulatory agencies as mandated. The principal investigator (or designated co-chair) will review SAE reports, and unexpected AEs within two (2) working days for considerations of amendments or immediate study suspension.

The NRG Data Monitoring Committee (DMC) will review accumulating summaries of AEs and the safety review committee (SRC) will review SAEs

reports on an ongoing basis. Biannual study reports will be generated by treatment and reviewed by the NRG DMC at NRG semi-annual business meetings in February and July each year.

Safety reports will be representative and relative to a database locked no more than two months prior to NRG semi-annual meeting date. The report will include: patient accrual institutional accession info, projected completion data, and frequency and severity of all AEs. In addition, safety reports will include narratives describing specific treatment related SAEs and deaths occurring within 30 days of being off study therapy.

The Phase II study included one early safety analysis supported by the first 40 (~20 per arm) NRG-GY006 patients off study therapy and all NCI #9434 patients. The goal was to review toxicities by treatment arm. In July 2018, the DMC voted to continue the study as planned.

The NRG DMC will continue to review accumulating study reports on an ongoing basis. This committee will also perform detailed reviews of all deaths in which the study treatment may have been a contributing cause. The NRG DMC may recommend study amendments pertaining to poor accrual rate (< 50% of planned accrual rate), patient safety, treatment compliance, or results from external studies.

13.8 Interim Futility / Efficacy Monitoring **(05/30/2017)**

No interim analysis for efficacy is planned

The phase III design includes one non-binding interim futility analysis to occur when at least 64 OS events (50% information time) are observed in both arms. An O'Brien and Fleming-like spending function will determine the futility boundary. Accrual will not be stopped for the interim analysis.

If the assumptions above hold, the interim futility stopping rule will recommend rejecting the alternative hypothesis if the standardized log-rank test statistic $z \geq -0.571$. In repeated sampling, the DMC would have the option of closing the study early for futility about 72% of the time when the treatment hazard ratio is truly one, and 7% of the time if the alternative hypothesis is true. This non-binding futility boundary provides the study with the desired overall 80% power, but it can be overruled without inflating the overall type I error rate.

The results of this interim analysis will be reviewed by the NRG Data Monitoring Committee (DMC) at its semi-annual meeting. This committee meets in January and July each year. The precise dates for these meetings are set more than one year in advance by individuals who have no knowledge of efficacy results. Approximately eight weeks prior to each of these meetings,

the database is locked in order to prepare a progress report. If the prerequisite number of events has been attained, an interim analysis is also prepared and presented to the DMC at their next scheduled meeting. The decision to terminate accrual will include consideration of toxicities, treatment compliance, and progression-free survival and other endpoints, and results from external studies.

13.9 Suspending Follow-up for the Primary Analysis

The OS endpoint is expected to mature about 42 months after accrual is complete. Timing for primary efficacy analysis (based on number of events) is determined by ongoing accrual and the estimated 34% cure rate in this population.

To ensure timely and efficient dissemination of the study results, follow-up for the primary OS analysis may be suspended 42 months after the last patient is enrolled on the study. If the primary endpoint has not matured by this time, the DMC may recommend closing the study for analysis. This decision will be informed by the number of events observed to date, the number of patients still at risk, the estimated hazard of death, and other factors as appropriate.

Using the same simulation assumptions as in Section 13.6, Table 13.3 shows the estimated number of OS events in both arms. The third column shows the power for detecting a hazard ratio of 0.60. The fourth column shows maximum detectable hazard ratio with 80% power. The estimates assume a one-sided α=0.025 and a nonbinding futility analysis at 50% information. From the patient perspective, follow-up may continue beyond this time, as described in Section 5.5.

Table 13.3: Projected number of OS events and corresponding power

Follow-up time (months)	# OS events	Power for HR=0.60	HR for Power = 0.80
24	105	0.722	0.570
30	117	0.767	0.587
36	125	0.794	0.597
42	127	0.800	0.600

Table 13.4 shows the projected time for the interim and final analyses using GOG-0219 data for the control arm conditioned on NRG-GY006 accrual information.

