NRG ONCOLOGY
RTOG 1216

RANDOMIZED PHASE II/III TRIAL OF SURGERY AND POSTOPERATIVE RADIATION DELIVERED WITH CONCURRENT CISPLATIN VERSUS DOCETAXEL VERSUS DOCETAXEL AND CETUXIMAB FOR HIGH-RISK SQUAMOUS CELL CANCER OF THE HEAD AND NECK

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology, ECOG-ACRIN Medical Research Foundation, Inc., and SWOG.

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Protocol Agents

Agent	Supply	NSC #	IND #
Cisplatin	Commercial	N/A	Exempt
Docetaxel	Commercial	N/A	Exempt
Cetuximab	Commercial	N/A	Exempt

Participating Sites (2/19/13)

☐ US Only
☐ Canada Only
☒ US and Canada
☒ Approved International Member Sites

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CANCER TRIALS SUPPORT UNIT (CTSU) CONTACT INFORMATION (3/5/15)		
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CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	See Sections 5.0 and 5.5 for instructions for the Oncology Patient Enrollment Network (OPEN). Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com	Submit study data to: NRG Oncology 1818 Market Street, Suite 1720 Philadelphia, PA 19103 Submit data electronically via the NRG Oncology/RTOG web site, www.rtog.org Do **not** submit study data or forms to CTSU Data Operations. Do **not** copy the CTSU on data submissions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' web site 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.		
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NRG ONCOLOGY

RTOG 1216

Randomized Phase II/III Trial of Surgery and Postoperative Radiation Delivered with Concurrent Cisplatin versus Docetaxel versus Docetaxel and Cetuximab for High-Risk Squamous Cell Cancer of the Head and Neck

SCHEMA (2/20/14)

			Zubrod Performance		
S			**Status**	**S**	
T	**For all**	**S**	1. 0	**T**	**Arm 1:** IMRT 60 Gy in 6 weeks and
E	**patients:**	**T**	2. 1	**E**	cisplatin 40 mg/m^2 weekly x 6 doses
P	Mandatory	**R**		**P**	
1	submission	**A**	**Primary Tumor Site**	**2**	
	of tissue for	**T**	1. Oral Cavity		**Arm 2:** IMRT 60 Gy in 6 weeks and
R	EGFR	**I**	2. Larynx	**R**	weekly docetaxel (15 mg/m^2)
E		**F**	3. Hypopharynx	**A**	x 6 doses
G	**For**	**Y**	4. p16-negative	**N**	
I	**oropharyngeal**		oropharynx	**D**	**Arm 3:** IMRT 60 Gy in 6 weeks and
S	**cancer**			**O**	cetuximab (loading 400 mg/m^2, then
T	**patients:**		**EGFR Expression**	**M**	250 mg/m^2 weekly x 6 doses)
E	Mandatory		1. High	**I**	and docetaxel (15 mg/m^2) weekly
R	p16 analysis		2. Low	**Z**	x 6 doses
			3. Inevaluable	**E**	

NOTE: If the trial proceeds to the phase III component, Arm 2 or Arm 3 will be chosen as the experimental arm. Patients accrued in the phase II component of the trial will complete the treatment to which they are randomized (Arm 1, 2, or 3) and will be followed as specified in the protocol.

Prior to stratification and randomization, **all patients** must consent to submission of tissue for required EGFR analysis; analysis results are expected in approximately 5 business days. At that time, patients with non-oropharyngeal carcinoma can be randomized. In addition, **patients with oropharyngeal carcinoma** must consent to use of the submitted tissue for required HPV analysis by p16 assessment at the same time as the EGFR assessment; analysis results of both EGFR and p16 are expected in approximately 5 business days total. At that time, patients with oropharyngeal carcinoma can be randomized. **See** Section 5.4 **for details of registration/randomization.**

IMRT is mandatory; IGRT is optional. **Margin reduction is not permitted, even when IGRT is used.** RT dose may include an optional integrated boost of 6 Gy for a total dose of 66 Gy/30 fractions.

See next page for Patient Population and Required Sample Size

Patient Population: (See Section 3.0 for Eligibility) **(3/5/15)**
Patients with pathologic stage III or IV head and neck squamous cell carcinoma (HNSCC) involving the oral cavity (excluding lips), oropharynx (p16 negative), larynx, or hypopharynx. Patients must have at least 1 of the following high-risk pathologic features: extracapsular nodal extension or invasive cancer seen at the primary tumor resection margin (tumor on ink).

Required Sample Size: **Randomized Phase II Component: 200**
Phase III Component: 475

ELIGIBILITY CHECKLIST – STEP 1 (3/5/15)
(page 1 of 4)

NRG Oncology Institution #
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Case #

_____ (Y) 1. Did the patient have a histologically proven diagnosis of squamous cell carcinoma (HNSCC) involving the oral cavity (excluding lips), oropharynx (p16 negative), larynx, or hypopharynx?

_____(Y) 2. Was there a gross total surgical resection of high-risk oral cavity, oropharynx (p16 negative) larynx, or hypopharynx within 63 days prior to registration?

_____(Y) 3. Is the tumor pathologic stage III or IV HNSCC?

_____(Y) 4. Does the surgical pathology demonstrate one or more of the following high risk factors?

- Extracapsular nodal extension
- Invasive cancer at the primary tumor resection margin (tumor on ink)

_____(N) 5. Does the patient have distant metastases?

_____(Y) 6. Were the following assessments done within the timeframes specified in Section 3.1: A general H&P by a Radiation Oncology and/or Medical Oncologist, imaging of the head and neck (a neck CT with contrast or CT/PET with contrast and/or an MRI [T1 with Gadolinium and T2] of the neck), and imaging of the chest (a chest CT +/- contrast or CT/PET that included the chest +/- contrast)?

_____(Y) 7. Was an examination by an ENT/Head & Neck Surgeon done prior to surgery?

_____(Y) 8. Was the patient's Zubrod Performance Status 0-1 within 14 days prior to registration?

_____(Y) 9. Is the patient $\geq$ 18 years of age?

_____(Y) 10. Does the patient have adequate bone marrow, hepatic, and renal function as specified in Section 3.1?

_____(Y) 11. Was the patient's Na, K, Cl, glucose, Ca, Mg, and albumin levels assessed as required within 14 days prior to the start of registration?

_____(Y) 12. For women of childbearing potential, was a urine or serum pregnancy test completed within 14 days of registration?

_____(Y) If yes, was the pregnancy test negative?

___(Y/NA) 13. If a woman of child bearing potential or sexually active male, is the patient willing to use effective contraception while on treatment?

_____(Y) 14. Did the patient provide study specific informed consent prior to study entry including consent for mandatory tissue submission for EGFR analysis and for oropharyngeal patients, HPV analysis?

_____(N/Y) 15. Did the patient have a prior invasive malignancy?

_____(Y) If yes, is the prior malignancy within the parameters specified in Section 3.2?

Continued on next page

NRG Oncology Institution #
RTOG 1216
Case #

_____(N) 16. Does the patient have simultaneous primaries or bilateral tumors, with the exception of patients with bilateral tonsil cancers or patients with T1-2, N0, M0 resected differential thyroid carcinoma?

_____(N) 17. Did the patient have previous systemic chemotherapy or anti-EGF therapy for the study cancer?

_____(N) 18. Did the patient have previous irradiation to the head and neck that would result in overlap in radiation fields?

_____(N) 19. Does the patient have severe, active co-morbidity, as defined in Section 3.2?

_____(N) 20. Does the patient have grade 3-4 (CTCAE, v. 4) electrolyte abnormalities as specified in Section 3.2?

_____(N) 21. Does the patient have a prior history of allergic reaction to cetuximab?

_____(Y) 22. Did the patient consent to complete the MDASI-HN at the required time points detailed in Section 4.0?

The following questions will be asked at Study Registration:
CREDENTIALING FOR IMRT IS REQUIRED BEFORE REGISTRATION.

_____ 1. Institutional person randomizing case.

_____(Y) 2. Has the Eligibility Checklist been completed?

_____(Y) 3. In the opinion of the investigator, is the patient eligible?

_____ 4. Date informed consent signed

_____ 5. Patient's Initials (Last First Middle)

_____ 6. Verifying Physician

_____ 7. Patient ID

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

_____ 13. Zip Code (U.S. Residents)

Continued on next page

NRG Oncology Institution #
RTOG 1216
Case #

_____ 14. Method of Payment

_____ 15. Any care at a VA or Military Hospital?

_____ 16. Calendar Base Date

_____ 17. Registration date

_____ 18. Medical oncologist's name

_____(Y/N) 19. Have you obtained the patient's consent for his or her tissue to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 20. Have you obtained the patient's consent for his or her blood to be kept for use in research to learn about, prevent, treat, or cure cancer?

_____(Y/N) 21. Have you obtained the patient's consent for his or her tissue to be kept for use in research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease)?

_____(Y/N) 22. Have you obtained the patient's consent for his or her blood to be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

_____(Y/N) 23. Have you obtained the patient's consent to allow someone from this institution to contact him or her in the future to take part in more research?

_____ 24. Zubrod Performance Status (specify 0 vs. 1)

_____(Y/N) 25. Does the patient have an oropharynx primary?

_____ 26. Disease Type (specify oral cavity vs. larynx vs. hypopharynx vs. oropharynx p16-)

The Eligibility Checklist must be completed in its entirety prior to web registration. The completed, signed, and dated checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/NRG Oncology audit.

Completed by _____ Date _____

ELIGIBILITY CHECKLIST – STEP 2 (2/19/13)
(page 4 of 4)

NRG Oncology Institution #
RTOG 1216
Case #

_____ 1. Institutional person randomizing case

_____(Y/N) 2. Is the patient able to continue protocol treatment?

_____ 3. If no, specify the reason the patient cannot continue to Step 2:
1) progression of disease;
2) patient is p16 positive;
3) patient is p16 not evaluable;
4) patient refusal;
5) physician preference;
6) failure to submit tissue assay;
7) other

_____ Specify the reason the patient cannot continue to Step 2.

_____ 4. Patient's Initials

_____ 5. Verifying Physician

_____ 6. Patient ID

_____ 7. Calendar Base Date (for Step 2)

_____ 8. Randomization date: (for Step 2)

_____(Y/N) 9. Did the patient agree to participate in the quality of life component?

_____ If no, provide reason:
1. Patient refused due to illness
2. Patient refused for other reason: specify _____
3. Not approved by institutional IRB
4. Tool not available in patient's language
5. Other reason: specify_____

Completed by _____ Date _____

1.0 INTRODUCTION

1.1 Rationale for Selected Approach and Trial Design

Approximately 50% of head and neck cancer patients undergo primary surgery in the treatment of their malignancy. For patients with advanced local-regional disease with high-risk features, recurrence rates following surgery alone are high and therefore, postoperative treatment strategies have been actively investigated for several decades. RTOG 95-01 and EORTC 22931 randomized high-risk postoperative head and neck cancer patients to receive radiation alone or radiation in combination with cisplatin chemotherapy (Bernier 2004; Cooper 2004). These 2 randomized trials yielded positive results for their respective endpoints. The EORTC trial enrolled 334 patients and identified a benefit in local-regional disease control, disease-free survival (primary endpoint), and overall survival for patients receiving cisplatin chemotherapy concurrent with radiation. The RTOG trial enrolled 459 patients and identified a benefit in local-regional disease control (primary endpoint) but not overall survival with the addition of cisplatin. Both trials confirmed greater acute and overall toxicity with the addition of cisplatin chemotherapy. In a combined data analysis of these important trials, patients most likely to benefit from the addition of cisplatin chemotherapy to radiation were highlighted and included those with positive resection margins and/or extracapsular tumor extension in regional lymph nodes (Bernier 2005).

One promising strategy involves the incorporation of molecular targeting agents such as the EGFR inhibitor, cetuximab, since the EGFR is richly overexpressed by the majority of head and neck cancers. With phase III trial data confirming an improved survival outcome when combining radiation with cetuximab in the definitive treatment setting (Bonner 2006), the rationale to examine the impact of radiation combined with cetuximab in the postoperative setting has been pursued.

This provided the background for RTOG 0234 that enrolled 238 high-risk head and neck cancer patients in a randomized phase II trial to examine the feasibility and safety of delivering postoperative radiation combined with cetuximab plus either weekly cisplatin or docetaxel chemotherapy. This trial enrolled 238 patients and confirmed the feasibility and safety of this treatment approach as summarized further below (Harari 2007, Kies 2009). With the median follow up of 4.4 years, the cetuximab-docetaxel arm, “B”) compared favorably with the cetuximab-cisplatin arm with regard to overall compliance to radiation and chemotherapy (81.5% vs. 67.9%), 2-year disease-free survival (DFS: 66% (95% CI 56, 75) vs. 57% (47, 67)) and 2-year overall survival (79% (71, 87) vs. 69% (60, 79). When DFS was compared to historical control (the RTOG 95-01 chemoradiation arm) the hazard ratio was 0.76 for cetuximab-cisplatin vs. control, while it was 0.69 for cetuximab-docetaxel vs. control (p=0.012). The improvements appear to be largely due to an improvement in distant control with docetaxel-cetuximab [2-yr distant metastasis rates 13% (7, 20) vs. 26% (17, 35) in RTOG 95-01 (Please see appended abstracts 2007, 2009 for additional details).

1.1.1 RTOG 0234 and RTOG 0522: Preclinical Data Observations

Human tumor xenograft studies indicate that cetuximab is more effective in enhancing radiation + docetaxel combinations than radiation + platinum (see Figure 1 below). In addition, the data suggests that the addition of cetuximab substantially increases tumor growth delay in at least 2 xenograft models (Nakata 2004). The lack of cetuximab enhancement of a platinum compound may be explained by recent data indicating a novel mechanism of action for EGFR triggered by radiation. Unlike signaling induced by the EGF ligand, which only ignites cytoplasmic transduction, radiation triggers EGFR translocation into the nucleus. This process is accompanied by a nuclear influx of Ku70/80, an increase in nuclear DNA-PK activity, and formation of DNA end-binding complexes, which play a dominant role in repairing double-strand breaks through non-homologous end-joining. EGFR blockade by cetuximab abolished nuclear EGFR import, activation of DNA-PK, inhibited DNA repair, and enhanced cellular radiation sensitivity (Dittmann 2005). Since both cetuximab and platinum enhance the effect of radiation therapy by a similar mechanism of action, i.e. inhibition of radiation-induced DNA double strand break repair, their combination may not be expected to be better than the individual agents alone when combined concurrently with radiation. In other words, tumors that are resistant to platinum-mediated radiation sensitization are likely proficient in repairing DNA damage, and hence, circumvent the

effect of cetuximab. This could explain the results observed in RTOG 0522 and the lower DFS for the cetuximab-cisplatin arm in RTOG-0234. In contrast, because docetaxel and cetuximab enhance radiation cell kill via non-overlapping mechanisms, the combination may prove better than individual agent alone when combined with radiation, as suggested by the preclinical data (see Figure 1 below).

These preclinical and clinical data support the next proposed step which is a phase III randomized trial comparing weekly cisplatin to the weekly docetaxel-cetuximab combination delivered concurrently with radiation in postoperative patients with high-risk squamous cell carcinoma of the head and neck.

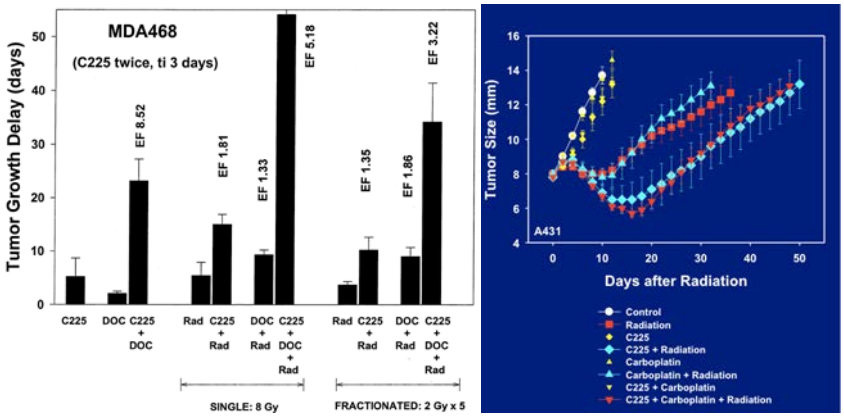

Figure 1:
Left: Tumor growth delay study showing that radiation therapy (RT) + cetuximab + docetaxel resulted in more than doubling or tripling of tumor growth delay compared with RT+ docetaxel or RT+ cetuximab alone.

Right: Tumor growth curve showing that the addition of carboplatin to cetuximab and radiation (solid red triangle) was not better than cetuximab and radiation (blue diamond)

1.2 Rationale for the Docetaxel-Alone Arm in the Phase II Component

Taxanes are active drugs against head and neck squamous cell carcinoma (HNSCC) and are potent radiosensitizers. Phase III randomized studies have shown that the addition of either paclitaxel or docetaxel to induction cisplatin/5-FU chemotherapy (TPF) yielded superior overall survival to PF alone in patients with locally advanced HNSCC (Posner 2007; Vermorken 2007). Small phase I-II studies have suggested that docetaxel monotherapy can be feasibly administered concurrently with radiation and yielded promising early results (Tischler 2006; Kovacs 2005). Probably most relevant to the proposal is a German phase II study, in which 94 patients with locally advanced HNSCC received neoadjuvant intra-arterial cisplatin chemotherapy, followed by surgical resection, followed by postoperative concurrent radiation therapy and weekly docetaxel (20-30 mg/m^2) (Kovacs 2005). They found that the dose above 25 mg/m^2 was not well tolerated due to the high incidence of grade 3-4 mucositis. In the study, the estimated 5-year survival was 83% for stage III patients and 59% for stage IV patients. Although the authors considered the maximal tolerated dose (MTD) for this regimen to be 25 mg/m^2, only half of the patients received all 5 scheduled cycles. Tischler and colleagues tested 4 weekly doses of 20 vs. 25 mg/m^2 docetaxel given concurrently with radiation after induction TPF in a group of patients with locally advanced HNSCC. They noted that the median duration of PEG dependence was much longer in the patients treated in the higher dose group, and virtually all patients developed grade 3-4 mucositis acutely. Because we hope to maximize the radiosensitizing effect of docetaxel, we propose lowering the weekly dose to 15 mg/m^2 and delivering this dose 6 times during the radiation course. We know that this schedule is feasible based on RTOG 0234 in which the compliance rate was high with 15 mg/m^2 given concurrently with weekly cetuximab.

1.3 Importance of This Trial

The proposed randomized phase II-III trial will address several important issues in head and neck cancer. Approximately 50% of head and neck cancer patients undergo primary surgery for their malignancy. For those with high-risk clinical and pathologic features (eg bone destruction, extracapsular nodal extension, tumor involving resection margins) [Peters 1993; Ang 2001; Bernier 2005), the local-regional failure rates remain high and efforts to reduce recurrence include the use of postoperative radiation, and more recently, postoperative chemoradiation. The beneficial impact of adding cisplatin chemotherapy to radiation in the high-risk setting is modest and is accompanied by significant incremental toxicity (including ototoxicity, nephrotoxicity, neutropenia, nausea, and other). A substantial cohort of head and neck cancer patients do not tolerate and cannot successfully complete the regimen of 100 mg/m^2 cisplatin every 3 weeks during radiation. Meanwhile, the RTOG has conducted several phase II studies testing the optimal regimen delivered with radiation in the postoperative setting and have identified the docetaxel-cetuximab regimen as the most promising to date.