Table 13.4: Projected times for interim and final analyses

Sample size	450 (430 eligible)
Total # patients enrolled (as 08/19/2019)	218
Time to accrual (from 08/19/2019)	22 months
Time to 50% of the information time (from 08/19/2019)	24 months. At this time, 64 OS events in both arms will be expected.
Time to 100% of the information time (from 08/19/2019)	About 64 months to reach 127 OS events in the both arms.

13.10 Analysis Plan

13.10.1 *NRG GY006 Database and Analysis Set*

For the Phase II study, the target accrual estimates assumed 10 to 13% of patients would come from NCI #9434, pending data sharing compliance and adequate patient consent. Analysis was stratified by study cohort (NCI # 9434 patients or new NRG GY006 accrual). The data manager and/or statistician responsible for NCI #9434 provided patient data (in a pre-specified data file format) and requisite data dictionary to NRG SDMC once the data matured and were query free. Case Western terminated NCI #9434 in the summer of 2016, with no further patient follow-up. On this basis, the NCI #9434 patient data will not be included in the Phase III study in any way.

The NRG-GY006 database includes only patients accrued through NRG-GY006. Evaluation of treatment efficacy including the primary endpoint (OS) and secondary endpoints, PFS and mCR will follow an "intent to treat" analysis utilizing all eligible patients in NRG-GY006 database (Begg, 2000; Lachin, 2000). Evaluation of toxicity will include all patients who have received any randomized study treatment in NRG-GY006 database.

13.10.2 *Evaluation of OS and PFS Endpoints*

Product-limit estimates according to the method of Kaplan and Meier and the one-sided stratified log-rank test (α=0.025) will be used in primary OS analysis between treatment arms. The log-rank test will be stratified by radiation modality (IG-IMRT yes vs no), type of brachytherapy (LDR vs HDR) and disease stage (clinical stage $\leq$ II vs clinical stage $\geq$III). Crude and adjusted hazard ratios and respective 95% confidence intervals will be estimated via Cox proportional hazards modeling, stratified as discussed above. Analysis of the secondary PFS outcome will be conducted by similar methods (α=0.025).

13.10.3 *Evaluation of Site(s) of Recurrence*

Site(s) of first recurrence will be classified as: pelvic region only, distant region only, both pelvic and distant or none (did not recur), and tabulated by treatment group and by radiation modality. The test of the hypothesis that the probability of local failure as the first site of recurrence is independent of randomized treatment will be assessed with Exact Logistic Regression adjusting for known prognostic

factors (Mehta, 1995). To account for competing risks, cumulative incidence for recurrence will be assessed.

13.10.4 *Toxicity and Treatment Compliance*
Adverse events will be graded according to CTCAE v4.0. Maximum grade of adverse effect will be categorized and tabulated as for each AE and significance of observed differences between treatments arms within each AE category will be assessed using Chi-square or Fisher's exact test (Agresti, 1992). In addition, detailed narratives will be provided for any deaths (grade 5) occurring during and within 30 from study treatment end date.

Treatment compliance will be evaluated and reported by treatment arm. Optimal treatment compliance is defined for patients who received at least 4 cycles of chemotherapy and complete 25 fractions (45 Gy) of external beam radiation within 35 days of starting protocol therapy. In addition, toxicity and treatment compliance will also be assessed by radiation modality.

Adverse events will be graded according to CTCAE v. 4 (Grades 0 - 5). Grades will be categorized into three groups; none (0), mild (1 or 2) and severe (3 or 4). Detailed narratives will be provided for any treatment related deaths (grade 5). In addition to displaying frequency of AE for each grade category for the entire cohort, if feasible, Fishers' exact test will be used to assess significance of observed differences between subgroups.

13.10.5 *Evaluation of metabolic complete response, mCR*
Frequency of mCR will be tabulated and the probability of attaining a mCR will be estimated. Differences in mCR rate between treatment arms will be assessed using Fisher's exact test. The relationship between patients' mCR status (yes or no) at 3 months post being off study therapy and PFS (and/or OS) will be assessed using regression models to evaluate mCR as a secondary short term endpoint for capturing treatment effect on patient outcome.

With 430 eligible patients, there will be at least 80% power to detect a difference in mCR rates, between the treatment arms, of 72% vs. 60%, at the 1-sided .05 significance level. This corresponds to an odds ratio of 1.7, a 70% improvement in the odds of mCR for the experimental therapy compared to reference the control.

13.10.6 *Evaluation of blood methemoglobin levels before and after triapine infusion*
Difference in peak blood methemoglobin levels before and after triapine infusion will be assessed using two tailed paired T-test at alpha=0.05 significance level.

Depending on the observed within subjects correlation, repeated measures ANOVA may be utilized instead.

13.11 Planned Minority Inclusion

Table: Anticipated local and international accrual by ethnicity and race. This table provides race and ethnicity distribution anticipated for this trial (based on GOG-0219).

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	3	0	1	0	4
Asian	7	0	1	0	8
Native Hawaiian or Other Pacific Islander	2	0	0	0	2
Black or African American	32	0	2	0	34
White	86	0	13	0	99
More Than One Race	1	0	6	0	7
Total	131	0	23	0	154

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	3	0	0	0	3
Native Hawaiian or Other Pacific Islander	2	0	0	0	2
Black or African American	1	0	1	0	2
White	7	0	2	0	9
More Than One Race	1	0	1	0	2
Total	14	0	4	0	18

Update (08/09/2018): The following are the race and ethnicity distribution anticipated for this trial based on GOG-0219 for a targeted sample size of 330.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	5	0	1	0	6
Asian	12	0	0	0	12

Native Hawaiian or Other Pacific Islander	3	0	0	0	3
Black or African American	66	0	3	0	69
White	173	0	30	0	203
More Than One Race	1	0	0	0	1
Total	260	0	34	0	294

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	2	0	0	0	2
Asian	0	0	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	33	0	0	0	33
More Than One Race	0	0	0	0	0
Total	35	0	2	0	36

Update (08/23/2019): The following are the race and ethnicity distribution anticipated for this trial based on GOG-0219 for a targeted sample size of 450.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	7	0	1	0	8
Asian	16	0	0	0	16
Native Hawaiian or Other Pacific Islander	4	0	0	0	4
Black or African American	90	0	4	0	94
White	236	0	41	0	277
More Than One Race	1	0	0	0	1
Total	354	0	46	0	400

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	3	0	0	0	3

Asian	0	0	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	46	0	0	0	46
More Than One Race	0	0	0	0	0
Total	49	0	1	0	50

14.0 Publication Information and Administrative Agreements

This section is left blank intentionally.

15.0 ^{18}F-FDG PET CT Scanner Qualification and Evaluation

The PET/CT scanner must meet qualification prior to enrollment of any patients onto the protocol and meet specific qualification criteria by the ACR/IROC Core Laboratory.

For the forms and information about how to qualify your PET/CT scanner, please visit: https://quic.acr.org or email: imagearchive@acr.org

Requalification of the PET/CT scanner must occur for any of the following scenarios:
- One year from the initial qualification approval
- A new scanner is installed that will be used to scan trial participants
- Any PET/CT system that undergoes a major upgrade (i.e., any upgrade that may affect quantitative (SUV) determination.

15.1 Quality Control Procedures

A daily QC check must be performed at the beginning of the day a subject is to be scanned. The QC check must include the PET scanner and dose calibrator, in accordance with the manufacture recommendations.

NOTE: if any of the QC results are outside of the manufacturer's guidelines, the study must be rescheduled (while within the imaging window) and the problem resolved prior to scanning a subject.