This study will therefore address the question whether docetaxel alone is as active as docetaxel and cetuximab combination and whether either taxane-based regimen is better than cisplatin monotherapy given to this high-risk group of patients with concurrent radiation. The less toxic weekly cisplatin regimen is selected to enhance compliance in the control arm and to parallel to weekly regimen proposed for the 2 experimental arms. If positive, this study will provide a new standard of care with a non-cisplatin regimen for patients with high-risk head and neck squamous cell carcinoma in the postop setting.

1.4 Translational Research (3/5/15)

Note: The following correlative studies are proposed as outlined below; however, these proposed studies require the results of the parent study. Specifically, the number of events for the 2 clinical endpoints, DFS and OS, which are necessary to carry out a realistic statistical power justification cannot be ascertained until the parent study is completed. Therefore, no marker assays will be conducted (i.e., ERCC1, p53, and EGFR for correlative studies) on the collected specimens other than those required for patient stratification (i.e., p16, EGFR). When sufficient information is available from the parent study, a full correlative study document for the marker studies will be submitted to and reviewed by CTEP.

This trial enrolls advanced stage head and neck cancer patients who are treated with primary surgical resection. This affords a critical opportunity to collect valuable tissue specimens for correlative biomarker analyses to test specific hypotheses. The proposed correlative studies for the proposed trial will assist in the development of tissue-based biomarkers to identify patients who would benefit from each treatment regimen and those who are at high risk for relapse for future treatment intensification.

We plan to: 1) Utilize archival formalin fixed paraffin embedded (FFPE) tumor tissues (either as tumor blocks, tumor cores or tumor section) that are collected at the time of surgical resection to construct tissue microarrays (TMAs) and for p53 mutational analysis; and 2) obtain plasma and serum samples from all participating patients prior to starting radiation (RT). Since the blood samples will be obtained after removal of all gross disease, they are unlikely to provide useful biomarkers for prognosis. However, they will be important for addressing future questions on normal tissue toxicity, once such markers are identified from other studies.

1.4.1 Nuclear EGFR Protein Localization and Src Family Kinase (SFK) Expression

The specific aim is to correlate protein expression of nuclear/total EGFR and SFK to treatment outcome (disease-free and overall survival) in all patients treated on this trial to determine whether their expression can predict for treatment resistance in the RT/docetaxel/cetuximab arm as compared to the other 2 arms.

The EGFR is a ubiquitously expressed receptor tyrosine kinase (RTK) involved in the growth and behavior of many human cancers. Following ligand binding, the membrane bound EGFR initiates

a spectrum of signaling pathways that promote cell proliferation, differentiation, migration, motility, and cellular adhesion. Accumulating evidence over the last decade has revealed a second and less appreciated EGFR pathway: the nuclear EGFR signaling pathway. This pathway is characterized by EGFR shuttling from the membrane to the nucleus where it functions as a transcriptional co-factor to regulate genes including Cyclin D1 (Lin 2001); iNOS (Lo 2005); B-myb (Hanada 2006); Aurora Kinase A (Hung 2008); and COX2 (Lo 2020). Furthermore, high nuclear EGFR levels correlate with poor clinical outcome in patients with breast cancer, oropharyngeal SCC, and ovarian cancer. Promising new data from the laboratory of Dr. Deric Wheeler at the University of Wisconsin has implicated the nuclear EGFR signaling network in resistance to cetuximab therapy (Li 2009). These findings suggest that nuclear EGFR may play an important role not only in the progression of human cancers but also their response to EGFR targeting agents.

To examine mechanisms of acquired resistance to cetuximab, Dr. Wheeler's group has developed a model of cetuximab-resistant cancer cell lines (HNSCC1 and NCI-H226) [Li 2009; Li 2010; Wheeler 2009]. During studies to elucidate molecular mechanisms, they found that cells with resistance to cetuximab exhibited: 1) increased SFK activity; 2) enhanced binding/cooperation between SFKs and EGFR; and 3) increased nuclear expression of EGFR. In addition, treatment of cells with acquired resistance to cetuximab with the SFK inhibitor dasatinib leads to loss of nuclear EGFR, decreased cyclin D1 and B-Myb expression, and subsequent re-sensitization to cetuximab therapy. Furthermore, screening a battery of non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), and colorectal cancer (CRC) lines indicated nuclear expression of EGFR strongly correlated with intrinsic resistance to cetuximab. Based on these findings, we would like to collaborate with the Wheeler group to investigate the nuclear EGFR and SFK levels in human tumor samples and correlate them to treatment outcomes using tissue from this clinical trial. Please see "Methods" section below for details.

1.4.2 ERCC1 Expression

The specific aim is to correlate ERCC1 nuclear protein expression to treatment outcomes (disease-free and overall survival) in all patients treated on this trial to determine whether it can predict for treatment resistance to cisplatin.

DNA repair mechanisms are important for tumor resistance to cisplatin. A major component of cisplatin cytotoxicity is the formation of platinum-DNA adducts, which can covalently cross-link DNA strands and inhibit DNA replication. The activity of ERCC1 protein (Excision repair cross-complementation group 1), which plays a critical role in the nucleotide excision repair (NER) pathway, has been shown to be important for the development of cisplatin resistance. Lower levels of ERCC1 have been associated with cisplatin resistance in several solid tumor cell lines (Altara 2004). The role of ERCC1 as a clinical marker for platinum resistance has recently been confirmed in a large study of patients treated with adjuvant platinum-based chemotherapy for early stage NSCLC (Olaussen 2006). In this large study evaluating 761 tumor samples from the IALT trial, investigators showed that lower expression of ERCC1 protein (assessed by IHC staining) was associated with better disease-free and overall survival in patients with early stage NSCLC treated with surgery and adjuvant cisplatin-based chemotherapy but not in those treated with surgery alone. Based on these data, we propose to assess the level of ERCC1 nuclear protein expression and to correlate it with treatment outcome (disease-free and overall survival) in RTOG 1216 patients.

1.4.3 p53 Mutation

The specific aim is to comprehensively analyze tumor p53 mutations using the Amplichip p53 and to correlate certain p53 mutations to progression-free and overall survival for all patients.

p53 mutation is common in HNSCC, present in approximately 40-60% of cases, and has been correlated with poor outcome and poor response to induction chemotherapy (Perrone 2010). In 2007, Poeta, et al. reported on p53 mutations in the largest series of HNSCC patients to date, and showed that mutation in TP53 was associated with decreased overall survival. They went on to show that 'disruptive mutations', a class of p53 point mutations that are predicted to

significantly alter the structure of the DNA-binding domain, were associated with the worst outcome in this patient set (Perrone 2010). Despite evidence that p53 mutation correlates with poor outcome in HNSCC, there is limited data examining the role of p53 mutation in specific subsites of the head and neck, and few studies that have examined the correlation between p53 mutation and response to treatment. Overall, the utility of p53 as a biomarker in HNSCC has not been established. While the prognostic impact of mutant p53 expression has been well substantiated, its role as a predictive marker remains to be further explored, as patients whose tumors bear p53 mutations, particularly disruptive p53 mutations appear to have poor outcomes with most standard therapy. This study offers a unique opportunity to investigate whether this high risk population will have better disease-free and overall survival with postoperative chemoradiotherapy independent of the systemic agent administered.

Methods

Tissue microarrays will be constructed using FFPE HNSCC specimens from patients enrolled in this clinical trial who have archival tissue available. Cores will be 0.6 mm in diameter and arranged 0.2 mm apart vertically and horizontally using the automated TMA array housed at the NRG Oncology Biospecimen Bank. Each specimen will have triplicate cores. Immunofluorescent staining and AQUA analyses will be carried out according to standard procedure (Le 2009); we have had significant experience performing AQUA analysis for several membrane, nuclear, and cytoplasmic proteins. Commercially available antibodies directed against EGFR & SFKs (EGFR: sc-03, Santa Cruz, Total Src: #2108, Cell Signaling, Phospho-SFK - #2101, Cell Signaling) and ERCC1 (FL297; Santa Cruz Biotechnology) will be optimized and used in AQUA analyses of protein expression. The FL297 antibody was chosen over the 8F1 antibody (Thermo Fisher Scientific) for ERCC1 testing because the Maggiocco group has tested both antibodies with AQUA in a group of patients with head and neck squamous cell carcinoma and showed that the FL297 antibody demonstrated better correlation with tumor ERCC1 mRNA expression than the 8F1 antibody and was strongly associated with treatment outcomes in HPV negative tumors treated with cisplatin-based chemotherapy (Hao 2011). Areas of tumor will be labeled using a mouse anti-cytokeratin (AE1/AE3) antibody (Dakocytomation) and visualized using the goat anti-mouse Alexa 555 SFX kit from Invitrogen. The areas of tumor are distinguished from stromal elements by creating a mask from the cytokeratin signal. The DAPI signal within this mask is used to identify tumor nuclei. Automated image acquisition and analysis using AQUA as described previously (Le 2009) will be performed and the levels of cytoplasmic and nuclear EGFR, SFK and ERCC1 will be reported. Since AQUA analysis will generate results as a continuous variable, the results will be analyzed as a dichotomous variable (by the median) as well as on the continuum.

For p53 mutation analysis, 1-2 FFPE slides will be used to extract DNA, which will then be analyzed using a p53 Amplichip as per manufacturer's instructions (Roche Molecular System, Indianapolis, IN). Results will be dichotomized as presence or absence of the mutation.

1.5 Measuring Patient-Reported Outcomes (PROs) and Quality Adjusted Survival

For this trial, all protocol eligible-patients will be asked to participate in the quality of life (QOL) component of this study. In this study, as well as other NRG Oncology studies, baseline QOL is not mandated as part of the pretreatment evaluation. NRG Oncology feels that this allows patients who want to participate in a clinical trial but who do not want to participate in the QOL component to still have access to the trial and its potential benefits.

The QOL data in the phase II portion of the study will assist in evaluating the burden of toxicity from the patient's perspective between the two docetaxel based chemoradiation regimens in conjunction with CTCAE, v. 4 graded toxicity and disease-free survival (DFS), when determining the choice of the docetaxel arm in the phase III portion of the study. If QOL is omitted during the phase II portion, the opportunity to understand the relationships of toxicities between the regimens and their effect on QOL will be lost. In addition, including QOL in the phase II component will make for a larger and more robust dataset for this trial.

1.5.1 Impact of Severity of Acute Mucosal Toxicity on QOL and Prediction for Long-Term Swallowing Dysfunction

The specific aim is to measure patient-reported symptom burden, including mucus, choking/coughing, taste, and mouth/throat sores that may relate to the severity of acute mucositis between cisplatin-based and docetaxel-based chemoradiation and determine whether the severity of patient-reported symptoms relating to mucositis predict for long-term swallowing dysfunction and decreased global QOL.

The quality of survival, in addition to the length of survival, is now accepted by oncologists as an important clinical endpoint in trial design for patients with locally advanced cancers (Burris 1997). While clinician-reported toxicity is able to detect adverse clinical events, PROs are paramount in this regard because they directly measure the patient's perception of symptom burden from the treatment of their disease and its impact on QOL without bias from the clinician (Basch 2009; Bruner 2007; Trotti 2007).

Acute mucositis is a significant acute toxicity during chemoradiotherapy that may cause severe oral pain, adversely affecting the patient's ability to chew and swallow and can cause unplanned treatment interruptions that may impact local control. Furthermore, acute reactions during radiotherapy may lead to significant "consequential" late reactions such as long-term dysphagia. In this study, it is expected that the weekly cisplatin regimen in combination with RT will have improved tolerance and a more favorable toxicity profile than high-dose cisplatin that was used in RTOG 95-01. Similarly, data from the randomized phase II trial, RTOG 0234, (ASTRO abstract 2009) suggest that for patients with high-risk operative staged III or IV non-metastatic HNSCC, RT in combination with docetaxel and cetuximab is associated with improved disease-free survival (DFS) and a more favorable toxicity profile as compared to high-dose, cisplatin-based chemoradiation. However, docetaxel alone with RT has not been studied by NRG Oncology, although Tischler and colleagues have reported higher acute grade 3-4 mucositis and PEG tube dependence with 4 weekly doses of 25 mg/m2 compared to 20 mg/m2 docetaxel given concurrently with RT after induction TPF in a group of patients with locally advanced HNSCC (Tischler, 2006). Higher mucosal toxicity also has been demonstrated in the postoperative setting, by Willey and colleagues (2007); early study termination resulted due to excessive rates of mucosal toxicity with 25 mg/m2 of docetaxel delivered concurrently with postoperative RT.

Since all patients on this study will be receiving IMRT, correlation of dosimetric data from the IMRT plans with QOL data could inform patient care by identifying dosimetric factors that predict the severity of acute symptoms relating to acute mucositis and late effects on swallowing. Standardization of normal tissue constraints for IMRT optimization in the cooperative group setting and prospectively measuring doses to organs at risk, including oral cavity, oropharynx, and mucosal surfaces in the head and neck and correlation with QOL endpoints may inform guidelines for head and neck IMRT normal tissue constraints. Measuring acute mucositis with clinician graded CTCAE, v. 4 alone without patient-reported outcome (PRO) tools may not effectively capture the differences in severity of acute and late symptoms between docetaxel and cisplatin-based chemoradiation on this study. Furthermore, CTCAE toxicity grading alone, may underestimate the symptom burden on patients as it does not evaluate the distress caused by symptoms on the patient secondary to the treatment and disease. If there are differences in QOL relating to the severity of mucositis between docetaxel and cisplatin- based treatment, this could potentially inform differential dose volume constraints of the IMRT plan for normal tissue by chemotherapy regimen for future patient care and also identify which postoperative head and neck cancer subsites are at the most risk. Finally, differences in acute mucosal and long-term swallowing toxicity from these chemoradiation regimens from the patient's perspective may also inform future studies evaluating symptom management trials directed towards ameliorating these symptoms.

Methods

Three instruments will be used to measure PROs and QOL: the Functional Assessment of Cancer Therapy-Head and Neck Cancer (FACT-H&N), version 4; the MD Anderson Symptom

Inventory–Head and Neck (MDASI-HN); and the MD Anderson Dysphagia Inventory-Head and Neck (MDADI-HN).

A combination of these assessments will be completed prior to the start of treatment (baseline), at completion of chemoradiation (allowable 3 weeks before or 6 weeks after this time point), and then at 3 months (allowable 3 weeks before or 6 weeks after this time point), 6, 12 and 24 months (allowable 3 months before or after those time points) from the end of radiation. In addition, to assess acute symptom burden during chemoradiation, patient-reported outcomes will be completed q2 weeks during RT (corresponding to factions 10 (end of week 2), 20 (end of week 4), and 30 or 33 (at completion of RT) using the MDASI-H&N.

The FACT-H&N

The FACT-H&N will be used to measure global QOL and functional decline from the patient's perspective. The FACT-HN is an internationally validated QOL tool that has been used on many prior RTOG head and neck studies. The FACT-H&N is a multidimensional, patient-self report QOL instrument that has been specifically designed and validated for this patient population (List 1996). The questionnaire consists of 27 core items that assess patient function in 4 domains: Physical, Social/Family, Emotional, and Functional well-being, which is further supplemented by 12 site specific items to assess for head and neck related symptoms. Each item is rated on a 0 to 4 Likert type scale, and then combined to produce subscale scores for each domain, as well as a global QOL score; higher scores represent better QOL. The FACT-H&N can be completed by the patient in 5-10 minutes, is available in 26 languages, and will be completed at baseline, completion of RT, and at 1 year from the end of RT.

The MDASI-HN

The MDASI-HN (Rosenthal 2007; Rosenthal 2008; Basch 2009) will be used to measure the symptom burden on each arm from the patient's perspective. The MDASI-HN is a validated 28-item PRO instrument consisting of 3 subscales: 13 relate to the severity of general symptoms associated with the malignancy, 6 interference items assess how severely the symptoms affect activities of daily living, and 9 questions are head and neck specific items which rate the severity of specific symptoms relating to head and neck cancer within the past 24 hours. The questionnaire can be completed by the patient in 5-10 minutes and is available in a 5 languages.

While there are some overlap in questions between the MDASI-HN and FACT-HN (physical domain), when compared to the FACT-H&N, the MDASI-HN showed greater association with severity of radiation-induced mucositis than the FACT-HN on multivariate regression analysis (Rosenthal 2008). Symptoms studied on the MDASI-HN, but not included in the FACT-H&N include patient-reporting of mucus, choking/coughing, taste, mouth/throat sores, symptoms relating to dentition, and constipation. FACT-HN carefully evaluates the impact of head and neck cancer on the patient's social/family, emotional and functional well-being, which are not assessed in the MDASI-HN.

The MDASI will be administered at baseline, every 2 weeks during RT corresponding to fractions 10 (end of week 2), 20 (end of week 4), and 30 or 33(at completion of RT) +/- a 1-week window, and at 3, 6, 12, and 24 months after completion of RT.

In order to minimize participation burden, we will only use both instruments (FACT-HN and MDASI-HN) together at 3 time points (at baseline, end of RT [acute], and as 12 months [late]) to assess acute and late symptom burden (MDASI-HN) and QOL (FACT-HN), the latter which has been used on previous RTOG head and neck studies using high-dose, cisplatin-based chemoradiation.Inclusion of the FACT-HN at these limited time points may allow future cross comparison of QOL outcomes across RTOG head and neck studies and evaluate QOL outcomes between high-dose, cisplatin-based chemoradiation in prior RTOG trials and weekly cisplatin in the control arm and docetaxel-based regimens in the 2 experimental arms of the current study.

The MDADI

The MDADI is a 20-item PRO instrument, scored on a scale from 1 to 5, consisting of global, emotional, functional, and physical subscales. The questionnaire can be completed by the patient in 5-10 minutes and available only in English. The MDADI evaluates the effects of dysphagia on QOL. The MDADI has been validated in head and neck cancer patients in single institutional series (Chen 2001) and also has been used to evaluate patient-reported swallowing outcomes in the postoperative setting. Data from prospective single institutional series (Sinclair 2011) suggest that patients undergoing surgery have an initial decrease in mean scores using the MDADI-HN in the immediate postoperative period, which would correspond to the time of enrollment of this study, although increasing improvement was observed over time. Additionally, global and physical subscales were most affected during the immediate postoperative period with recovery of scores observed at last follow up. In the postoperative setting, advanced tumor stage and the type of surgery +/- reconstruction is significantly associated with decreased QOL scores in the global, physical, functional, and emotional domains (Dwivedi 2011) that may be further affected by adjuvant chemotherapy and radiation.

The MDADI will be administered at baseline and at 3, 6, 12, and 24 months after completion of RT to capture patient-reported changes in QOL relating to swallowing function in this high-risk postoperative population of head and neck cancer patients. We also will compare patient-reported swallowing outcome to objective clinical measures using CTCAE, v.4 clinician-reported toxicity and documenting gastrostomy tube retention rates at each follow-up visit corresponding to the PRO measurements.