For the qualified scanner to be used during the study:
- Keep calibrated in accordance with the manufacturer's recommendations.
- Routinely asses the scanner for quantitative integrity and stability by scanning quality control phantom with the same acquisition and reconstruction protocols as those used for trial subjects.
- Perform standard uptake value (SUV) verification measurements to include the dose calibrator used to measure the doses of subjects, to ensure that the dose calibrator and PET scanner are properly cross-calibrated (i.e., the dose measured in the dose calibrator and injected into the phantom matches the results obtained from analysis of the phantom images).
- Perform all manufacturer recommended and site-specific daily quality control procedures which must include an acquisition of an emission sonogram. The QC sonogram should be visually inspected for abnormalities.

For the dose calibrator:
- Perform QC of the dose calibrator throughout the course of the study. This typically will include daily constancy, quarterly linearity, and annual accuracy tests, all of which should be documented.

For scanners, clocks and watches:
- Keep the dose calibrator clock synchronized with the scanner clock.
- Clocks should be synchronized and or periodically monitored against a reference standard for internal consistency.

NOTE: The same scanner must be used consistently across all time points for the same subject.

15.2 Subject Preparation

Prior to Arrival
- Subjects must fast (except for water) for at least 4 hours before administration of 18F-FDG for the PET/CT exam.
- Subjects should avoid strenuous exercise for 24 hours before the FDG injection to minimize uptake of the radiotracer in muscles.

Upon Arrival
- Upon arrival at the PET facility, confirm subject compliance with pre-procedure instructions, particularly that the fasting requirement was met.
- The subject's weight and height shall be measured and recorded (not verbally relayed by the subject).
- The pre-injection blood glucose level must be < 200 mg/dL (measured ideally within one hour of FDG injection). If the serum glucose is > 200 mg/dL, the study should be rescheduled. The referring physician or primary physician of the subject should be contacted to optimize blood glucose control.
- A large-bore intravenous line (typically, a 20 or 22 gauge angiocatheter) or a butterfly needle in a vein of the participant's arm.
- Prior to positioning the subject on the PET scanner the subjects should be asked to urinate.
- Use of a Foley catheter and a single furosemide administration per institutional policy is permitted.

Injection of ^{18}F-FDG
- The dose of FDG to be administered is 10-20 mCi.
- The exact time of calibration of the dose should be recorded and the exact time of injection noted to permit correction of the administered dose for radioactive decay. In addition, the dose remaining in the tubing or syringe, or that was spilled during injection should be recorded. The injection should be performed through an intravenous catheter.

FDG-PET/CT Imaging Procedure
- The time between the injection of FDG and PET emission scan start (tracer uptake time) should begin between 50-70 minutes after injection.
- The injection to start of imaging time for the 3-month and 6-month post therapy PET/CT scans should be within 10 minutes of that for the baseline study.
- The CT component of the PET/CT study will be performed for attenuation correct and anatomical localization (AC, AL).
- All participants must void prior to imaging to ensure clearance of bladder activity.
- A Foley catheter and a single furosemide administration per institutional policy is permitted.

- Participants will be positioned with their arms above their head or on their chest if unable to keep their arms above the head.

15.3 Typical acquisition parameters for the low-dose CT scan for attenuation correction should be: kVp = 120; effective mAs = 30–80 (participant dependent); gantry rotation time ≤ 0.5 sec; maximum reconstructed width = 3–5 mm without overlap. The parameters should use the standard reconstruction algorithm, without any iodinated intravenous contrast agent. Dilute oral contrast is acceptable, if part of typical institutional practice.

15.4 The presence or absence of para-aortic lymph node metastasis will be based on pre-therapy ^{18}F-FDG PET/CT. If the baseline ^{18}F-FDG PET/CT identifies hypermetabolic para-aortic disease, such patients will NOT be eligible for participation.

15.5 All PET/CT images will undergo centralized review to be organized by the Imaging and Radiation Oncology Core (IROC). On-going quality control review will be performed by an ACR/IROC Imaging Specialist (Dr. Jean Lee [face page] or other designated ACR/IROC imaging specialists) to ensure protocol images meet the study-specific parameters. If PET/CT scanners are upgraded or new scanners installed, the scanners will need to be re-qualified by the ACR/IROC Imaging Core Laboratory.

15.6 The preferred image transfer method is via TRIAD, a software application that ACR/IROC provides for installation on a site's computer. Internet access is required. When properly configured, the TRIAD software anonymizes, encrypts, and performs a lossless compression of the image before transmission to archives in the IROC Philadelphia, PA archive.

For more information, contact: TRIAD-support@phila.acr.org or call 215-940-8820.

In the event that image transfer is not available by TRIAD, ^{18}F-FDG PET/CT images should be recorded on CD as DICOM images and mailed to the ACR/IROC Core laboratory. Image may be mailed to:
American College of Radiology Imaging Network
ACR/IROC Imaging Core Laboratory
ATTN: NRG-GY006
1818 Market Street 16th Floor
Philadelphia, PA 19103

The Imaging Transmittal Worksheet (ITW) must accompany all submissions.

15.7 ^{18}F-FDG PET/CT Reporting: Images will be evaluated on baseline and 3-month scans qualitatively for focal areas of abnormally increased ^{18}F-FDG uptake in the primary tumor. This will be performed by visually identifying ^{18}F-FDG uptake. Assessment of uptake in regional lymph nodes also will be performed by visual inspection. New sites of confirmed^{18}F-FDG PET/CT activity at 3-months post therapy will be classified as progressive metabolic disease. Local institution nuclear medicine reports should be submitted (section 12.1). Dr. Jean Lee and local institution investigators will resolve discrepancies by teleconference.

15.8 Semi-quantitative^{18}F-FDG PET/CT Reporting of Standardized Uptake Value (SUV): Images will be evaluated quantitatively for abnormally increased ^{18}F-FDG uptake in the primary tumor by measurement of the maximum standardized uptake value normalized for body mass (SUV_{max}). As a second metric, SUV normalized by lean body mass (SUL) will be calculated. On the baseline, 3-month scans, the SUV_{max} and SUL within the primary cancer will be recorded. The PET/CT Form recording this data must accompany pre-therapy and 3-month data submissions. As a secondary analysis, an ^{18}F-FDG PET/CT post therapy: pre-therapy SUV_{max} ratio will be calculated. Ratios greater than 1.25 will be classified as progressive metabolic disease. Ratios of 0.76 to 1.25 will be classified as stable metabolic disease. Ratios of 0.34 to 0.75 will be considered partial metabolic response. Ratios lower than 0.33 will be marked as complete metabolic response. Ratios indistinguishable from cardiac or liver blood pool activity because of complete resolution of tumor ^{18}F-FDG uptake (i.e., a cervix indistinguishable from surrounding normal tissue on post therapy imaging) will be labeled also as quantitative metabolic complete response.

15.9 Evaluation of ^{18}F-FDG PET CT Target (9, 10):

Complete Response (CR): A metabolic complete response on PET/CT will be defined as greater than -66% reduction in tumor FDG uptake at sites of abnormal tumor FDG uptake noted on pre-treatment FDG-PET study (considering normal cardiac or liver blood pool).

Partial Response (PR): A metabolic partial response on PET/CT will be defined as -25% to -66% reduction in tumor FDG uptake at sites of abnormal tumor FDG uptake noted on pre-treatment FDG-PET study (considering normal cardiac or liver blood pool).

Progressive Disease (PD): Progressive metabolic disease on PET/CT is classified as an increase in tumor FDG uptake greater than +25% within the tumor region defined on baseline scan (considering normal cardiac or liver blood pool), or appearance of new FDG uptake in new metastatic lesions.