1.5.2 Improved Quality-Adjusted Survival

Quality-adjusted survival is an endpoint that incorporates a patient's utility or preference of the health state that is combined with the time spent in that health state. The result is a quality-adjusted life-year (QALY). With the potential survival gains that may be achieved with postoperative treatment intensification for head and neck cancer, the quality of the survivorship also is of increasing importance. The impact of late radiation toxicity on health-related quality of life (HRQOL) was studied by Ramaekers and colleagues (2011) in a cross section survey in head and neck cancer patients who completed head and neck radiotherapy with at least 6 months of follow up and without evidence of disease recurrence. Using the EuroQol (EQ-5D) and correlation with RTOG graded toxicity, the HRQOL was compared between subgroups of patients with treatment-related toxicity, including xerostomia and dysphagia. It was found that patients with xerostomia and/or dysphagia had significantly lower utility and VAS scores on multivariate analysis, although dysphagia was noted to affect the patients' HRQOL more strongly than xerostomia.

If docetaxel-based chemoradiotherapy is found to improve outcome (disease-free or overall survival) compared to cisplatin and radiation, the aim of this study is to determine if differences in late toxicity including dysphagia will impact quality- adjusted survival when compared to the current standard of care regimen of radiation and cisplatin.

Methods

The EuroQol (EQ-5D) is a well-accepted instrument to measure general QOL and cost-utility analysis (Pickard 2007) and will be used to assess quality-adjusted survival for this study. It is a 2-part questionnaire that the patient can complete in 5 minutes (Schulz 2002) and has been translated into multiple languages. The first part consists of 5 items covering 5 dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels including: 1-no problem, 2-moderate problems, and 3-extreme problems. There are 243 potential health states. The second part is a visual analogue scale (VAS) valuing current health state, measured on a 20 cm, 10 point-interval scale. Either the index score or the VAS score can be used in the quality-adjusted survival analysis (Wu 2002). The benefit of measuring quality-adjusted survival is that the product, quality-adjusted survival, can be compared to the outcomes of other interventions across disease sites and can be used by health policy makers to rank interventions. Protocol-eligible patients will be included in the quality-

adjusted survival analysis only if they have provided baseline and at least 1 subsequent measurement. Patients will complete the EQ-5D at the following time points: pretreatment (baseline), at 1 and 2 years after completion of radiation. Quality-adjusted survival is then calculated as the weighted sum of different time in different health states added up to a total quality-adjusted survival time [U=sum of quality (q_i) of health states K times the duration (s_i) spent in each health state,

$$\sum_{i=1}^{k} q_i s_i$$

]. (Glasziou 1990).

2.0 OBJECTIVES

2.1 Randomized Phase II Component Primary Objective

2.1.1 To select the better experimental arm to improve disease-free survival (DFS) over the control arm of radiation and cisplatin

2.2 Phase III Component Primary Objective

2.2.1 To determine whether the selected experimental arm will improve overall survival (OS) over the control arm of radiation and cisplatin

2.3 Randomized Phase II and Phase III Components Secondary Objectives

2.3.1 To improve local-regional disease control;
2.3.2 To compare distant metastasis;
2.3.3 To compare patterns of cancer failure (local, regional, distant) and correlate with radiation dose and technique;
2.3.4 To compare acute toxicity profiles during RT and at completion of treatment;
2.3.5 To compare late toxicity profiles at 1, 3, and 5 years after treatment;
2.3.6 To compare overall quality of life;
2.3.7 To compare patient-reported outcome;
2.3.8 To compare swallowing function at 1 and 2 years;
2.3.9 To investigate associations between acute mucosal toxicity, swallowing function, and QOL;
2.3.10 To compare quality adjusted life years (QALY);
2.3.11 To investigate associations between late toxicity (dysphagia) and QALY;
2.3.12 To determine whether specific molecular profiles are associated with clinical outcomes.

3.0 PATIENT SELECTION (9/2/14)

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED. For questions concerning eligibility, contact the study data manager.

3.1 Conditions for Patient Eligibility (3/5/15)

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of head and neck squamous cell carcinoma (HNSCC) involving the oral cavity (excluding lips), oropharynx (p16 negative), larynx, or hypopharynx;

3.1.2 Patients must have undergone gross total surgical resection of high-risk oral cavity, oropharynx (p16 negative), larynx, or hypopharynx within 63 days prior to registration. **Note**: Patients may have biopsy under general anesthesia in an operating room followed by definitive ablative cancer surgery representing gross total resection. The gross total resection has to be done within 63 days prior to registration. If, however, patients have ablative resection but shortly recur or are determined to have persisting disease requiring re-resection to achieve gross total resection, then the patient is not eligible.

3.1.3 Patients must have at least 1 of the following high-risk pathologic features: extracapsular nodal extension or invasive cancer at the primary tumor resection margin (tumor on ink).

3.1.4 Pathologic stage III or IV HNSCC, including no distant metastases, based upon the following minimum diagnostic workup:

- General history and physical examination by a Radiation Oncologist and/or Medical Oncologist within 84 days prior to registration;
- Examination by an ENT or Head & Neck Surgeon prior to surgery; a laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure), if appropriate, is recommended but not required. Intra-operative examination is acceptable documentation.
- Pre-op Imaging of the head and neck: A neck CT (with contrast) or CT/PET (with contrast) and/or an MRI of the neck (T1 with Gadolinium and T2) within 84 days prior to surgery; **Note**: this imaging data (diagnostic pre-operative scan showing gross disease) is to be submitted in DICOM format via TRIAD. The report is to be uploaded into Rave; see Section 11.2.
- Chest CT scan (with or without contrast) or CT/PET that includes the chest (with or without contrast) either within 84 days prior to surgery or within 120 days prior to registration; **Note**: If the CT/PET with or without contrast is done within 84 days prior to surgery, it fulfills the chest imaging requirement.

3.1.5 Zubrod Performance Status of 0-1 within 14 days prior to registration;

3.1.6 Age ≥ 18;

3.1.7 CBC/differential obtained within 14 days prior to registration on study, with adequate bone marrow function defined as follows:
- Absolute granulocyte count (AGC) ≥ 1,500 cells/mm^3;
- Platelets ≥ 100,000 cells/mm^3;
- Hemoglobin ≥ 8.0 g/dl (**Note**: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable).

3.1.8 Adequate hepatic function, defined as follows:
- Total bilirubin < 2 x institutional ULN within 14 days prior to registration;
- AST or ALT < 3 x institutional ULN within 14 days prior to registration.

3.1.9 Adequate renal function, defined as follows:
- Serum creatinine institutional ULN within 14 days prior to registration or;
  creatinine clearance (CC) ≥ 50 ml/min within 14 days prior to registration determined by 24-hour collection or estimated by Cockcroft-Gault formula:

$$\text{CCr male} = \frac{[(140 - \text{age}) \times (\text{wt in kg})]}{[(\text{Serum Cr mg/dl}) \times (72)]}$$

$$\text{CCr female} = 0.85 \times (\text{CrCl male})$$

3.1.10 Negative urine or serum pregnancy test within 14 days prior to registration for women of childbearing potential;

3.1.11 The following assessments are required within 14 days prior to registration: Na, K, Cl, glucose, Ca, Mg, and albumin. **Note**: Patients with an initial magnesium < 0.5 mmol/L (1.2 mg/dl) may receive corrective magnesium supplementation but should continue to receive either prophylactic weekly infusion of magnesium and/or oral magnesium supplementation (eg, magnesium oxide) at the investigator's discretion.

3.1.12 Patients with feeding tubes are eligible for the study.

3.1.13 Women of childbearing potential and male participants who are sexually active must agree to use a medically effective means of birth control;

3.1.14 Patient must provide study specific informed consent prior to study entry, including consent for mandatory tissue submission for EGFR analysis and for oropharyngeal cancer patients, HPV analysis.

3.2 Conditions for Patient Ineligibility

3.2.1 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 1095 days [3 years]; noninvasive cancers (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible) are permitted even if diagnosed and treated < 3 years ago;

3.2.2 Patients with simultaneous primaries or bilateral tumors are excluded, with the exception of patients with bilateral tonsil cancers or patients with T1-2, N0, M0 resected differentiated thyroid carcinoma, who are eligible.

3.2.3 Prior systemic chemotherapy or anti-EGF therapy for the study cancer; note that prior chemotherapy for a different cancer is allowable;

3.2.4 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;

3.2.5 Severe, active co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within 6 months prior to registration;
- Transmural myocardial infarction within 6 months prior to registration;
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
- Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
- Idiopathic pulmonary fibrosis or other severe interstitial lung disease that requires oxygen therapy or is thought to require oxygen therapy within 1 year prior to registration;
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for coagulation parameters are not required for entry into this protocol.
- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; **note**: HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.

3.2.6 Grade 3-4 electrolyte abnormalities (CTCAE, v. 4):

- Serum calcium (ionized or adjusted for albumin) < 7 mg/dl (1.75 mmol/L) or > 12.5 mg/dl (> 3.1 mmol/L) despite intervention to normalize levels;
- Glucose < 40 mg/dl (< 2.2 mmol/L) or > 250 mg/dl (> 14mmol/L);
- Magnesium < 0.9 mg/dl (< 0.4 mmol/L) or > 3 mg/dl (> 1.23 mmol/L) despite intervention to normalize levels;
- Potassium < 3.5 mmol/L or > 6 mmol/L despite intervention to normalize levels;
- Sodium < 130 mmol/L or > 155 mmol/L despite intervention to normalize levels.

3.2.7 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.8 Prior allergic reaction to cetuximab.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 Required Evaluations/Management

4.1.1 Patients must consent to completing the MDASI-HN (at baseline, every 2 weeks during RT, at completion of RT, and at 3, 6, 12, and 24 months after completion of RT). This instrument is needed as part of the assessment of the primary endpoint of the study.

If the patient consents to participate in the other patient-reported outcomes (PROs) and quality adjusted survival assessments in the study, sites are required to administer the following baseline assessments prior to the start of protocol treatment: the FACT-H&N, the MDADI, and the EQ-5D. See Section 11.4 for details.

4.2 Highly Recommended Evaluations/Management

4.2.1 An audiogram within 84 days (12 weeks) of the start of treatment;

4.2.2 Dental evaluation and if applicable, prophylaxis, within 84 calendar days prior to the start of treatment (see Appendix IV, Dental Management);

4.2.3 Nutritional evaluation for a prophylactic gastrostomy (PEG) tube placement any time prior to the start of treatment;

5.0 REGISTRATION PROCEDURES (9/2/14)

Access requirements for OPEN, Medidata Rave, and TRIAD:
Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user id and password) used for the CTSU members' web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam.

NOTE: FOR THIS STUDY IMRT, IS MANDATORY, AND IGRT IS OPTIONAL (margin reduction is not permitted even when IGRT is used).

5.1 Pre-Registration Requirements for IMRT (3/5/15)

Credentialing is required for IMRT. The IMRT credentialing requires head & neck phantom irradiation. Institutions having previously irradiated this phantom and received approval to proceed with another head & neck trial will not be required to repeat this procedure.

In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information as indicated in the table below. Instructions for completing these requirements or determining if they already have been met are available on the Imaging and Radiation Oncology Core (IROC) Houston web site at http://irochouston.mdanderson.org by selecting "Credentialing".

5.1.1 For detailed information on the specific technology requirement required for this trial, 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 notify the institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study.

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 and Cyberknife treatment delivery modalities must be credentialed individually.
Credentialing Notification Issued to:		
Institution		IROC Houston QA Center will notify the institution and NRG Headquarters that all desired credentialing requirements have been met.

5.2 Digital RT Data Submission to TRIAD (9/25/13)

TRIAD is the American College of Radiology's (ACR) image exchange application and it is used by NRG Oncology. TRIAD provides sites participating in NRG Oncology clinical

trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with The Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to Section 5.0 of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must have been assigned the 'TRIAD site user' role on the relevant Group or CTSU roster. Users should contact your site Lead RA to be added to your site roster. Users from other cooperative groups should follow their procedures for assignment of roster roles.
- RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:
When a user applies for a CTEP-IAM account with proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found on the RTOG/NRG Oncology web site Core lab tab.

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

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

5.3 Regulatory Pre-Registration Requirements (9/2/14)

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

Prior to the recruitment of a patient for this study, investigators must be registered members of a lead protocol organization. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch (PMB), CTEP, DCTD, NCI. These forms are available on the CTSU web site: http://ctep.cancer.gov/investigatorResources/investigator_registration.htm. For questions, please contact the CTEP Investigator Registration Help Desk by e-mail at pmbregpend@ctep.nci.nih.gov

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account. Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.) An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) web sites and applications, including the CTSU members’ web site. Additional information can be found on the CTEP web site at http://ctep.cancer.gov/branches/pmb/associate_registration.htm . For questions, please contact the CTEP Associate Registration Help Desk by email at ctepreghelp@ctep.nci.nih.gov.

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office

before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org . For sites under the CIRB initiative, IRB data will automatically load to RSS.

Site registration forms may be downloaded from the RTOG 1216 protocol page located on the CTSU members' web site. Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password

- Click on the Protocols tab in the upper left of your screen
- Click on the (state organization type e.g. P2C, CITN, NCTN Groupname) link to expand, then select trial protocol, RTOG 1216
- Click on the Site Registration Documents link

Requirements for RTOG 1216 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form (if applicable)

NOTE: Per NCI policy, all institutions that participate on protocols with a radiation therapy component must participate in the IROC Houston monitoring program. If this form has been previously submitted to CTSU, it does not need to be resubmitted unless updates have occurred at the RT facility.

- IRB/REB approval letter
- IRB/REB approved consent (English and native language versions*)

  *Note: Institutions must provide certification of consent translation to NRG Oncology.
- IRB/REB assurance number renewal information, as appropriate
- See the additional pre-registration requirements in Section 5.1.

Non-English Speaking Canadian and Non-North American Participating Sites

*****Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG Oncology will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU web site. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

5.3.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

Prior to clinical trial commencement, Canadian institutions must complete and fax (215-569-0206) or e-mail (**CTSURegulatory@ctsu.coccg.org**) the following Health Canada forms to the CTSU Regulatory Office:

- Clinical Trial Site Information Form
- Qualified Investigator Undertaking Form
- Research Ethics Board Attestation Form

5.3.3 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS

- ***For institutions that do not have an approved LOI for this protocol*:**
  International sites must receive written approval of submitted LOI forms from NRG Oncology prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/Researchers/InternationalMembers.aspx .
- ***For institutions that have an approved LOI for this protocol*:**
  All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.4 Registration (3/5/15)

5.4.1 Summary of Procedures

This study incorporates a two-step registration process.

All patients must consent to submission of tissue for EGFR analysis; see Section 10.0 for details of submission. **Oropharyngeal carcinoma patients** also must consent to submit tissue for HPV analysis; see Section 10.0 for details of submission. All patients can be registered after completing the Eligibility Checklist, STEP 1 via online registration; see the text below for online registration instructions.

Institutions must submit the required tissue block for EGFR analysis to the NRG Oncology Biospecimen Bank (see Section 10.0 for shipping information), using the case number obtained from STEP 1 registration. The Biospecimen Bank will determine the adequacy of the tissue, and the Pathology Co-Chair, Richard Jordan, DDS, PhD will do the EGFR analysis. The results of EGFR analysis are expected in approximately 5 business days, and NRG Oncology will inform sites by e-mail of the completion of the EGFR analysis. At this point, **non-oropharyngeal carcinoma patients** may be randomized; sites must complete the Eligibility Checklist, STEP 2 via online registration. **Note: EGFR analysis must be performed for all patients before proceeding to STEP 2.**

For patients with oropharyngeal carcinoma: the Biospecimen Bank will process 4 unstained slides from the tissue block submitted (also submitted for EGFR analysis), and the Pathology Co-Chair, Richard Jordan, DDS, PhD will perform the p16 analysis. The results of the EGFR assessment and p16 analysis are expected in approximately 5 business days total, and NRG Oncology will inform sites by e-mail of the completion of the HPV analysis. At this point, oropharyngeal carcinoma patients may be randomized; sites must complete the Eligibility Checklist, STEP 2 via online registration.

Physicians or institutions can request the patient's EGFR level and/or HPV status from NRG Oncology (215-574-3154 or 215-574-3170).

5.4.2 OPEN Registration Instruction

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.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and a 'Registrar' role on either the LPO or participating organization roster. See Section 5.0 for obtaining CTEP-IAM account. All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

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

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

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

5.4.3 In the event that the OPEN system is not accessible, participating sites can contact web support for assistance with web registration: websupport@acr.org or call the Registration Desk at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

6.0 RADIATION THERAPY (9/2/14)

NOTE: FOR THIS STUDY, IMRT IS MANDATORY, and IGRT IS OPTIONAL (Margin reduction is not permitted even when IGRT is used).

Protocol treatment must begin within 14 days after Step 2 registration (randomization).

6.1 Dose Specifications (2/20/14)

The prescribed radiotherapy dose will be 60 Gy in 2 Gy once-daily fraction size (total of 30 fractions).

Radiotherapy should begin on a Monday, Tuesday or Wednesday. The daily dose of 2 Gy will be prescribed such that 95% of the PTV60 volume receives at least 60 Gy. As described in Section 6.4, PTV56 is also used, and PTV66 (given as an integrated boost) may be optionally defined. 3D-CRT followed by a 6 Gy boost is not permitted. Dose-limiting normal tissue constraints are listed in Section 6.5.2.

6.2 Technical Factors

6.2.1 All patients will be treated with IMRT.

6.2.2 Any treatment planning and delivery system that has been credentialed for head and neck IMRT for previous NRG Oncology trials is acceptable. Other IMRT techniques, eg physical compensators for intensity modulation are acceptable as long as dose specifications and constraints are satisfied.

6.3 Localization, Simulation, and Immobilization

6.3.1 Patients must have an immobilization device for the head and neck (shoulders optional) (eg, aquaplast mask) made prior to the treatment planning CT scan that is required for all patients.

6.3.2 The treatment planning CT scan can be performed with or without IV contrast The treatment planning CT scan must be performed with the immobilization device and in the treatment position. Slice thickness should be maximum 3 mm.

6.3.3 Daily image guidance (IGRT) is recommended but not required. Weekly verification imaging is required. This information will be archived by the submitting institution, so it can be made available for possible future review.

6.4 Treatment Planning/Target Volumes (2/20/14)

6.4.1 CTV60: This volume will receive 2 Gy per day. CTV60 will include the primary tumor bed (based on preoperative imaging, preoperative physical exam/endoscopy, operative findings, pathologic findings) plus regions of grossly involved lymphadenopathy. CTV60 may include the broader **operative resection bed** in the region of gross primary and nodal disease. The entire nodal regions in the involved hemi-neck may be included in CTV60 at the discretion of the investigator for perceived higher-risk cancers.

CTV60 will include the ipsilateral pathologically positive hemineck (if both sides of the neck are proven pathologically positive, CTV60 will include both sides). This generally means encompassing nodal levels 2a, 3, and 4 for most cases. Nodal levels 1, 2b, 5a, and 5b are included in CTV60 in selected circumstances. For example, level 1 should be included for oral cavity cancer but is not mandatory for larynx cancer. Level 5a should be included for oropharynx cancer but is not mandatory for larynx cancer.

For questions, investigators should contact one of the Co-Principal Investigators, Drs. Rosenthal or Harari**.**

6.4.2 CTV56: This will include all other lesser risk regions in the operative bed (that were involved with surgery in any way) but felt to be at risk for harboring microscopic cancer that do not meet the criteria for CTV60. For example, this could apply to the broad operative bed, the contralateral hemineck being irradiated electively. This volume should not directly approach the skin < 5 mm. This volume will receive 1.85 Gy per day (see the table in Section 6.7).