Stable Disease (SD): Stable metabolic response will be defined as a change in tumor FDG uptake by less than +25% (increase) or by less than -25%

(decrease) at sites of abnormal tumor FDG uptake (considering normal cardiac or liver blood pool) when compared to pre-treatment FDG-PET study.

Patients with a global deterioration of health status requiring discontinuation of treatment or die without objective evidence of disease progression at that time should be reported to be off study treatment due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

15.9.1 Duration of Response

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

16.0 REFERENCES

Agresti A. A survey of exact inference for contingency tables. Statistical Science. 1992; 7: 131-177.

Balter J, Benedict S, Bissonnette J-P, al e. The role of in-room kV x-ray imaging for patient setup and target localization. . AAPM.Task Group Report No. 104.

Baxter NN, Habermann EB, Tepper JE, Durham SB, Virnig BA. Risk of pelvic fractures in older women following pelvic irradiation. *JAMA* 2005;294:2587-93.

Begg CB. Ruminations on the intent-to-treat principle. Controlled Clinical Trials. 2000; 21:241-243.

Cantor A. Power calculation for the log rank test using historical data. Controlled Clinical Trials. 1996;17(2):11-116.

Cantor A. Extending SAS Survival Analysis Techniques for Medical Research. Vol. 103. SAS Institute Inc. Cary, NC; 1997.

Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. J Clin Oncol. 11(3):570-9, 1993.

Collett D. Survival data in medical research. Boca Raton: Chapman & Hall; 2003.

Cox D. Regression models and life tables (with discussion). J R Stat Soc. 1972;34(Series B):187-220.

Duenas-Gonzalez A, Cetina-Perez L, Lopez-Graniel C, Gonzalez-Enciso A, Gomez-Gonzalez E, Rivera-Ruby L, et al. Pathologic response and toxicity assessment of chemoradiotherapy with cisplatin versus cisplatin plus gemcitabine in cervical cancer: a randomized phase II study. Int J Radiat Oncol Biol Phys. 2005;61(3):817-23.

Duenas-Gonzalez A, Zarba J, Patel F, Alcedo J, Beslija F, Casanova L, et al. A phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. J Clin Oncol. 2011;29(13):1678-85.

East 6, version 6.4, Cytel Inc., www.cytel.com.

Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of

radiation therapy oncology group trial (RTOG) 90-01. J Clin Oncol. 2004;22:872-880.

Elicin O, Callaway S, Prior JO, Bourhis J, Ozsahin M, Herrera FG. [(18)F]FDG-PET standard uptake value as a metabolic predictor of bone marrow response to radiation: impact on acute and late hematological toxicity in cervical cancer patients treated with chemoradiation therapy. Int J Radiat Oncol Biol Phys. 2014;90(5):1099-107.

Gieser PW, Chang MN, Rao PV, Shuster JJ, Pullen J. Modelling cure rates using the Gompertz model with covariate information. Statistics in Medicine. 1998;17: 831-839.

Glasziou PP, Simes RJ, Gelber RD. Quality adjusted survival analysis. Stat Med. 1990;9(11):1259-76.

Green JA, Kirwan JM, Tierney JF, Symonds P, Fresco L, Collingwood M, Williams CJ. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. Lancet. 2011; 358: 781-86.

Hintze, J. 2008. PASS 2008. NCSS, LLC. Kaysville, Utah. www.ncss.com

Kaplan E, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457-81.

Kidd E, Siegel B, Dehdashti F, al e. Clinical outcomes of definitive intensity-modulated radiation therapy with fluorodeoxyglucose-positron emission tomography simulation in patients with locally advanced cervical cancer. Int J Radiat Oncol Biol Phys. 2010;77:1085-91.

Klopp A, Moughan J, Portelance L, Miller B, Salehpour M, D'Souza D, et al. Hematologic toxicity on RTOG 0418: A phase II study of post-operative IMRT for gynecologic cancer. Int J Radiat Oncol Biol Phys. 2010:S121: 258.

Korfage IJ, Essink-Bot ML, Mols F, van de Poll-Franse L, Kruitwagen R, van Ballegooijen M. Health-related quality of life in cervical cancer survivors: a population-based survey. Int J Radiat Oncol Biol Phys. 2009;73:1501-1509.

Kunos C, Chiu S, Pink J, Kinsella T. Modulating radiation resistance by inhibiting ribonucleotide reductase in cancers with virally or mutationally silenced p53 protein. Radiation Res. 2009;172(6):666-76.

Kunos C, Ferris G, Pyatka N, Pink J, Radivoyevitch T. Deoxynucleoside salvage facilitates DNA repair during ribonucleotide reductase blockade in human cervical cancers. Radiat Res. 2011;176(4):425-33.

Kunos C, Radivoyevitch T, Abdul-Karim F, Faulhaber P. 18F-fluoro-2-deoxy-d-glucose positron emission tomography standard uptake value as an indicator of cervical cancer chemoradiation therapeutic response. Int J Gynecol Cancer. 2011;21(6):1117-23.

Kunos C, Radivoyevitch T, Ingalls S, Hoppel C. Management of 3-aminopyridine-2-carboxaldehyde thiosemicarbazone induced methemoglobinemia. Future Oncol. 2012;8(2):145-50.

Kunos C, Radivoyevitch T, Pink J, Chiu S, Stefan T, Jaccobberger J, et al. Ribonucleotide reductase inhibition enhances chemoradiosensitivity of human cervical cancers. Radiation Res. 2010;174(5):574-81.

Kunos C, Radivoyevitch T, Waggoner S, DeBernardo R, Zanotti K, Resnick K, et al. Radiochemotherapy plus 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP, NSC #663249) in advanced-stage cervical and vaginal cancers. Gynecol Oncol. 2013;130(1):75-80.

Kunos C, Sherertz TM. Long-Term Disease Control with Triapine-Based Radiochemotherapy for Patients with Stage IB2-IIIB Cervical Cancer. Front Oncol. 2014;4:184.

Kunos C, Tian C, Waggoner S, Rose PG, Lanciano R. Retrospective analysis of concomitant Cisplatin during radiation in patients aged 55 years or older for treatment of advanced cervical cancer: a gynecologic oncology group study. Int J Gynecol Cancer. 2009;19:1258-1263.

Kunos C, Waggoner S, Von Gruenigen V, Eldermire E, Pink J, Dowlati A, et al. Phase I trial of intravenous 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (3-AP, NSC #663249) in combination with pelvic radiation therapy and weekly cisplatin chemotherapy for locally advanced cervical cancer. Clin Cancer Res. 2010;16(4):1298-306.

Lachin JM. Statistical considerations in the intent-to-treat principle. Controlled Clinical Trials. 2000; 21:167-189.

Lakatos, Edward. 2002. 'Designing Complex Group Sequential Survival Trials', Statistics in Medicine, Volume 21, pages 1969-1989.

Lakatos, Edward. 1988. 'Sample Sizes Based on the Log-Rank Statistic in Complex Clinical Trials', Biometrics, Volume 44, March, pages 229-241.

Lan KKG and DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983; 70: 659 – 663.

Li N, Noticewala SS, Williamson CW, Shen H, Sirak I, Tarnawski R, Mahantshetty U, Hoh CK, Moore KL, Mell LK. Feasibility of atlas-based active bone marrow sparing intensity modulated radiation therapy for cervical cancer. Radiother Oncol. 2017;123(2):325-330.

Liang Y, Bydder M, Yashar CM, Rose BS, Cornell M, Hoh CK, Lawson JD, Einck J, Saenz C, Fanta P, Mundt AJ, Bydder GM, Mell LK. Prospective study of functional bone marrow-sparing intensity modulated radiation therapy with concurrent chemotherapy for pelvic malignancies. Int J Radiat Oncol Biol Phys. 2013;85(2):406-14.