6.4.3 CTV66 **Optional**: This volume may be defined at the discretion of the treating radiation oncologist. This would include regions felt to be at particularly high risk for recurrence (eg, an area of the ECS or positive margin of resection). **Note**: This area will be receiving a daily fraction size of 2.2 Gy and thus, the volume of CTV66 should be kept **as small as possible**.

6.4.4 Planning Target Volumes (PTVs): In general, the PTV should not extend beyond the skin surface, except if the skin was involved with tumor. If it does extend beyond the skin surface, the application of bolus material over this portion of the PTV may be considered. It is also allowable to define 2 PTV's for a given CTV: 1) PTV for planning, which extends beyond the skin surface and is used for planning treatment segments; and 2) PTV Evaluation (PTV_Eval), which does not reach the skin surface within 2 mm and is used for evaluation of the dose volume histogram to determine if treatment goals have been met.

PTV Expansion With and Without Daily IGRT (no difference in PTV expansion +/- daily IGRT)

The minimum CTV-to-PTV expansion should be 5 mm (a larger expansion may be necessary for a target volume subject to significant inter-fraction variability such as the tongue). In general, the CTV-to-PTV expansion should not exceed 10 mm.

6.4.5 Management of the Low Neck/Supraclavicular Region (Match vs. No Match for IMRT treatment modality)

It is recognized that comprehensive head and neck irradiation incorporating IMRT can be done in 1 of 2 ways, either of which is permitted for this study.

1. *Match*: The upper cervical lymphatics and primary tumor bed are treated with IMRT. The lower cervical lymphatics and supraclavicular region are treated with a single AP (or

occasionally APPA for larger patients with posterior neck at high risk) non-IMRT technique. The latter non-IMRT field(s) is matched to the upper neck IMRT fields. This technique requires comprehensive mid-line spinal cord blocking in the lower neck fields. This technique also allows for a simultaneous blocking of portions of the larynx, hypopharynx, and cervical esophagus in the lower neck fields. In general, this technique is appropriate for irradiation of cancers of the oral cavity or oropharynx.

2. *No Match*: The entire clinical target volume (CTV) [upper and lower neck and primary tumor bed] is irradiated with IMRT. There is no match line between upper and lower portions of the regions at risk. In this technique, limiting radiotherapy dose to organs at risk (OARs), eg, the cervical esophagus, is entirely achieved by inverse treatment planning via IMRT algorithms. This technique in general is appropriate for irradiation of cancers of the larynx and/or oral/pharyngeal cancers that involve the hypopharynx.

6.4.6 Dose to Supraclavicular Nodal Region

Regardless of whether technique 1 (Match) or technique 2 (No Match) is used, the dose to the supraclavicular nodal region may be limited to 56 Gy for the non-operated, node negative hemi-neck, and for an involved hemi-neck if level 4 nodes were dissected and found to be negative.

6.4.7 IMRT Dose Prescription to PTVs

The prescribed radiotherapy dose will be 60 Gy in 2 Gy once-daily fraction size 5 days a week. For inverse planning IMRT, the goal is for 95% of the PTV60 to receive ≥ 2 Gy with a minimum dose (cold spot) of no less than 56 Gy. It is recognized that portions of the PTV60 close to the skin may receive significantly less than 56 Gy.

6.4.8 Unspecified Tissue Outside the Targets**:** See Section 6.5.2.

6.4.9 Prioritization for IMRT Planning

1. Spinal Cord
2. Brainstem
3. PTV60
4. PTV56 (required if applicable)
5. PTV66 (if applicable)
6. a. OARpharynx
7. b. Parotid gland contralateral to primary tumor site
8. a. GSL
9. b. Esophagus
10. a. Lips
11. b. Oral Cavity
12. a. Parotid gland ipsilateral to primary tumor site
13. b. Mandible
14. Unspecified tissue outside the targets

6.5 Definitions and Constraints for Normal Tissues/Organs at Risk (OARs) (3/5/15)

6.5.1 Definitions

- Spinal Cord:
  The cord begins at the cranial-cervical junction (ie, the top of the C1 vertebral body). Superior to this is brainstem and inferior to this is cord. The inferior border of the spinal cord is at approximately T3-4 (ie, just below the lowest slice level that has PTV on it). The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined. The PRVcord = cord +5 mm in each dimension. This is irrespective of whether or not IGRT is used.
- Brainstem: The inferior most portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purposes of this study, the superior most portion of the brainstem is approximately at the level of the top of the posterior clinoid. The brainstem shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) brainstem shall be defined. The PRVbrainstem = brainstem + 3 mm in each dimension.
- Lips and Oral Cavity: These should be contoured as 2 separate structures as the goal is to keep the lip dose much lower than the oral cavity dose. The definition of lips is self-

explanatory. For non-oral cavity cancers, the oral cavity will be defined as a composite structure consisting of the anterior ½ to 2/3 of the oral tongue/floor of mouth, buccal mucosa, and palate. For oral cavity cancers, the oral cavity will be defined as the subset of this composite structure that does not overlap with PTV.

- Parotid Glands: Parotid glands will be defined in their entirety (superficial and deep lobes) based on the treatment planning CT scan. Parotid gland volume may include portions of any of the CTVs if the primary or nodal volumes involved or closely approached the parotid, although they can overlap the PTVs.
- OARpharynx: This will be defined as the "uninvolved" posterior pharyngeal wall plus adjacent constrictor muscles. This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level). This should not overlap the PTVs.
- Cervical Esophagus: This will be defined as a tubular structure that starts at the bottom of OARpharynx and extends to the thoracic inlet.
- Glottic/Supraglottic Larynx (GSL): Obviously, for patients who have had a total laryngectomy, this structure is not applicable. This will be defined as a "triangular prism shaped" volume that begins just inferior to the hyoid bone and extends to the cricoid cartilage inferiorly and extends from the anterior commissure to include the arytenoids. This includes the infrahyoid but not suprahyoid epiglottis.
- Mandible: This includes the entire boney structure of the mandible from TMJ through the symphysis. It is recognized that for oral cavity cancers, this may overlap with CTVs and PTVs.
- Unspecified Tissue Outside the Targets: This will be defined as tissue located between the skull base and thoracic inlet.

6.5.2 IMRT Dose Constraints to Normal Structures

All of the following structures are to be contoured:

- Spinal Cord: The PRVcord (as defined in Section 6.4.2.1) should not exceed 48 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). The spinal cord PRV should not exceed 50 Gy to any volume in excess of 0.01 cc. In treatment planning, the spinal cord PRV should be given the highest priority.
- Brainstem: The PRVbrainstem (as defined in Section 6.4.2.2) should not exceed 52 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the PRVbrainstem should be given less priority than the PRVcord but more priority than the other critical structures listed below.
- Lips: Reduce the dose as much as possible. The mean dose should be < 20 Gy. For non-oral cavity cancers, the maximum dose will be < 30 Gy. For oral cavity cancers, the maximum dose will be < 50 Gy.
- Oral Cavity: Reduce the dose as much as possible. For non-oral cavity cancers, the mean dose should be < 30 Gy. Efforts should be made to avoid hot spots (> 60 Gy) within the oral cavity, particularly for non-oral cavity cancers.
- Parotid Glands: In many cases, it may be easier to spare one parotid than the other. The treatment planning goal will be for this individual parotid gland to receive: 1) Per Protocol: a mean dose of < 26 Gy; 2) Variation Acceptable: 26-30 Gy; 3) Deviation Unacceptable: > 30 Gy.
- OARpharynx: Reduce the dose as much as possible. Some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the OARpharynx exceeds 50 Gy; 2) Mean dose < 45 Gy; 3) No more than 15% of the OARpharynx exceeds 60 Gy.
- Cervical Esophagus: Reduce the dose as much as possible. For oral or oropharyngeal cancer, some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the esophagus exceeds 45 Gy; 2) Mean dose < 35 Gy; 3) No more than 15% of the esophagus exceeds 54 Gy. For larynx cancer, higher doses are expected and permitted. Some recommended doses (but not mandatory) treatment goals include: 1) No more than 33% of the esophagus exceeds 50 Gy; 2) Mean dose < 45 Gy; 3) No more than 15% of the esophagus exceeds 60 Gy.

- Glottic and Supraglottic larynx (GSL): Reduce the dose as much as possible. In patients with resected oral or oropharyngeal carcinoma, it is recommended that the dose to the larynx should be kept < 45 Gy whenever feasible.
- Mandible: Reduce the dose as much as possible. It is recognized that particularly for oral cavity cancers, significant portions of the mandible will overlap the CTVs and/or PTVs; however, hot spots within the mandible should be avoided. It is recommended that maximum dose within the mandible be < 66 Gy.
- Cochlea: Reduce the dose as much as possible; maximum dose < 35 Gy.
- Unspecified Tissue Outside the Targets: For the typical case in which there is no CTV66, no more than 0.03cc or approximately 3x3x3 mm unspecified tissue can receive 66 Gy or more. When a boost is used to increase the dose to high risk regions to as much as 66 Gy, these numbers can be increased. In this case, no more than 0.03cc or approximately 3x3x3 mm of the unspecified dose should exceed the boost dose value plus 10% or 72.6 Gy.

6.6 Critical Structures (3/5/15)

Note: All required structures must be labeled for digital RT data submission as listed in the table below. Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name as listed.

The following table outlines the naming of the various normal and critical structures for submission to TRIAD:

Standard Name	Description	
CTV_6000	CTV60	Required
PTV_6000	PTV60	Required
PTV_6000_Eval	PTV_60_Eval	Required when applicable
NonPTV_6000	External minus PTV_6000	Required
CTV_5600	CTV56	Required when applicable
PTV_5600	PTV56	Required when applicable
PTV_5600_Eval	PTV56_Eval	Required when applicable
CTV_6600	CTV66	Required when applicable
PTV_6600	PTV66	Required when applicable
PTV_6600_Eval	PTV66_Eval	Required when applicable
SpinalCord	Spinal Cord	Required
SpinalCord_05	Spinal Cord PRV	Required
BrainStem	Brain Stem	Required
BrainStem_03	Brain Stem PRV	Required
Lips	Lips	Required
OralCavity	Oral Cavity	Required
Parotid_R	Right Parotid Gland	Required
Parotid_L	Left Parotid Gland	Required
Pharynx	OARpharynx	Required
Esophagus_Up	Cervical Esophagus	Required
LarynxGSL	Glottic/Supraglotic Larynx (GSL)	Required
Mandible	Mandible	Required
Cochlea_R	Right Cochlea	Required
Cochlea_L	Left Cochlea	Required
External	Skin	Required
NonPTV	Unspecified tissue outside the targets (tissue located between the skull and the	Required

	thoracic inlet)	

6.7 Documentation Requirements

6.7.1 For IMRT Treatment Approach

- Pre-treatment Radiation therapy planning CT scan;
- If IGRT is not used, then weekly orthogonal portal images that localize the isocenter placement of IMRT are required. This information will be archived by the submitting institution, so it can be made available for possible future review;

6.8 Compliance Criteria (3/5/15)

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, ideally should not exceed five treatment days at a time and ten treatment days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Any treatment break(s) exceeding two treatment days for reasons other than toxicity/illness will be considered a protocol deviation.

It is recommended that patients receive BID treatments with minimum 6-hour inter-fraction interval to compensate for missed days including holidays and those for toxicity or illness once sufficiently recovered with the goal of keeping the overall treatment time confined to 6 weeks or 45 consecutive days.

	Per Protocol	**Variation Acceptable**
Total RT dose to PTV_6000 or PTV_6000_Eval (to 95% of PTV_6000 or PTV_6000_Eval)	60-64 Gy	< 60 and ≥ 58Gy or > 64 and ≤ 66 Gy
Minimum dose for a volume of 0.03 cc (“cold spot” within PTV_6000 or PTV_6000_Eval, not including portion of PTV near (<8 mm) skin)	≥ 56 Gy	≥ 54 and < 56 Gy
Maximum dose (hot spot) within PTV_6000* or PTV_6000_Eval for a volume of 0.03 cc	≤ 69 Gy	> 69 and ≤ 72 Gy
Maximum dose (hot spot) outside of PTV_6000 or PTV_6000_Eval for a volume of 0.03 cc	≤ 66 Gy	> 66 and ≤ 70 Gy
Total RT dose to PTV_5600 or PTV_5600_Eval (to 95% of PTV_5600 or PTV_5600_Eval)	56-58 Gy	< 56 and ≥ 53.2 Gy or > 58 and ≤ 60 Gy
Minimum dose (cold spot) within PTV_5600 or PTV_5600_Eval for a volume of 0.03 cc	45 Gy	40 Gy
Total RT dose to PTV_6600 or PTV_6600_Eval (to 95% of PTV_6600 or PTV_6600_Eval)	66-68 Gy	< 66 and ≥ 62.7 Gy or > 68 and ≤ 70.6 Gy
Minimum dose (cold spot) within PTV_6600 or PTV_6600_Eval for a volume of 0.03 cc	61.4 Gy	59 Gy
Maximum dose (hot spot) within PTV_6600 or PTV_6600_Eval	1. No more than 20% of PTV66 is at or above 72.6	1. No more than 40% of PTV66 is at or above

	Gy 2. No more than 0.03 cc of PTV66 can go above 75.9 Gy	72.6 Gy 2. No more than 0.03 cc of PTV66 can go above 78.0 Gy
Total RT dose to spinal cord PRV (0.03 cc)	< 48 Gy	≥ 48 but ≤50 Gy
Total RT dose to brainstem PRV (0.03 cc)	≤ 50 Gy	> 50 Gy and < 52 Gy
Overall RT treatment time	< 45 days	≥ 45 and ≤ 50 days**
Non-Medically Indicated Treatment Interruptions	0-2	3-4

Note: All contouring of PTVs and CTVs will be reviewed by the Co-Principal Investigators. If the criteria for Per Protocol and Variation Acceptable have not been met, the score will be "Deviation Unacceptable".

***Not including the region of PTV60 that falls within PTV66 (if applicable)

****Deviation Unacceptable:** > 50 days (without a medically appropriate indication for delay).

Recommended Dose Acceptance Criteria for Other Normal Tissue (not to be used for plan score)

Lips maximum dose to 0.03 cc for non-oral cavity cancers	≤ 25Gy
Lips maximum dose to 0.03 cc for oral cavity cancers	≤ 45Gy
Oral cavity (for non-oral cavity cancers) mean dose	≤ 30Gy
Parotid gland: Mean dose to individual parotid gland	< 26Gy
Esophagus (for oral and oropharyngeal cancers) mean dose	<35Gy
Esophagus (for larynx cancer) mean dose	<45Gy
LarynxGSL	<35Gy
Cochlea: Maximum dose to individual cochlea	<35Gy

6.9 R.T. Quality Assurance Reviews (3/5/15)

The Co-Principal Investigators, Paul M. Harari, MD, and David I. Rosenthal, MD, and the designated Radiation Oncology reviewer, Matthew Witek, MD will perform RT Quality Assurance Reviews. These reviews will be ongoing. IROC Philadelphia RT will facilitate these reviews.

6.10 Radiation Therapy Adverse Events (9/2/14)

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event (AE) reporting. The CTCAE version 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

Grade 3 therapy-induced mucositis and/or dysphagia are expected to develop in about one third to one half of patients. Nutritional evaluation prior to the initiation of therapy for a prophylactic gastrostomy (PEG) tube placement is highly recommended. Placement of a feeding tube should be recorded on the appropriate case report form (see Section 12.1), as should use of a feeding

tube during and after treatment (e.g., greater than or less than 50% of nutrition by tube). Other common radiation adverse events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, and skin erythema and desquamation within the treatment fields.

Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis. Much less common radiation adverse events include: mandibular osteoradionecrosis (< 5% incidence with attention to the dental recommendations provided in Appendix IV), and cervical myelopathy (< 1% with restriction of spinal cord dose to ≤ 45 Gy).

6.11 Radiation Therapy Adverse Event Reporting

See Section 7.8 for details.

7.0 DRUG THERAPY (9/2/14)

Protocol treatment must begin within 14 days after Step 2 registration (randomization).

7.1 Randomized Phase II Component: Treatment (2/20/14)

7.1.1 Arm 1: Weekly Cisplatin with Concurrent Radiation Therapy (RT)

Patients will receive cisplatin, 40 mg/m^2, administered intravenously over 1-2 hours once a week for 6 weeks.

Use the actual body weight for all patients. There should be no dose modifications because of obesity.

Cisplatin must be administered on Monday, Tuesday, or Wednesday of each treatment week and can be given either before or after the radiation therapy fraction that is given on the same day. It is not permitted to make up missed doses.

Cisplatin, 40 mg/m^2, is a highly emetogenic drug. Institutional guidelines for moderately emetogenic regimens should be followed. In the absence of such guidelines:

For acute nausea and vomiting, premedication should include a 5-HT3 antagonist, such as granisetron 1 mg iv; ondansetron, up to 16 mg iv; or palonosetron, 0.25 mg iv; plus a corticosteroid, such as dexamethasone, up to 20 mg iv, or aprepitant (150 mg iv), Palonosetron has a longer half-life (40h) than the first generation 5HT3 antagonists.

Breakthrough nausea and vomiting should be managed at the discretion of the medical oncologist or radiation oncologist. Delayed nausea and vomiting (greater than 24 hours after chemotherapy administration) may be managed by the following potential nausea regimens: dexamethasone 8 mg bid x 2 days, followed by dexamethasone 4mg bid x 2 days, beginning on the day after chemotherapy; or oral metoclopramide 0.5 mg/kg (usually 20-40 mg) qid x 2-4 days. A 5HT3 antagonist (eg granisetron, ondansetron) may also be given for up to 3 days after cisplatin administration, only if palonosetron was not given prior to chemotherapy.

Patients must receive vigorous hydration and diuresis. Recommendations are to administer mannitol, 12.5 g iv. bolus immediately prior to cisplatin or cisplatin, 40 mg/m^2, in NS 1000 ml. Additional fluid, potassium chloride, and/or magnesium sulfate may be administered at the discretion of the attending physician.

7.1.2 Arm 2: Weekly Docetaxel with Concurrent Radiation Therapy (RT)

Patients will receive docetaxel, 15 mg/m^2, administered intravenously once a week for 6 weeks. It is not permitted to make up missed doses.

Premedication with dexamethasone IV should be administered per the package insert, unless there is a medical contraindication.

Docetaxel must be administered on Monday, Tuesday, or Wednesday of each treatment week and can be given either before or after the radiation therapy fraction that is given on the same day.

Use the actual body weight for all patients. There should be no dose modifications because of obesity.

7.1.3 Arm 3: Weekly Docetaxel and Cetuximab with Concurrent Radiation Therapy **(2/19/13)**

Cetuximab Initial Dose (prior to RT and Docetaxel)

Patients on Arm 3 will receive an initial dose of cetuximab, 400 mg/m^2, intravenously (iv) over 120 minutes. No radiation or docetaxel will be given this day, and the 400 mg/m^2 initial dose of cetuximab will precede the first 250 mg/m^2 dose of cetuximab and the first radiation treatment and docetaxel by at least 5, but no more than 7, days (the day of the loading dose is not included in these 5 days). The infusion rate of cetuximab must never exceed 5 mL/min.