Lim K, Small WJ, Portelance L, Creutzberg C, Jurgenliemk-Schulz M, Mundt A, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer. Int J Radiat Oncol Biol Phys. 2011;79(2):348-55.

Mehta CR, Patel NR. Exact logistic regression: theory and examples. Stat in Med. 1995;14:2143-2160.

Moore KL, Brame RS, Low DA, Mutic S. Experience-based quality control of clinical intensity-modulated radiotherapy planning. Int J Radiat Oncol Biol Phys. 2011 Oct 1;81(2):545-51.

Noticewala SS, Li N, Williamson CW, Hoh CK, Shen H, McHale MT, Saenz CC, Einck J, Plaxe S, Vaida F, Yashar CM, Mell LK. Longitudinal Changes in Active Bone Marrow for Cervical Cancer Patients Treated With Concurrent Chemoradiation Therapy. Int J Radiat Oncol Biol Phys. 2017;97(4):797-805.

Park SY, Bae DS, Nam JH, et al. Quality of life and sexual problems in disease-free survivors of cervical cancer compared with the general population. Cancer. 2007; 110: 2716-2725.

Pocock SJ, Simon. R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics.* 1975; 31:103-115.

Rose BS, Aydogan B, Liang Y, et al. Normal tissue complication probability modeling of acute hematologic toxicity in cervical cancer patients treated with chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2011;79(3):800-7.

Rose BS, Liang Y, Lau SK, et al. Correlation between radiation dose to ^{18}F-FDG-PET defined active bone marrow subregions and acute hematologic toxicity in cervical cancer patients treated with chemoradiotherapy. Int J Radiat Oncol Biol Phys. 2012;83(4):1185-91.

Rose PG, Degeest K, McMeekin S, Fusco N. A phase I study of gemcitabine followed by cisplatin concurrent with whole pelvic radiation therapy in locally advanced cervical cancer: a Gynecologic Oncology Group study. Gynecol Oncol. 2007;107(2):274-9.

Schoenfeld D, Richter J. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. Biomettrics. 1982;38(1):8.

Schwartz J, Siegel B, Dehdashti F, Grigsby P. Association of post-therapy positron emission tomography with tumor response and survival in cervical carcinoma. JAMA. 2007;298(19):2289-95.

Shankar L, Hoffman J, Bacharach S, Graham M, Karp J, Lammertsma A, et al. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. J Nucl Med. 2006;47(6):1059-66.

Simpson DR, Song WY, Moiseenko V, Rose BS, Yashar CM, Mundt AJ, et al. Normal tissue complication probability analysis of acute gastrointestinal toxicity in cervical cancer patients undergoing intensity modulated radiation therapy and concurrent cisplatin. Int J Radiat Oncol Biol Phys. 2012;83(1):e81-6.

Small W, Jr., Mell LK, Anderson P, Creutzberg C, De Los Santos J, Gaffney D, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer. Int J Radiat Oncol Biol Phys. 2008;71(2):428-34.

Spencer JA, Ferraro F, Roussakis E, et al. Direct measurement of local oxygen concentration in the bone marrow of live animals. Nature. 2014;508(7495):269-73.

Swisher EM, Swensen RE, Greer B, Tamimi H, Goff BA, Garcia R, et al. Weekly gemcitabine and cisplatin in combination with pelvic radiation in the primary therapy of cervical cancer: a phase I trial of the Puget Sound Oncology Consortium. Gynecol Oncol. 2006;101(3):429-35.

Young H, Baum R, Cremerius U, Herholz K, Hoekstra O, Lammertsma A, et al. Measurement of clinical and subclinical tumor response using 18F-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. Eur J Cancer. 1999;35(13):1771-82.

Yuan YC. Multiple Imputation for Missing Data: Concepts and New Developments. Rockville, MD: SAS Institute; 2002.

APPENDIX I - COLLABORATIVE AGREEMENT

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

APPENDIX II

APPEI ORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.