Use the actual body weight for all patients. There should be no dose modifications because of obesity.

Cetuximab Weeks 2-7 (concurrent with RT and Docetaxel)

Patients on Arm 3 will receive cetuximab, 250 mg/m^2, intravenously (iv) over 60 minutes on a weekly schedule. Docetaxel will be administered at least 30 minutes following the cetuximab. It is not permitted to make up missed doses of cetuximab or docetaxel.

The infusion rate of cetuximab must never exceed 5 mL/min. Cetuximab will be given once a week on Monday, Tuesday, or Wednesday for a total of 6 doses concurrent with radiation therapy and docetaxel.

Note: Patients receive a total of 7 doses of cetuximab over 7 weeks, including the initial loading dose, 6 doses concurrent with radiation therapy. If a dose of cetuximab is omitted, it will not be made up or added to the end of treatment. The omitted dose and the reason for the omission should be recorded in the site's source documentation.

CAUTION: Infusion reactions may occur during or following cetuximab administration. Most infusion reactions occur with the first infusion of cetuximab, but some patients' first infusion reactions have been reported following subsequent doses (a severe reaction occurred in one patient following the 8th dose). The infusion reaction may occur during the infusion or be delayed until any time after the infusion. All patients will be premedicated with diphenhydramine hydrochloride, 50 mg, (or an equivalent antihistamine) by iv 30-60 minutes prior to the first dose of cetuximab in an effort to prevent an infusion reaction. At the discretion of the treating physician, dexamethasone, 20 mg, and an H2 blocker also may be administered iv. Premedications are recommended prior to subsequent doses, but at the Investigator's discretion, the dose of diphenhydramine or dexamethasone may be reduced.

It is recommended that the medical staff closely observe patients for treatment-related adverse events, especially infusion reactions (see Section 7.6 for management) during the cetuximab infusion and during a post-infusion observation hour. For the initial cetuximab infusion, vital signs (blood pressure, heart rate, respiratory rate, and temperature) should be monitored prior to the administration of cetuximab, a half hour into the infusion, at the completion of the infusion, and 60 minutes post the infusion in an area with resuscitation equipment and other agents (epinephrine, prednisone equivalents, etc.) available. It is recommended that a nurse be present in the immediate treatment area throughout the infusion and observation period, and that a physician be in close proximity to the patient treatment area. In the event that a patient experiences an infusion reaction, see Section 7.6 for proper management.

For subsequent infusions, vital signs should be taken pre- and post-infusion; however, it is recommended that the patient be observed for 1 hour post-infusion. For the duration that patients are on study therapy, adverse event monitoring will be done continuously. Patients will be evaluated for adverse events at each visit and are to be instructed to call their physician to report any clinically significant adverse events between visits. **Patients should be instructed to report any delayed reactions to the investigator immediately.**

Weekly Docetaxel with Cetuximab and Concurrent Radiation Therapy (RT)
Patients will receive docetaxel, 15 mg/m^2, administered intravenously once a week for 6 weeks. See Section 7.1.2 for details of treatment.

7.2 Phase III Component: Treatment

7.2.1 Arm 1: Weekly Cisplatin with Concurrent Radiation Therapy (RT)
See Section 7.1 for details of treatment.

7.2.2 Arm 2: Weekly Docetaxel with Concurrent Radiation Therapy (RT)
See Section 7.1 for details of treatment.

7.2.3 Arm 3: Weekly Docetaxel and Cetuximab with Concurrent Radiation Therapy (RT)
Cetuximab Initial Dose (prior to RT and Docetaxel)
See Section 7.1 for details of treatment.

7.3 Cisplatin (8/7/13)

Refer to the package insert for detailed pharmacologic and safety information.

7.3.1 Formulation: Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 9 mg NaCl and HCL or NaOH to adjust pH.

7.3.2 Mechanism of Action: The dominant mode of action of cisplatin appears to be inhibition of the incorporation of DNA precursors, although protein and RNA synthesis are also inhibited. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents.

7.3.3 Administration: After administering appropriate antiemetics, cisplatin will be infused over 1-2 hours or according to institutional guidelines along with vigorous hydration.

7.3.4 Storage and Stability: Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C and should be protected from light if not used within 6 hours. The vials and injection should not be refrigerated. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

7.3.5 Adverse Events: Human toxicity includes nausea, vomiting, anaphylaxis, neuropathies, ocular disturbances, renal toxicity (with an elevation of BUN and creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage, which appears to be transient), ototoxicity (with hearing loss that initially is in the high-frequency range, as well as tinnitus), and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Myelosuppression, often with delayed erythrosuppression, is expected.

7.3.6 Supply: Cisplatin is commercially available. The use of drug(s) or combination of drugs in this protocol meets the criteria described under Title 21 CFR 312.2(b) for IND exemption.

Non-Canadian International Institutions
Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study. Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document.

7.4 Docetaxel (Taxotere®) **(8/7/13)**

Refer to the package insert for detailed pharmacologic and safety information related to specific docetaxel formulations.

7.4.1 *Formulation:* Docetaxel for Injection concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, diluent (13% ethanol in water for injection) vial. The following strengths are available:

- Docetaxel (NDC 0075-8001-80) 80 mg Concentrate for Infusion: 80 mg docetaxel in 2 mL polysorbate 80 and diluent for docetaxel80 mg. 13% (w/w) ethanol in Water for Injection. Both items are in a blister pack in one carton.
- Docetaxel (NDC 0075-8001-20) 20 mg Concentrate for Infusion: 20 mg docetaxel in 0.5 mL polysorbate 80 and diluent for docetaxel 20 mg. 13% (w/w) ethanol in Water for Injection. Both items are in a blister pack in one carton available as 80 mg/m² mL vials (15% overfilled) with a 7 mL vial of solvent (ethanol 95%in water, 15% overfilled). (The vials contain 94.4 mg/2.36 mL docetaxel and 7.33 mL ethyl alcohol 95% to compensate for liquid lost during preparation.)

7.4.2 *Storage and Preparation:* Store between 2 and 25°C (36 and 77ºF). Retain in the original package to protect from bright light. Freezing does not adversely affect the product. Docetaxel is stored at 4°C and should be protected from light. The solvent vials may be stored at room temperature or at 4°C. Docetaxel infusion solution, if stored between 2 and 25ºC (36 and 77ºF) is stable for 4 hours. Fully prepared docetaxel infusion solution (in either 0.9% sodium chloride solution or 5% dextrose solution) should be used within 4 hours (including the administration time).

Contact of the docetaxel concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Preparation and Administration Precautions

1) Docetaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing docetaxel solutions. The use of gloves is recommended. Please refer to Handling and Disposal below.
2) If docetaxel concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If docetaxel concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.
3) Docetaxel for Injection Concentrate requires two dilutions prior to administration. Please follow the preparation instructions provided below. Note: Both the Docetaxel for Injection Concentrate and the diluent vials contain an overfill.

Preparation of the Initial Diluted Solution

1) Gather the appropriate number of vials of docetaxel for Injection Concentrate and diluent (13% ethanol in water for Injection). If the vials were refrigerated, allow them to stand at room temperature for approximately 5 minutes.
2) Aseptically withdraw the contents of the appropriate diluent vial into a syringe and transfer it to the appropriate vial of docetaxel for Injection Concentrate. If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.
3) Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.
4) The initial diluted docetaxel solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

Preparation of the Final Dilution for Infusion

1) Aseptically withdraw the required amount of initial diluted docetaxel solution (10 mg docetaxel/mL) with a calibrated syringe and inject into an infusion bag or bottle of either 0.9% sodium chloride solution or 5% dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL.
2) Thoroughly mix the infusion by manual rotation.
3) As with all parenteral products, docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel for Injection initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.

   The final docetaxel dilution for infusion should be administered intravenously as per protocol under ambient room temperature and lighting conditions.

   Handling and Disposal: Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

7.4.3 *Administration*: Intravenous over 60 minutes.

7.4.4 *Pharmacology:* Docetaxel is an anti-microtubule agent. Docetaxel, a semi-synthetic analog of taxol, promotes the assembly of tubulin and inhibits microtubule depolymerization. Bundles of microtubules accumulate and interfere with cell division.

7.4.5 Adverse Events: Cardiac: arrhythmias, pericardial effusions. Hematologic: dose-related neutropenia, leukopenia, thrombocytopenia, and anemia. Gastrointestinal: nausea and vomiting, diarrhea, oral mucositis. Neurologic: reversible dysthesias or paresthesias, peripheral neuropathy, mild or moderate lethargy or somnolence, headache, seizures. Hypersensitivity: hypersensitivity (local or general skin rash, flushing, pruritus, drug-fever, chills and rigors, low back pain), severe anaphylactoid reactions (flushing with hypo- or hypertension, with or without dyspnea). Dermatologic: alopecia, desquamation following localized pruriginous maculopapular eruption, skin erythema with edema, extravasation reaction (erythema, swelling, tenderness, pustules), reversible peripheral phlebitis, nail changes. Hepatic: increased transaminase, alkaline phosphatase, bilirubin; hepatic failure; hepatic drug reaction. Pulmonary: dyspnea with restrictive pulmonary syndrome, pleural effusions. Other: asthenia, dysgeusia, anorexia, conjunctivitis, arthralgia, muscle aches, myopathy, peripheral edema, fluid retention syndrome, ascites.

7.4.6 *Supplier*: Commercially available. The use of drug(s) or combination of drugs in this protocol meets the criteria described under Title 21 CFR 312.2(b) for IND exemption

Non-Canadian International Institutions

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study. Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document.

7.5 Cetuximab (2/20/14)

Refer to package insert for detailed pharmacologic and safety information. Note the black box warning for cardiopulmonary arrest in patients receiving radiation therapy in combination with cetuximab. Serious hypersensitivity reactions most commonly occur at the initiation of the cetuximab loading dose, and the patient should be carefully monitored, especially at this time.

7.5.1 Formulation

Cetuximab is an anti-EGFR receptor humanized chimeric monoclonal antibody. Cetuximab is expressed in SP2/0 myeloma cell line, grown in large scale cell culture bioreactors, and purified to a high level purity using several purification steps including protein A chromatography, ion

exchange chromatography, low pH treatment, and nanofiltration. Cetuximab is not known to be a vesicant.

7.5.2 Safety Precautions

Appropriate mask, protective clothing, eye protection, gloves and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling.

7.5.3 Preparation and Administration

Cetuximab must not be administered as an iv push or bolus. Cetuximab must be administered with the use of a low protein binding 0.22-micrometer in-line filter.

Cetuximab is supplied as a 50-mL, single-use vial containing 100 mg of cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible white amorphous cetuximab particulates. DO NOT SHAKE OR DILUTE.

Cetuximab can be administered via infusion pump or syringe pump.

Infusion Pump:

1. Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).
2. Fill cetuximab into a sterile evacuated container or bag such as glass containers, polyolefin bags (eg, Baxter Intravia), ethylene vinyl acetate bags (eg, Baxter Clintec), DEHP plasticized PVC bags (eg, Abbott Lifecare), or PVC bags.
3. Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
4. Administration must be through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
5. Affix the infusion line and prime it with cetuximab before starting the infusion.
6. Maximum infusion rate should not exceed 5 mL/min.
7. Use 0.9% saline solution to flush line at the end of infusion.

Syringe Pump:

1. Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike may be used).
2. Place the syringe into the syringe driver of a syringe pump and set the rate.
3. Administration must be through a low protein binding 0.22-micrometer in-line filter rated for syringe pump use (placed as proximal to the patient as practical).
4. Connect up the infusion line and start the infusion after priming the line with cetuximab.
5. Repeat procedure until the calculated volume has been infused.
6. Use a new needle and filter for each vial.
7. Maximum infusion rate should not exceed 5 mL/min.
8. Use 0.9% saline solution to flush line at the end of infusion.

Cetuximab should be piggybacked to the patient's infusion line.

Following the cetuximab infusion, a one-hour observation period is recommended.

7.5.4 Adverse Events

Cetuximab may be associated with significant toxicities, most commonly fatigue, skin rash/folliculitis and paronychia, and gastrointestinal effects, nausea and diarrhea. Hypomagnesia is common. Of greatest concern is the potential for an allergic reaction, possibly anaphylaxis; see Section 7.6.4 for details.

Other adverse events:

- Blood and lymphatic system: Anemia;
- Ear and labyrinth disorders: External ear inflammation, tinnitus;
- Eye disorders: Conjunctivitis, dry eye, uvelitis, watering eyes;
- Gastrointestinal disorders: Diarrhea, nausea, abdominal pain, cheilitis, constipation, dry mouth, dyspepsia, oral mucositis, vomiting;

- General disorders and administration site conditions: Fatigue, fever, chills, edema limbs, flu-like symptoms, infustion-related reaction, non-cardiac chest pain;
- Metabolism and nutritional disorders: Anorexia, dehydration, hypocalcemia, hypomagnesemia;
- Musculoskeletal and connective tissue disorders: arthralgia, back pain, myalgia;
- Nervous system disorders: Headache, syncope;
- Respiratory, thoracic, and mediastinal disorders: Allergic rhinitis, bronchospasm, cough, dyspnea, hoarseness, and rarely, pneumonitis and non-cardiogenic pulmonary edema;
- Skin and subcutaneous tissue disorders: dry skin, rash acneiform, rash maculo-papular, alopecia, nail loss, photosensitivity, pruritus, purpura, skin ulceration, urticaria, and rarely, Palmar-plantar erythrodysesthesia syndrome;
- Vascular disorders: hypotension, thromboembolic event.

Note: Cetuximab 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.

7.5.5 Storage Requirements/Stability

Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). DO NOT FREEZE. Increased particulate formation may occur at temperatures at or below 0°C. This product contains no preservatives. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) and up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° to 8° C. Discard any unused portion of the vial.

7.5.6 Supply **(3/18/13)**

Cetuximab is commercially available in the U.S. Canadian sites must obtain their own supply of cetuximab.The use of drug(s) or combination of drugs in this protocol meets the criteria described under Title 21 CFR 312.2(b) for IND exemption.

Non-Canadian International Institutions

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study. Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document.

7.6 Dose Modifications (9/2/14)

Note: Serum chemistries are to be monitored weekly during chemotherapy (see Appendix I). It is expected that appropriate adjustments in electrolyte therapy will be addressed by the patient's attending physician.

7.6.1 Cetuximab/Docetaxel/Cisplatin Dose Levels

	Starting Dose	**Dose Level –1**	**Dose Level –2**
Cetuximab	400 mg/m^2 (week -1) 250 mg/m^2 (weekly)	200 mg/m^2 (weekly)	150 mg/m^2 (weekly)
Docetaxel	15 mg/m^2 (weekly)	12 mg/m^2 (weekly)	–
Cisplatin	40 mg/m^2 (weekly)	20 mg/m^2 (weekly)	–

7.6.2 Cetuximab/Docetaxel/Cisplatin Dose Modification for Hematologic Toxicity

NCI CTCAE	**Cetuximab Dose at**	**Docetaxel Dose[a,b] at Start of**	**Cisplatin Dose[c,d] at Start**

Toxicity Grade (CTCAE v. 4)	Start of Subsequent Cycles of Therapy	Subsequent Cycles of Therapy	of Subsequent Cycles of Therapy
Neutropenia			
1 (1500-1999/mm^3)	Maintain dose level	Maintain dose level	Maintain dose level
2 (1000-1499/mm^3)	Maintain dose level	Maintain dose level	Maintain dose level
3 (500-999/mm^3)	Maintain dose level	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and resume when reaches Grade 2	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and resume when reaches Grade 2
4 (<500/mm^3)	Maintain dose level	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and resume when reaches Grade 2	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and resume when reaches Grade 2
Neutropenic Fever[e]	Maintain dose level	Decrease by 1 dose level	Decrease by 1 dose level
Thrombocytopenia			
1 (75,000/mm^3-LLN)	Maintain dose level	Maintain dose level	Maintain dose level
2 (50,000- 74,999/mm^3)	Maintain dose level	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and resume when reaches Grade 1	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and resume when reaches Grade 1
3 (25,000- 49,999/mm^3)	Maintain dose level	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and resume when reaches Grade 1	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and resume when reaches Grade 1
4 <25,000/mm^3)	Maintain dose level	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and resume when reaches Grade 1	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and resume when reaches Grade 1
Other Hematologic toxicities: Dose mods for leukopenia are based on NCI CTCAE and are the same as recommended above.			

[a]Dose levels are relative to the starting dose in the previous cycle. Dose reductions of docetaxel below the –1 dose level will not be allowed.
[b]Docetaxel will be delivered only if there is no indication for holding the radiation and if all other hematologic and non-hematologic toxicity criteria are met. If these parameters are not met, continue radiation therapy and omit docetaxel that week.
[c]Dose levels are relative to the starting dose in the previous cycle. Dose reductions of cisplatin below the –1 dose level will not be allowed.
[d]Cisplatin will only be delivered if there is no indication for holding the radiation and if all other hematologic and non-hematologic toxicity criteria are met. If these parameters are not met, continue radiation therapy and omit cisplatin that week.
[e] CTCAE, v. 4, grade 3 neutropenic fever : ANC < 1000/mm^3 with a single temperature of > 38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than 1 hour.

7.6.3 Dose Modifications for Non-Hematologic Toxicity

NCI CTCAE Toxicity[a] Grade (CTCAE v. 4)	Cetuximab Dose[c,g]	Docetaxel Dose[d]	Cisplatin Dose[e]
Renal-serum Creatinine[b]			
≤ Grade 1 (ULN-1.5)	Maintain dose levels	Maintain dose levels	Maintain dose levels
Grade 2 (> 1.5-3.0)	Maintain dose levels	Maintain dose levels	Decrease by 1 dose level
≥ Grade 3 (>3.0-6.0)	Hold drug until ≤ grade 2	Hold drug until ≤ grade 2	Hold drug until ≤ grade 1,

			then decrease by one level
Fatigue Grade 3	Decrease by 1 dose level	Decrease by 1 dose level	Decrease by 1 dose level
Nausea/Vomiting ≤ Grade 2 with maximal medical management ≥ Grade 3 with maximal medical management	Maintain dose levels Hold drug until ≤ grade 2	Maintain dose level Hold drug until ≤ grade 2	Maintain dose level Hold drug until ≤ grade 2
Other non-hematologic Toxicities[f,h]			
Neuropathy Grade 2 Grade 3-4	See footnote i	See footnote i	Decrease by 1 dose level Discontinue cisplatin
Other: LFT abnormalities Grade 3-4		Hold drug until ≤ grade 1 Decrease dose by 1 level	
Other: Mucositis in RT field Grade 0-3 Grade 4	 Maintain dose levels Hold drug until ≤ grade 3	 Maintain dose levels Hold drug until ≤ grade 3	 Maintain dose levels Hold drug until ≤ grade 3
Rash, in RT field ≤ Grade 2 Grade 3 Grade 4	 Maintain dose levels Hold drug until ≤ grade 2 Hold drug until ≤ grade 2	 Maintain dose levels Maintain dose levels Hold drug until ≤ grade 3	 Maintain dose levels Maintain dose levels Hold drug until ≤ grade 3
Rash, out of RT field ≤ Grade 2 Grade 3 Grade 4	 Maintain dose levels Hold drug until ≤ grade 2 Hold drug until ≤ grade 2	 Maintain dose levels Maintain dose levels Hold drug until ≤ grade 3	 Maintain dose levels Maintain dose levels Hold drug until ≤ grade 3
Grade 4/Other non-hematologic AEs	Hold drug until ≤ grade 1	Hold drug until ≤ grade 1	Hold drug until ≤ grade 1

[a]For CTCAE Grade < 2 non-hematologic toxicity not described above, maintain dose level of drug.
[b] Choose one or the other study to assess renal function and base treatment decision.
[c]Dose levels are relative to the previous dose. Dose reductions of cetuximab below the –2 dose level will not be allowed.
[d]Dose levels are relative to the previous dose. Dose reductions of docetaxel below the –1 dose level will not be allowed.
[e]Dose levels are relative to the previous dose. Dose reductions of cisplatin below the –1 dose level will not be allowed.
[f]Cetuximab: With the exception of allergic/hypersensitivity
[g]In any case of cetuximab treatment delay, there will be no reloading infusion, and all subsequent treatments will be at the assigned dose level.
[h]For depressed K or Mg, administer replacement therapy. Chemotherapy should continue at the discretion of the treating physician.
[i]Neuropathy is not expected with cetuximab or docetaxel. If toxicity seems related to cetuximab or docetaxel, contact Dr. Kies, Medical Oncology Co-Chair.

7.6.4 CTCAE v. 4 Infusion Reaction Management

CTCAE Grade	Treatment Guidelines	
Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated	**Cetuximab**[a]	**Docetaxel**
	For mild infusion reactions manifesting only as delayed drug fever, consider administering prophylactic antihistamine medications for subsequent doses. Maintain the cetuximab dose but slow the infusion rate by 50%. Acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) may be administered prior to subsequent cetuximab infusions, if not otherwise contraindicated in subjects.	Consider decreasing the rate of infusion until recovery from symptoms. Stay at bedside and monitor patient, then complete docetaxel infusion at the initial planned rate.
Grade 2 : Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs.	For moderate infusion reactions manifesting only as delayed drug fever, slow the infusion rate for cetuximab by 50%, and consider administration of antihistamine medications and/or steroidal medications. Maintain the cetuximab dose. Acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) may be administered prior to subsequent cetuximab infusions, if not otherwise contraindicated in subjects.	-Interrupt docetaxel infusion and give diphenhydramine 50 mg IV with or without dexamethasone 10mg IV. -Monitor patient until resolution of symptoms. -Resume docetaxel infusion after recovery of symptoms. -Depending on the physician's assessment of the patient, docetaxel infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate. (e.g., infuse at a 4-hr rate for 3 minutes, then at a 2-hr rate for 3 minutes, then at a 1-hr rate for 3 minutes, then finally, resume at the initial planned rate.) -Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the **next cycle** of treatment, and the rate of infusion should be decreased initially and then increased back to initial planned rate, (e.g., infuse at a 4-hr rate for 3 minutes, then at a 2-hr rate for 3 minutes, then at a 1-hr rate for 3 minutes, and finally, administer at the initial planned rate.)

CTCAE v. 4 Infusion Reaction Management (Continued)		
CTCAE GRADE	**Treatment Guidelines**	
	Cetuximab[a]	**Docetaxel**
Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Severe infusion reactions **require immediate interruption of cetuximab infusion and permanent discontinuation from further treatment with cetuximab.** Appropriate medical therapy including epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.	Immediately discontinue docetaxel infusion. Give diphenhydramine 50mg IV with or without dexamethasone 10mg IV and/or epinephrine as needed. Monitor patient until resolution of symptoms. Follow the same treatment guidelines outlined for Grade 2 symptoms.
Grade 4: Life-threatening consequences; urgent intervention	**NO FURTHER STUDY DRUG THERAPY** Life-threatening infusion reactions **require immediate interruption of cetuximab infusion and permanent discontinuation from further treatment with cetuximab.** Appropriate medical therapy including epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.	**NO FURTHER STUDY DRUG THERAPY** Appropriate medical therapy including epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.

[a] Study Therapy Retreatment Following Infusion Reactions: Once a cetuximab infusion rate has been decreased due to an infusion reaction, it will remain decreased for all subsequent infusions. If the subject has a second infusion reaction with the slower infusion rate, the infusion should be stopped, and the subject should receive no further cetuximab treatment. If a subject experiences a Grade 3 or 4 infusion reaction at any time, the subject should receive no further cetuximab treatment. If there is any question as to whether an observed reaction is an infusion reaction of Grades 1-4, the Medical Oncology Co-Chair, Dr. Kies, should be contacted immediately to discuss and grade the reaction.

7.6.5 Cetuximab Special Instructions

If cetuximab is omitted for more than four consecutive infusions for adverse events due to cetuximab, or for an intercurrent illness (eg, infection) requiring interruption of therapy, the subject should be discontinued from further cetuximab therapy. If adverse events prevent the administration of cetuximab, the subject may continue to receive radiation therapy.

If a dose of cetuximab is omitted, it will not be made up or added to the end of treatment. The omitted dose and the reason for the omission should be recorded in the site's source documentation.

Management of Cetuximab Infusion Reactions

Severe or life threatening (grade 3 or 4) infusion reactions require the immediate interruption of cetuximab therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

In clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of cetuximab and by continued use of antihistamine pre-medications (eg, diphenhydramine) in subsequent doses. If the patient experiences a mild or moderate (grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced by 50%. For grade 1 or 2 reactions manifesting only as delayed drug fever, see below.

Treatment of Isolated Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the study drug or to an infectious etiology.

If a patient experiences isolated drug fever, for the next dose, pre-treat with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion), repeat antipyretic dose 6 and 12 hours after cetuximab infusion. The infusion rate will remain unchanged for future doses.

If a patient experiences recurrent isolated drug fever following pre-medication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further cetuximab.

Cetuximab-related Rash

- Manifestations
  Rash associated with EGFR-inhibitors is a relatively new dermatologic condition. It appears to be "acneiform" but it is NOT considered a form of acne; rather, it is a form of folliculitis. Skin changes may be manifested in a number of ways: erythema; follicle based papules, which may ulcerate; pain; itching; cosmetic disturbance; and/or nail disorders. The rash may become infected and transform into cellulitis.
- Grading of Cetuximab-induced Rash
  According to physician judgment, if a patient experiences ≥ grade 3 rash (according to either the "outside of the radiation field" or the "inside of the radiation field" definitions below), cetuximab treatment adjustments should be made according to the Cetuximab Dose Modification table that follows. In patients with mild and moderate skin adverse events, cetuximab should continue without adjustment.

NOTE: Rash intensity (i.e., the size and number of papules or the level of discomfort and extent of erythema) may be an important consideration. However, the absolute number of lesions, **without associated physical discomfort**, does not necessarily constitute a basis for a dose reduction or delay. Rash considered "intolerable" (because of pain, itching, or appearance) or that has failed to respond to symptomatic management may be considered grade 3 and thus prompt dose reduction or delay of cetuximab. **The clinical judgment of the treating physician is critical to grading and will ultimately dictate dose modification.**

- Acute Skin Changes
  - Rash Occurring **Outside** of the Radiation Field: Should be graded using the following CTCAE, v. 4 terms. A rash complicated by secondary infection or cellulitis should be graded per additional CTCAE terms.

Acute Dermatologic Changes				
	1	2	3	4
Pruritus*	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	-
Rash/acneiform*	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADLI; Responds promptly to symptomatic treatment	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated; Prolonged.	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life threatening consequences
Paronychia*	Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-

*Onset of grade 3 will require modification. See the table below, "Cetuximab Dose Modification Guidelines for Dermatologic Changes".

- Rash Occurring **Inside** the Radiation Field: Acute radiation dermatitis may be exacerbated by cetuximab or chemotherapy. The severity of such rash should be graded using CTCAE, v. 4 criteria for radiation dermatitis (table below).

Acute Dermatologic Changes				
	1	2	3	4
Radiation recall reaction (dermatologic); Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated

➢ *Late Skin Changes* A potential late change of interest is consequential scarring/pock marking **in or out of the radiation field**. This may be reported by using the MedDRA code, "Skin and subcutaneous tissue disorders - Other, specify" with the following protocol-specific grading scale as guidance:

- Grade 1: Mild (seen only on close inspection)
- Grade 2: Moderate (scarring, intervention or cosmetic coverage/intervention indicated)
- Grade 3: Severe (significant disfigurement, deep scarring, or ulceration)
- Grade 4: Deep cratering/scarring, skin necrosis, or disabling

Cetuximab Dose Modification Guidelines for Dermatologic Changes (≥ Grade 3)			
	Cetuximab	Outcome	Cetuximab Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement to ≤ Grade 2	Resume at 250 mg/m^2
		No Improvement; remains grade 3	Discontinue cetuximab
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement to ≤ Grade 2	Resume at Dose Level -1 (200 mg/m^2)
		No Improvement; remains grade 3	Discontinue cetuximab
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement to ≤ Grade 2	Resume at Dose Level -2 (150 mg/m^2)
		No Improvement; remains grade 3	Discontinue cetuximab
4th occurrence	Discontinue cetuximab		

Drug Related Rash Management

Patients developing dermatologic adverse events while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Below are suggestions for managing cetuximab-induced rash*:

- **Antibiotics**: The benefit of routine antibiotics in uncomplicated (uninfected) rash is unclear. Some clinicians have used oral minocycline (Minocin), mupirocin (Bactroban), or topical clindamycin (Cleocin) lotion. Rash complicated by cellulitis should be treated with appropriate antibiotics based on clinical judgment or microbial sensitivity analysis.
- **Antihistamines**: Benadryl or Atarax may be helpful to control itching.
- **Topical Steroids**: The benefit of topical steroids is unclear.
- **Retinoids**: No data to support use. Use is not advised.
- **Benzoyl peroxide**: Should NOT be used--may aggravate rash.
- **Makeup**: Rash can be covered with makeup; this should not make it worse (use a dermatologist-approved cover-up, eg, Dermablend, or any other type of foundation). Remove makeup with a skin-friendly liquid cleanser, eg, Neutrogena, Dove, or Ivory Skin Cleansing Liqui-Gel.
- **Moisturizers**: Use emollients to prevent and alleviate the skin dryness, eg, Neutrogena Norwegian Formula Hand Cream or Vaseline Intensive Care Advanced Healing Lotion is strongly advised.
- **Sunlight**: It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.
- **Over-the-counter medications**: Over-the-counter acne vulgaris medications (eg, benzoyl peroxide) are not advised. This rash is not like acne vulgaris and these treatments could make it worse.

*Adapted from Perez-Soler R, Delord J, Halpern A, et al. HER1/EGFR inhibitor-associated rash: Future directions for management and investigation outcomes from the HER1/EGFR Inhibitor Rash Management Forum. *The Oncologist*. 10:345–356, 2005.

7.7 Modality Review

The Medical Oncology Co-Chair, Merrill S. Kies, MD, will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **Per Protocol, Acceptable Variation, Unacceptable Deviation, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

The Medical Oncology Co-Chair, Merrill S. Kies, MD, will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at NRG Oncology. Dr. Kies will perform the next review after complete data for the next 20 cases enrolled has been received at NRG Oncology. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at NRG Oncology, whichever occurs first.

7.8 Adverse Events (9/2/14)

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for adverse event (AE) reporting. The CTCAE version 4.0 is located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

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

NRG Oncology is responsible for reporting adverse events to the FDA.

7.8.1 Adverse Events (AEs)

Definition of an 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). [CTEP, NCI Guidelines: Adverse Event Reporting Requirements. February 29, 2012; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm]

7.8.2 Serious Adverse Events (SAEs) — Serious adverse events (SAEs) that meet expedited reporting criteria defined in the table in Section 7.9 will be reported via CTEP-AERS. SAEs that require 24 hour CTEP-AERS notification are defined in the expedited reporting table in Section 7.9. **Contact the CTEP-AERS Help Desk if assistance is required.**

Definition of an SAE: Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

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.

7.8.3 Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS)

AML or MDS that is diagnosed as a secondary malignancy during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the CTEP-AERS system within 30 days of AML/MDS diagnosis.

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 following treatment with an agent under an NCI IND/IDE 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.

7.9 CTEP-AERS Adverse Event Reporting Requirements (2/20/14)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via CTEP-AERS, the CTEP Adverse Event Reporting System, 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 Oncology and satisfies NRG Oncology 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 Oncology Operations Office at 1-800-227-5463, ext. 4189, for instances when Internet fails. Once internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS.

- CTEP-AERS-24 Hour Notification requires that an CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by an CTEP-AERS 5 Calendar Day Report. Serious adverse events that require 24 hour CTEP-AERS notification are defined in the expedited reporting table below.
- Supporting source document is not mandatory. However, if the CTEP-AERS report indicates in the *Additional Information* section that source documentation will be provided, then it is expected. If supporting source documentation accompanies an CTEP-AERS report, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation **to the NRG Oncology dedicated SAE FAX, 215-717-0990.**
- A serious adverse event that meets expedited reporting criteria outlined in the following table but is assessed by the CTEP-AERS System as “expedited reporting NOT required” must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the “NOT

Required" assessment; the CTEP-AERS System allows submission of all reports regardless of the results of the assessment.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies Utilizing a Commercially Available Agent within 30 Days of the Last Administration of the 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	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 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; 5 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 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

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

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 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.

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a Non-CTEP IND: None

8.0 SURGERY (2/20/14)

Patients must have undergone gross total surgical resection of high-risk oral cavity, oropharynx (p16 negative), larynx, or hypopharynx within 63 days of registration.

8.1 Surgical Quality Assurance Reviews

The Surgical Oncology Co-Chair, Jeffrey N. Myers, MD, will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at NRG Oncology, he will review pathology and operative reports for compliance with eligibility based on documentation of the pathologic descriptors for high-risk disease: extracapsular nodal extension or invasive cancer seen on microscopic evaluation of resection margins. Dr. Myers will perform the next review after complete data for the next 20 cases enrolled has been received at NRG Oncology. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at NRG Oncology, whichever occurs first.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medications. This would include use of analgesics, antiemetics, oral rinses, and skin creams or ointments. Moreover, there should be a listing of medications for each patient, which would include aspirin, antibiotics, anticoagulants, cardiac medications, and dietary supplements/vitamins. Red blood cell transfusion is recommended to maintain hemoglobin above 10 gm/dl and should be recorded

9.2 Non-permitted Supportive Therapy

The use of amifostine as a radioprotector, erythropoietin, and granulocyte colony stimulating factors are not allowed. Any exceptions must be approved by one of the Co-Principal Investigators, Paul Harari, MD or David Rosenthal, MD, or the Medical Oncology Co-Chair, Merrill Kies, MD.

10.0 TISSUE/SPECIMEN SUBMISSION (3/5/15)

NOTE: Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission or quality of life assessment.

If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified in Section 10.0 of the protocol. **Note:** Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission

The NRG Oncology Biospecimen Bank at the University of California, San Francisco acquires and maintains high quality specimens from NRG Oncology trials. Tissue from each block is preserved through careful block storage and processing. NRG Oncology encourages participants in protocol studies to consent to the banking of their tissue. The NRG Oncology Tissue Bank provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate

important biologic questions. **Note**: The NRG Oncology Biospecimen Bank will provide collection kits and instructions at no charge for the submission of specimens in this protocol.

In this study, **it is required that tissue be submitted to the NRG Oncology Biospecimen Bank for the purpose of EGFR analysis for all patients and p16 assay for oropharyngeal carcinomas.** In addition, it is highly recommended (but optional) that archival tissues and blood specimens be submitted for banking for future translational research. The NRG Oncology Biospecimen Bank provides tissue specimens to investigators for approved studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

10.2 Mandatory Tissue Collection for EGFR (All Patients) and HPV/p16 Testing (Only for Patients with Oropharyngeal Cancer) (8/7/13)

All patients must consent to participate in submission of tissue for EGFR expression levels, and patients with oropharyngeal cancer also must consent to participate in submission of tissue for HPV testing by p16 analysis.

Tissue from a biopsy or surgical specimen will be obtained from formalin fixed and paraffin embedded (FFPE) in tissue blocks. Institutions must ship FFPE tissue as outlined in Sections 10.2.1 and 10.2.2 below from patients to the NRG Oncology Biospecimen Bank-San Francisco by overnight courier. Prepaid Federal Express Labels can be requested from the Biospecimen Bank (rtog@ucsf.edu) for this purpose (see Section 10.3 for complete contact information). Upon determination that the specimen is adequate, the Pathology Co-Chair, Dr. Jordan will perform the quantitative analysis of EGFR by immunohistochemistry for all patients and p16 (surrogate for HPV) analysis for patients with oropharyngeal cancer. Analysis results are expected in approximately 5 business days upon receipt at the Biospecimen Bank. The specific hypotheses are:

A. The degree of improvement with the experimental treatment, especially the docetaxel-cetuximab arm, in disease-free survival (DFS) will be similar for patients with high (defined as ≥ 80% of tumor cells staining positive for EGFR) or low EGFR expression (defined as < 80% of tumor cells staining positive). However, the absolute value for DFS will be significantly greater for patients with low EGFR expressing tumor. Physicians or institutions can request the patient's EGFR level from NRG Oncology (215-574-3154 or 215-574-3170) after the patient has completed study treatment.

B. **Only patients with p16 negative oropharyngeal carcinoma qualify for this study** because patients with p16 positive oropharyngeal carcinoma have excellent prognosis and are unlikely to benefit from the intensified treatment regimens tested here. NRG Oncology will notify institutions when p16 results have been received and the patient is able to continue to Step 2 Registration.

Physicians or institutions can request the patient's EGFR level and/or HPV status from NRG Oncology (215-574-3154 or 215-574-3170) after the patient has completed study treatment.

The following material must be provided to the NRG Oncology Biospecimen Bank for EGFR expression and p16 analysis **(Mandatory for this study):**

10.2.1 Representative H & E stained slides: (slide can be a duplicate cut stained H&E; it does not have to be the diagnostic slide)

10.2.2 Corresponding FFPE Material

Preferred: tissue block containing tumor tissue (at least one); **Note**: If the NRG Oncology Biospecimen Bank cannot retain the block for tissue banking purposes, sites should not send the block. Instead, send the following acceptable alternatives (punches or unstained):

- H&E, 4-6 unstained slides **WITH** two 3mm punches from the tumor block (4 slides for non-oropharyngeal patients; 6 slides for oropharyngeal patients); see the note below for details;
- **OR** H&E and 15 unstained slides from the tumor block (all cases).

Note: Institutions that are unable to submit a tissue block for the required EGFR analysis (and for patients with oropharyngeal carcinoma, the required HPV analysis) may, as an alternative, make an H&E, then take 4 (for non-oropharyngeal cases) or 6 unstained sections from the block (for oropharyngeal cases) then obtain two 3 mm core punches of the block and re-imbed the core punches into a recipient paraffin for submission. Institutions can request an FFPE specimen plug kit (**see** Appendix V) from the NRG Oncology Biospecimen Bank free of charge for this purpose: 415-476-7864/FAX 415-476-5271; RTOG@ucsf.edu.

If institutions are unable to submit a block or punches, then a minimum submission of one H&E and 15 unstained slides is an acceptable alternative for all cases.

- A Pathology Report documenting that the submitted block contains tumor; the report must include the NRG Oncology protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

  The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.
- A copy of the gross description of the tumor must accompany the specimen in order to evaluate the closest margin and distance. The pathology report documenting presence or absence of extracapsular spread and preferably, the location in the neck also should be included.
- A Specimen Transmittal (ST) Form stating that the tissue is being submitted for central review. Sites can access the form (no password required) at. http://www.rtog.org/ClinicalTrials/NonStudySpecificForms.aspx. The form must include the NRG Oncology protocol number and the patient's case number. If the patient is also enrolled on other NRG Oncology trials, this should be indicated on the form.
- EGFR analysis will be performed for every case and HPV p16 testing for oropharyngeal cases by the Pathology Co-Chair, Richard Jordan, DDS, PhD, FRCPath.

10.3 Specimen Collection for Tissue Banking and Translational Research: Highly Recommended (But Optional) (3/5/15)

For patients who have consented to participate in the tissue/blood component of the study (See sample consent).

Patients must be offered the opportunity to participate in the tissue/specimen collection for banking and translational research. If the patient consents to participate in this component, the site is required to submit the patient's specimens as specified below. **Note**: Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent form.

See Section 1.4 for the proposed translational research studies for this trial.

The following must be provided in order for the case to be evaluable for the Biospecimen Bank:

10.3.1 One H&E stained slide of the tumor tissue (slide can be a duplicate cut stained H&E; it does not have to be the diagnostic slide) .

10.3.2 Corresponding FFPE Tumor Tissue Block (at least one, and the block must match the H&E being submitted) **OR** 4-6 unstained slides **WITH** two 3 mm punches from the block **OR** 15 unstained slides (This can be the same material submitted for the mandatory EGFR/HPV testing described in Section 10.2). **Note:** A kit with the punch, tube, and instructions can be obtained free of charge from the Biospecimen Bank. Block or core must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

10.3.3 A Pathology Report documenting that the submitted block or core contains tumor. The report must include the NRG Oncology protocol number and patient's case number. The patient's name

and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

The submitted material must be from malignant tumor, not necrotic or fibrotic tissue. If the submitted material is reviewed and is not tumor, the site may be assessed a protocol violation.

10.3.4 A Specimen Transmittal (ST) Form clearly stating that tissue is being submitted for the NRG Oncology Biospecimen Bank; if for translational research, this should be stated on the form. The form must include the NRG Oncology protocol number and patient's case number, patient initials, submitting institution name, and NCI ID (or NRG ID).

For serum, plasma, and whole blood: For collection, processing, and kit instructions, see Appendix V. The following materials must be provided to the NRG Oncology Biospecimen Bank: A Specimen Transmittal (ST) Form documenting the date of collection of the biospecimen; the NRG Oncology protocol number, the patient's case number, submitting institution name, and NCI ID (or NRG ID) time point of study, and method of storage, for example, stored at -80° C, must be included.

10.3.5 Storage Conditions

Store frozen specimens at -80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

  OR:
- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

  OR:
- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on ST Form the storage conditions used and time stored.

10.3.6 Specimen Collection Summary

Specimens for EGFR/HPV Analysis (Mandatory)			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide Pre-treatment	Slide shipped ambient
A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or 4-6 unstained slides plus two 3 mm diameter core of tissue, punched from the tissue block with a punch tool	Pre-treatment	Paraffin-embedded tissue block or 4-6 unstained slides and two 3mm punch biopsies. **Note**: 15 unstained slides are acceptable for sites unable to submit blocks/punches	Block or punch shipped ambient. (with a cold pack during summer)
Specimens for Banking/Translational Research (Recommended)			
Representative H&E stained slides of the primary tumor	Pre-treatment	H&E stained slide (can be additional or same as Central Review specimens)	Slide shipped ambient
A paraffin-embedded tissue block of the	Pre-treatment	Paraffin-embedded tissue block or two	Block or punch shipped ambient. (with a cold

primary tumor taken before initiation of treatment or two 3 mm diameter core of tissue, punched from the tissue block with a punch tool		3mm punch biopsies. Note: 15 unstained slides are acceptable for sites unable to submit blocks/punches (can be additional or same as Central Review specimens)	pack during summer)
SERUM: 5-10 mL of whole blood in red top tube and centrifuge	Pre-treatment	Frozen serum samples containing 0.5 mL per aliquot in 1 mL cryovials (five to eight)	Serum sent frozen on dry ice via overnight carrier
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge	Pre-treatment	Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (five to eight)	Plasma sent frozen on dry ice via overnight carrier
DNA: 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/ lavender top) and mix	Pre-treatment	Frozen whole blood samples containing 1 ml per aliquot in 1ml cryovials (three to five)	Whole blood sent frozen on dry ice via overnight carrier

10.3.7 Submit materials for Tissue Banking, Central Review, Translational Research as follows:

U. S. Postal Service Mailing Address: <u>For Non-Urgent or Non-Frozen Specimens Only</u>
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
Campus Box 1800
2340 Sutter St, room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): <u>For Urgent FFPE and ALL Frozen Specimens</u>
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
2340 Sutter St, room S341
San Francisco, CA 94115

Questions: 415-476-7864/FAX 415-476-5271; RTOG@ucsf.edu

10.4 Reimbursement (3/5/15)

NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the National Clinical Trials Network (NCTN). This information will be made available with the other registration materials in the Oncology Patient Enrollment Network (OPEN) portal system

10.5 Confidentiality/Storage

(See the Patient Tissue Consent Frequently Asked Questions, http://www.rtog.org/Researchers/BiospecimenResource/BiospecimenResourceFAQs.aspx for further details.)

10.5.1 Upon receipt, the specimen is labeled with the NRG Oncology protocol number and the patient's case number only. The NRG Oncology Biospecimen Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.5.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

See Appendix I for a summary of assessments and time frames. See the section below for details of evaluations and exceptions.

11.2 Details of Evaluations (3/5/15)

Preoperative, diagnostic imaging of the head and neck (showing initial gross disease): A neck CT (with contrast) or CT/PET (with contrast) and/or an MRI of the neck (T1 with Gadolinium and T2) within 84 days prior to surgery, must be submitted in DICOM format via TRIAD. The report is to be uploaded into Rave. (see Section 12.3).

11.2.1 Pretreatment Evaluation

- As required in Section 3.1.4, Chest CT scan (with or without contrast) or CT/PET that includes the chest (with or without contrast) either within 84 days prior to surgery or within 120 days prior to registration; note: If the CT/PET with or without contrast is done within 84 days prior to surgery, it fulfills the chest imaging requirement.
- An examination by an ENT or Head & Neck Surgeon must be done prior to surgery. A laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure), if appropriate, is recommended but not required. Intra-operative examination is acceptable documentation.

11.2.2 Evaluation during Treatment

- A general history & physical by a Radiation Oncologist and/or Medical Oncologist must be done weekly.
- CBC, Diff, & AGC will be done weekly; see Appendix I for all other lab assessments to be collected weekly.
- Patients must have Na, K, Cl, glucose, Ca, Mg tested weekly, and albumin tested every 3 weeks during radiation therapy.
- Patients must have bilirubin and AST or ALT tested q 3 weeks during radiation therapy.
- CT with contrast or CT/PET and/or MRI of head and neck should be done as clinically indicated.
- Chest imaging (at minimum a chest x-ray or chest CT or CT/PET of chest +/- contrast) should be done as clinically indicated.
- Biopsy of any lesion(s) suspicious for tumor recurrence is urged.

11.2.3 Evaluation in Follow Up

- A general history and physical by one of the following: a Radiation Oncologist, Medical Oncologist, an ENT, or a Head and Neck Surgeon must be done at 1 and 3 months post-RT, then q3 months for 2 years, every 6 months for 3 years, then annually. A laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) is recommended at these time points but is not required.
- CT (with contrast) or CT/PET (with contrast) and/or MRI (T1 with Gadolinium and T2**)** of head and neck is strongly recommended at 3-month follow up +/- 2 weeks. **Note**: For patients with local or regional neck failure, post-treatment imaging showing the failure at any time post-treatment must be submitted in DICOM format via TRIAD. The report is to be uploaded into Rave. (see Section 12.3).
- Chest imaging (at minimum a chest x-ray or chest CT or CT/PET of chest) should be done as clinically indicated.
- Biopsy of any lesion(s) suspicious for tumor recurrence is urged.

11.3 Outcomes Criteria

11.3.1 No evidence of disease (NED): All patients must not have measurable tumor following surgery.

11.3.2 Local-Regional Relapse: Recurrent cancer in the tumor bed and/or neck not clearly attributable to a second primary neoplasm; both imaging and biopsy confirmation are strongly recommended. LRR will be further subdivided into three subcategories:

- *In-Field Local-Regional Relapse*
  Review of the imaging of the local-regional relapse and the patient's previous IMRT treatment data reveals that the "epicenter" of the local-regional relapse is within CTV60 and received an estimated dose of at least 50 Gy.
- *Marginal Local-Regional Relapse*
  Review of the imaging of the local-regional relapse and the patient's previous IMRT treatment data reveals that the "epicenter" of the local-regional relapse was "near" CTV60. This is defined as an estimated dose to this region that is between 20 and 50 Gy.
- *Out-of-Field Local-Regional Relapse*
  Review of the imaging of the local-regional relapse and the patient's previous IMRT treatment data reveals that the "epicenter" of the local-regional relapse was not near CTV60 or CTV56 and received an estimated dose < 20 Gy. An example would be recurrence in the retropharyngeal nodal space for a patient with oral cavity cancer.

11.3.3 Distant Relapse: Clear evidence of distant metastases (lung, bone, brain, etc.); biopsy is recommended where possible. A solitary lung mass/nodule should be considered a second primary upper aerodigestive neoplasm unless proven otherwise. If there is any question whether or not a malignancy is a recurrence of the original primary cancer versus a new primary, contact the Co-Principal Investigators, Drs. Harari or Rosenthal.

11.3 4 Second Primary Neoplasm: All second primary neoplasms will be biopsy proven with documentation of specific histology. Modified rigorous criteria for a second primary (below) have been adapted from the definition by Warren and Gates (1932). Localized non-melanoma skin cancers are not considered new primary tumors.

- A distinct lesion separated from the primary tumor site by > 2 cm of normal epithelium;
- A new cancer with different histology;
- Any cancer, regardless of head and neck mucosal subsite, occurring 5 or more years after initial treatment;
- In the lung, new primary tumors, if squamous cell cancer, must have histologic findings of dysplasia or CIS.

11.3.5 Second Primary Upper Aerodigestive Neoplasm: The emergence of a new, invasive malignancy in the upper aerodigestive tract as a second primary should be documented. These neoplasms include lung cancer, esophageal cancer (including GE junction cancer), or 2nd primary head and neck cancer that is clearly remote from the index cancer (eg, pyriform sinus cancer developing in a patient whose original diagnosis was tongue cancer). If there is any question whether or not a malignancy is a recurrence of the original primary cancer versus a new primary, contact the Co-Principal Investigators, Drs Harari or Rosenthal.

11.4 Patient-Reported Outcomes and Quality Adjusted Survival Assessments (2/20/14)

NOTE: Patients must complete the MDASI-HN (see Section 11.4.2 below and the sample consent). This instrument is needed as part of the assessment of the primary endpoint of the study. The other assessments described below (the FACT-HN, the MDADI, and the EQ-5D), are optional.

In addition, all patients must be offered the opportunity to participate in the correlative components of the study, such as quality of life assessment. If the patient consents to complete the other patient-reported outcomes (PROs) and quality adjusted survival assessments in the study, sites are required to administer the baseline QOL and functional assessments prior to the start of protocol treatment.

Three instruments will be used to measure patient-reported outcomes (PROs) and QOL: the Functional Assessment of Cancer Therapy-Head and Neck Cancer (FACT-H&N), version 4; the MD Anderson Symptom Inventory–Head and Neck (MDASI-HN); and the MD Anderson

Dysphagia Inventory-Head and Neck (MDADI-HN). The EuroQol (EQ-5D) will be used to assess quality-adjusted survival for this study.

A combination of these assessments will be completed prior to the start of treatment (baseline), at completion of chemoradiation (allowable 3 weeks before or 6 weeks after this time point), and then at 3 months (allowable 3 weeks before or 6 weeks after this time point), 6, 12 and 24 months (allowable 3 months before or after those time points) from the end of radiation.

11.4.1 The FACT-H&N

The FACT-H&N is a multidimensional, patient-self report QOL instrument that has been specifically designed and validated for this patient population. The questionnaire consists of 27 core items that assess patient function in 4 domains. The FACT-H&N can be completed by the patient in 5-10 minutes, is available in 26 languages, and will be completed at baseline, completion of RT and at 12 months from the end of RT.

11.4.2 *The MDASI-HN*

Patients must complete the MDASI-HN, as this assessment is needed as part of the assessment of the primary endpoint of the study. The MDASI-HN will be used to measure the symptom burden on each arm from the patient's perspective. The MDASI-HN is a 28-item PRO instrument consisting of 3 subscales The questionnaire can be completed by the patient in 5-10 minutes and is available in a 5 languages. The patient will complete the MDASI at baseline, every 2 weeks during RT corresponding to factions 10 (end of week 2), 20 (end of week 4), and 30 or 33, (at completion of RT) +/- a 1-week window and at 3, 6, 12, and 24 months after completion of RT.

11.4.3 *The MDADI*

The MDADI is a 20-item PRO instrument, scored on a scale from 1 to 5, consisting of global, emotional, functional, and physical subscales. The MDADI evaluates the effects of dysphagia on QOL. The questionnaire can be completed by the patient in 5-10 minutes and available only in English. The MDADI will be administered at baseline and at 3, 6, 12, and 24 months after completion of RT

11.4.4 The EQ-5D

The EQ-5D is a 2-part questionnaire that the patient can complete in 5 minutes and has been translated into multiple languages. The first part consists of 5 items covering 5 dimensions. The second part is a visual analogue scale (VAS) valuing current health state. Patients will complete the EQ-5D at baseline and at 12 and 24 months from the end of RT.

11.5 Criteria for Discontinuation of Protocol Treatment

- Unacceptable toxicity; see Sections 6.9 and 7.0 for further information.
- Progression of disease;
- Development of a 2nd primary upper aerodigestive tract malignancy (eg, lung cancer, esophagus cancer, 2nd primary head and neck cancer);
- A delay in protocol treatment, as specified in Sections 6.7 and/or 7.0. Treatment breaks, if necessary, ideally should not exceed 5 treatment days at a time and 10 treatment days total.

If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

12.0 DATA COLLECTION (9/2/14)

This study will utilize Medidata Rave® for remote data capture (RDC) of all data. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS. To access iMedidata/Rave, see Section 5.2 of the protocol.

Each person responsible for data entry must be on the NRG Oncology roster in order to receive access to Medidata Rave®.

Upon initial site registration approval for the study in RSS (Regulatory Support System), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata (iMedidata-Notification@mdsol.com) to activate their account. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner

of the iMedidata page. Once an account is activated, eLearning modules will be available for Rave RDC instructions. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab 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.

12.1 Summary of Data Submission (9/25/13)

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 more timely monitoring of patient safety and care. The following sections provide information about expedited reporting. For this trial the *Protocol Specific Adverse Events* and *Other Adverse Events forms* are used for routine AE reporting in Rave.

Folder	Form/Item
Registration via the OPEN System	• ***Subject Enrollment Form***
Enrollment When pushed into RAVE there will be 5 forms representing registration	• ***Demography Form*** • ***Step Information Form*** • ***Treatment Assignment Form*** • ***Eligibility Checklist Form*** • ***Eligibility Checklist II Form***
Baseline	• ***Patient History Form*** *(formerly known as the A5)* • ***Work Up*** • ***Pre-op imaging report*** *(Upload of report required)* • ***Lab Results Baseline*** • ***Diagnostic Staging*** • ***Surgery*** • ***Operative note*** *(Upload of report required)* • ***Surgical pathology note*** *(Upload of report required)* • ***Prior Treatment*** • ***Exclusion Criteria*** • ***Protocol Specific AE Form*** • ***Scan Submission-*** *(Refer to section 12.3)* • ***MDASI-HN Cover Page*** • ***MDASI-HN –*** *if questionnaire completed = 'yes'* **IF CONSENTED FOR QOL:** • ***MDADI Cover page*** • ***MDADI –*** *if questionnaire completed = 'yes'* • ***FACT-H and N Cover Page*** • ***FACT-H and N–*** *if questionnaire completed = 'yes'*

	• ***EQ-5D Cover Page*** • ***EQ-5D–*** *if questionnaire completed = 'yes'*
Baseline RT	• ***Digital Data****-(Upload of e-mail confirmation from TRIAD submission required)*
WEEK 2 (during RT)	• ***MDASI Cover Page*** • ***MDASI –*** *if questionnaire completed = 'yes'* • ***Protocol Specific AE Form*** • ***Other Adverse Event Forms*** *– if new or continuing adverse events = 'yes'* • ***Follow Up Head and Neck***
WEEK 4 (during RT)	• ***MDASI Cover Page*** • ***MDASI –*** *if questionnaire completed = 'yes'* • ***Protocol Specific AE Form*** • ***Other Adverse Event Forms****– if* new or continuing adverse events = 'yes' • ***Follow Up Head and Neck***
WEEK 6 (end of RT)	• ***RT Administration*** • ***RT Treatment****-if was radiation therapy given = 'yes'* • ***RT Treatment Record-*** *if was radiation therapy given = 'yes' (Upload of report required)* • ***Cisplatin (Arm 1)*** • ***Docetaxel (Arm 2 or 3)*** • ***Cetuximab (Arm 3)*** • ***Protocol Specific AE Form*** • ***Other Adverse Event Forms*** *– if new or continuing adverse events = 'yes'* • ***Supportive Care*** • ***Hospitalization*** • ***Follow Up Head and Neck*** • ***MDASI Cover Page*** • ***MDASI –*** *if questionnaire completed = 'yes'* **IF CONSENTED FOR QOL:** • ***FACT-H and N Cover Page*** • ***FACT-H and N–*** *if questionnaire completed = 'yes'*
Weeks 1-8 Labs	• ***Lab Results Follow Up Weeks 1-8*** *(During Treatment Labs)*
MONTH 1 (Post RT)	• ***Patient Contacted*** • ***Follow-up-*** *if Patient able to be Contacted ='yes'* • ***Follow-up Head and Neck*** *-if Patient able to be Contacted ='yes'* • ***Disease Assessment-*** *if Documented clinical assessment = 'yes'* • ***Scan Submission-*** *if local or regional recurrence or progression = 'yes'* • ***New Primary Cancer-*** *If New Primary Cancer=*

	'yes' • ***Non-Protocol Treatment-*** *if non-protocol cancer therapy= 'yes'* • ***Protocol Specified AE Form-*** *if Patient able to be Contacted ='yes'* • ***Other Adverse Events****– if new or continuing adverse events = 'yes'* • ***Primary Cause of Death- –*** *if Patient's Vital Status = 'dead'*
MONTH 3 (Post RT) MONTH 6 (Post RT)	• ***Patient Contacted*** • ***Follow-up -*** *if Patient able to be Contacted ='yes'* • ***Follow-up Head and Neck-*** *if Patient able to be Contacted ='yes'* • ***Disease Assessment-*** *if Documented clinical assessment = 'yes'* • ***Scan Submission-*** *if local or regional recurrence or progression = 'yes'* • ***New Primary Cancer-*** *If New Primary Cancer= 'yes'* • ***Non-Protocol Treatment-*** *if non-protocol cancer therapy= 'yes'* • ***Protocol Specified AE Form-*** *if Patient able to be Contacted ='yes'* • ***Other Adverse Events****– if new or continuing adverse events = 'yes'* • ***Primary Cause of Death–*** *if Patient's Vital Status = 'dead'* • ***MDASI-HN Cover Page*** • ***MDASI-HN –*** *if questionnaire completed = 'yes'* **IF CONSENTED FOR QOL:** • ***MDADI Cover page*** • ***MDADI–*** *if questionnaire completed = 'yes'*
MONTH 9 (Post RT)	• ***Patient Contacted*** • ***Follow-up -*** *if Patient able to be Contacted ='yes'* • ***Follow-up Head and Neck-*** *if Patient able to be Contacted ='yes'* • ***Disease Assessment-*** *if Documented clinical assessment = 'yes'* • ***Scan Submission-*** *if local or regional recurrence or progression = 'yes'* • ***New Primary Cancer-*** *If New Primary Cancer= 'yes'* • ***Non-Protocol Treatment-*** *if non-protocol cancer therapy= 'yes'* • ***Protocol Specified AE Form-*** *if Patient able to be Contacted ='yes'* • ***Other Adverse Events****– if new or continuing adverse events = 'yes'* • ***Primary Cause of Death–*** *if Patient's Vital Status = 'dead'*

MONTH 12 (Post RT)	• ***Patient Contacted*** • ***Follow-up -*** *if Patient able to be Contacted ='yes'* • ***Follow-up Head and Neck-*** *if Patient able to be Contacted ='yes'* • ***Disease Assessment-*** *if Documented clinical assessment = 'yes'* • ***Scan Submission-*** *if local or regional recurrence or progression = 'yes'* • ***New Primary Cancer-*** *If New Primary Cancer= 'yes'* • ***Non-Protocol Treatment-*** *if non-protocol cancer therapy= 'yes'* • ***Protocol Specified AE Form-*** *if Patient able to be Contacted ='yes'* • ***Other Adverse Events****– if new or continuing adverse events = 'yes'* • ***Primary Cause of Death–*** *if Patient's Vital Status = 'dead'* • ***MDASI-HN Cover Page*** • ***MDASI-HN –*** *if questionnaire completed = 'yes'* **IF CONSENTED FOR QOL:** • ***MDADI Cover page*** • ***MDADI -*** *if questionnaire completed = 'yes'* • ***FACT-H and N Cover Page*** • ***FACT-H and N–*** *if questionnaire completed = 'yes'* • ***EQ-5D Cover Page*** • ***EQ-5D–*** *if questionnaire completed = 'yes'*
MONTH 15 (Post RT) MONTH 18 (Post RT) MONTH 21 (Post RT)	• ***Patient Contacted*** • ***Follow-up -*** *if Patient able to be Contacted ='yes'* • ***Follow-up Head and Neck-*** *if Patient able to be Contacted ='yes'* • ***Disease Assessment-*** *if Documented clinical assessment = 'yes'* • ***Scan Submission-*** *if local or regional recurrence or progression = 'yes'* • ***New Primary Cancer-*** *If New Primary Cancer= 'yes'* • ***Non-Protocol Treatment-*** *if non-protocol cancer therapy= 'yes'* • ***Protocol Specified AE Form-*** *if Patient able to be Contacted ='yes'* • ***Other Adverse Events****– if new or continuing adverse events = 'yes'* • ***Primary Cause of Death–*** *if Patient's Vital Status = 'dead'*
MONTH 24 (Post RT)	• ***Patient Contacted*** • ***Follow-up -*** *if Patient able to be Contacted ='yes'*

	• ***Follow-up Head and Neck-*** *if Patient able to be Contacted ='yes'* • ***Disease Assessment-*** *if Documented clinical assessment = 'yes'* • ***Scan Submission-*** *if local or regional recurrence or progression = 'yes'* • ***New Primary Cancer-*** *If New Primary Cancer= 'yes'* • ***Non-Protocol Treatment-*** *if non-protocol cancer therapy= 'yes'* • ***Protocol Specified AE Form-*** *if Patient able to be Contacted ='yes'* • ***Other Adverse Events****– if new or continuing adverse events = 'yes'* • ***Primary Cause of Death–*** *if Patient's Vital Status = 'dead'* • ***MDASI-HN Cover Page*** • ***MDASI-HN -*** *if questionnaire completed = 'yes'* **IF CONSENTED FOR QOL:** • ***MDADI Cover page*** • ***MDADI -*** *if questionnaire completed = 'yes'* • ***EQ-5D Cover Page*** • ***EQ-5D-*** *if questionnaire completed = 'yes'*
MONTH 30 (Post RT) MONTH 36 (Post RT) MONTH 42 (Post RT) MONTH 48 (Post RT) MONTH 54 (Post RT) MONTH 60 (Post RT)	• ***Patient Contacted*** • ***Follow-up -*** *if Patient able to be Contacted ='yes'* • ***Follow-up Head and Neck-*** *if Patient able to be Contacted ='yes'* • ***Disease Assessment-*** *if Documented clinical assessment = 'yes'* • ***Scan Submission-*** *if local or regional recurrence or progression = 'yes'* • ***New Primary Cancer-*** *If New Primary Cancer= 'yes'* • ***Non-Protocol Treatment-*** *if non-protocol cancer therapy= 'yes'* • ***Protocol Specified AE Form-*** *if Patient able to be Contacted ='yes'* • ***Other Adverse Events****– if new or continuing adverse events = 'yes'* • ***Primary Cause of Death–*** *if Patient's Vital Status = 'dead'*
YEAR 6 - YEAR 15 (Post RT)	• ***Patient Contacted*** • ***Follow-up -*** *if Patient able to be Contacted ='yes'* • ***Follow-up Head and Neck-*** *if Patient able to be Contacted ='yes'* • ***Disease Assessment-*** *if Documented clinical assessment = 'yes'* • ***Scan Submission-*** *if local or regional recurrence or progression = 'yes'* • ***New Primary Cancer-*** *If New Primary Cancer=*

	'yes' • ***Non-Protocol Treatment-*** *if non-protocol cancer therapy= 'yes'* • ***Protocol Specified AE Form*** *if Patient able to be Contacted ='yes'* • ***Other Adverse Events****– if new or continuing adverse events = 'yes'* • ***Primary Cause of Death–*** *if Patient's Vital Status = 'dead'*

12.2 Summary of Dosimetry Digital Data Submission (Submit to TRIAD; see Section 5.2 for account access and installation instructions.) (2/20/14)

Item	**Due**
Preliminary Dosimetry Information (DD)	
Digital Data Submission	Within 1 week of start of RT
Digital data submission includes the following, all in DICOM format:	
• CT data, critical normal structures, all GTV, CTV, and PTV contours	
• Digital beam geometry for initial and boost and composite beam sets	
• Doses for initial boost and composite sets of concurrently treated beams	
• Digital DVH data for all required critical normal structures, GTV, CTV, and PTVs for total dose plan • All required structures **MUST** be labeled per the table in Section 6.6. • *The "RTOG 1216 Datasheet" is available in the Forms section of the RTOG/NRG Oncology web* site: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1216 Submit via TRIAD with the digital data listed above.	
Upon submission of the digital data via TRIAD, complete an online DDSI form. http://www.rtog.org/CoreLab/RTQASubmissionInformation.aspx	
NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.	

12.3 Scan Submission via TRIAD (2/20/14)

Item	**Due**
Pre-op CT (with contrast) or CT/PET (with contrast) and/or MRI (T1 with Gadolinium and T2) of H/N submitted via TRIAD in DICOM format with report uploaded into Rave.	Within 2 weeks of study entry
Post RT: Local-Regional failure CT (with contrast), Within 1 week of scan date or CT/PET (with	Within 1 week of scan date

contrast), and/or MRI (T1 with Gadolinium, and T2), of H/N submitted via TRIAD in DICOM format with report uploaded into Rave.	

13.0 STATISTICAL CONSIDERATIONS

13.1 Randomized Phase II Component Primary Endpoint

13.1.1 Disease-free survival (DFS)

13.2 Phase III Component Primary Endpoint

13.2.1 Overall survival (OS)

13.3 Randomized Phase II and Phase III Components Secondary Endpoints

13.3.1 Local-regional failure (LRF);
13.3.2 Distant metastasis (DM);
13.3.3 Patterns of cancer failure (local, regional, distant) and correlation with radiation dose and technique;
13.3.4 Acute toxicity profiles during and at completion of treatment;
13.3.5 Late toxicity profiles at 1, 3, 5 years after treatment;
13.3.6 FACT-H&N;
13.3.7 MDASI-HN;
13.3.8 MDADI;
13.3.9 EQ-5D;
13.3.10 Quality adjusted life year (QALY);
13.3.11 Translational research analysis.

13.4 Stratification

Patients will be stratified by Zubrod Performance Status (0 vs. 1); primary tumor site (oral cavity vs. larynx vs. hypopharynx vs. p16-negative oropharynx); and EGFR expression (high vs. low vs. not evaluable).

13.5 Sample Size with Power Justification

13.5.1 Randomized Phase II Component

The DFS at 3 years was 50% for the RT+ cisplatin arm in RTOG 95-01 and 54% for the cisplatin arm in RTOG 0234. When limited to p16-negative oropharyngeal cancer and other sites, the 3-year DFS is 29% and the hazard ratio is 0.50 (p=0.004) between the 2 arms of RTOG 0234. For design purposes, we assume that the cisplatin arm of 1216 has a 3-year DFS of 35%. With a one-sided type I error rate of 0.15, 80% power, and a hazard ratio of 0.6, we will need 120 analyzable patients for each pairwise comparison against control (60 patients per arm, or 180 total) to be followed for 1.3 years for a total of 3.5 years. Allowing for approximately 10% of patients to be ineligible or otherwise not evaluable, **the total sample size for the 3-arm design is 200. Accrual will be suspended while we are following these patients before phase II final analysis.**

13.5.2 Phase III Component

The primary objective of this component is to compare the overall survival between the control arm (postoperative radiation and cisplatin) and the more effective experimental arm. The OS at 3 years was 58% for the RT+ cisplatin arm in RTOG 95-01 and 64% for the cisplatin arm in RTOG 0234. When limited to p16-negative oropharyngeal cancer and other sites, the 3-year OS is 39% and the hazard ratio is 0.62 (p=0.062) between the 2 arms of RTOG 0234. For design purposes, we assume that the cisplatin arm of 1216 has a 3-year OS of 45%. The null hypothesis is that the hazard ratio is 1 and the alternative hypothesis is the hazard ratio is 0.67.

For the proposed study, a group sequential design with 3 interim analyses and a final analysis based on O'Brien-Fleming boundary will be used. The significance level for a one-sided test, the statistical power, and the hazard ratio were set at 0.033 (adjusted for treatment arm selection in the randomized phase II component using correlated DFS such that overall error does not exceed

0.05 (Freidlin 2012), 0.8, and 0.67, respectively. A total of 408 patients will be randomized. The sample size for the phase III component is 408, including 134 patients enrolled during phase II to the control arm and the selected experimental arm (ie, 274 patients will be newly randomized during phase III). Including the 67 patients enrolled to the experimental arm dropped during phase II, **the total sample size is 475 patients**. A yearly accrual rate of 90 patients is projected after the study is opened 6 months. With this accrual rate, it will take 7 years to complete accrual, and the final definitive treatment analysis would occur 7.2 years after the study is opened 6 months. With this design, the expected study duration is 6.5 years if the alternative hypothesis is true.

13.6 Analysis Plan

13.6.1 Statistical Methods

Time-to-event endpoints will be measured from the date of randomization to the date of failure, competing risk, or last follow-up. The table below shows how each first event will be counted for LRF, DM, and DFS. Anything not explicitly in the table (eg second primary tumor) is not considered an event, and the patient will continue to be followed for failure. For OS, death from any cause will be considered a failure. The DFS and the OS rates will be estimated using the Kaplan-Meier method (1958) for each arm. Their distributions will be compared between treatment arms with a one-sided log rank test (Mantel 1966). The cumulative incidence method will be used to estimate LRF and DM rates, and the failure rates for the experimental treatment will be compared against the control using a failure specific log rank test. Multivariate analysis will be performed using the Cox (1972) proportional hazards model. The toxicity analysis will be done in 2 ways: 1) Analysis will be based upon only adverse events (AEs) attributed by investigator to be definitely, probably, or possibly related (if relationship is missing it will be considered related) to protocol treatment; 2) Analysis will be based upon all reported adverse events regardless of attribution. Rates of grade 3+ adverse events for the CTCAE system organ classes such as gastrointestinal and overall will be generated for each analysis method. These rates will be estimated using a binomial distribution along with their associated 95% confidence intervals and will be compared using Fisher's exact test between the treatment arms. All eligible patients will be included in analysis in the arm to which they were randomly assigned (intent-to-treat).

First Event	LRF	DM	DFS
None	Censored	Censored	Censored
Local-regional recurrence	Failure	Competing risk	Failure
Distant metastasis	Competing risk	Failure	Failure
Death due to study cancer or from unknown causes	Failure	Competing risk	Failure
Death due to any other reason	Competing risk	Competing risk	Failure

13.6.2 Routine Interim Analysis to Monitor Study Progress

Interim reports will be prepared twice each year until the final analysis has been accepted for presentation or publication. In general, these reports will contain information about the accrual rate with projected completion date for the accrual phase, exclusion rates and reasons, pretreatment characteristics of patients accrued, compliance rate of treatment delivered with respect to the protocol prescription, and the frequency and severity of adverse events.

13.6.3 Interim Analysis for the Data Monitoring Committee (DMC)

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis. In addition, this study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

Randomized Phase II Component

The interim analysis for futility will be performed when there are 28 events for DFS, and the results will be reported to the NRG Oncology DMC. We would recommend stopping for futility if

the p value base log rank test is > 0.547. The futility/stopping boundary is derived using Rho family of spending function with parameter of 1.5.

Phase III Component

The significance testing of efficacy will be performed when 46, 92, and 138 deaths occur for the 2 arms combined, and the results reported to the NRG Oncology DMC with a recommendation for possible early reporting. An O'Brien-Fleming boundary will be utilized for efficacy monitoring. For futility, the statistical monitoring boundary will be based on the LIB20 method, as recommended by Freidlin (2010).

13.6.4 Analysis for Reporting the Treatment Results

Randomized Phase II Component

Each of the experimental arms will be compared to the control arm when all patients are potentially followed for 1.3 years to have total of 56 events for DFS for 1 comparison. A one-sided log rank test will be used to compare the DFS at a significance level of 0.15. Detailed possible DFS results can be found in the following table and decision rules integrating toxicity data are described below:

Arm 2 vs. Arm 1	Arm 3 vs. Arm 1	Decision
Not significant	Not significant	Stop trial; report phase II results
Not significant	Significant	Arm 3 to phase III
Significant	Not significant	Arm 2 to phase III
Significant	Significant, but < 5% better than Arm 2	Arm 2 to phase III
Significant	Significant, but > 5% better than Arm 2	Arm 3 to phase III

We will perform an overall assessment of Grade 3-5 toxicities and QOL between the 2 experimental arms (as well as in comparison to the control arm) to identify if there is a significant difference. If only 1 experimental arm improves DFS, then it will be selected for phase III comparison. If both experimental arms show improved DFS and Arm 3 is not at least 5% better than Arm 2 with similar toxicities, QOL may be taken into consideration in selecting the winner. However, if Arm 3 is not at least 5% better than Arm 2, but substantially increased toxicity more than Arm 2, we will select Arm 2 for phase III comparison. If both arms improve DFS, and Arm 3 is at least 5% better in terms of DFS and has similar toxicity, then we will proceed with Arm 3. However, if Arm 3 is associated with a substantially increased toxicity in the last scenario, we would certainly consider very carefully (including QOL) in selecting the preferred arm for phase III comparison. To be specific, if both experimental arms show improved DFS and Arm 3 is not at least 5% better than Arm 2 with similar acute toxicities, MDASI-HN scores at weeks 4 and 6 during RT and at 3 months and 1 year after completion of RT will be compared between the treatment arms to select the winner. If Arm 3 is associated with a substantially increased acute toxicity and is at least 5% better in terms of DFS in the last scenario, the MDASI-HN scores at weeks 4 and 6 during RT and at 3 months after completion of RT will be compared between the arms in order to select the preferred arm for the phase III comparison and careful consideration of long-term dysphagia rates, PEG tube dependence, and MDASI-HN scores at 1 year.

Operating Characteristics

The operating characteristics of the design were approximated using asymptotic normal distributions. Let Y(1) and Y(2) be asymptotically normal statistics based on logrank test for comparing DFS of arms 2, 3 to the control arm in phase II and let Z(1) and Z(2) be the asymptotically normal statistics based on logrank test for comparing OS of arms 2, 3 to the control arm in phase III. The joint distribution of the four statistics is multivariate normal. The total error rate for phase IIIis adjusted through numerical integrations to account for the correlation between DFS and OS and arm selection in phase II. The upper bound of the error rate is adjusted to 0.033 (Freidlin, 2012 personal communication). Probabilities in the following tables are based on 10000 simulations. The results show that overall type I error rate has been controlled at the

nominal level and the power is reasonable under a range of treatment effects on DFS and OS given different correlations.

Submitted Design: Type 1 errors 0.15/0.033, 80% power — Phase II Size and Power

True DFS HRs		True OS HRs		Correlation between DFS and OS at Phase II				
Arm 2/1	Arm 3/1	Arm 2/1	Arm 3/1	1	0.85	0.75	0.5	0.25
1	1	1	1	0.2422	0.2407	0.2417	0.2417	0.2411
1	0.6	1	1	0.8096	0.8119	0.8136	0.8135	0.8142
1	0.6	1	0.67	0.8121	0.8131	0.8132	0.8148	0.8130
0.6	1	1	1	0.8121	0.8124	0.8119	0.8158	0.8138
0.6	1	0.67	1	0.8076	0.8087	0.8085	0.8100	0.8107
0.6	0.6	0.67	0.67	0.9201	0.9205	0.9209	0.9199	0.9127
0.6	0.6	0.7	0.67	0.9243	0.9242	0.9244	0.9253	0.9262
0.6	0.51	0.67	0.67	0.9664	0.9659	0.9659	0.9663	0.9654

Submitted Design: Type 1 errors 0.15/0.033, 80% power — Phase III Size and Power

True DFS HRs		True OS HRs		Correlation between DFS and OS at Phase II				
Arm 2/1	Arm 3/1	Arm 2/1	Arm 3/1	1	0.85	0.75	0.5	0.25
1	1	1	1	0.0297	0.0249	0.0218	0.0157	0.0111
1	0.6	1	1	0.0391	0.0381	0.0376	0.0337	0.0317
1	0.6	1	0.67	0.6890	0.6793	0.6747	0.6602	0.6465
0.6	1	1	1	0.0329	0.0320	0.0322	0.0310	0.0292
0.6	1	0.67	1	0.6988	0.6922	0.6865	0.6750	0.6648
0.6	0.6	0.67	0.67	0.8117	0.8013	0.7935	0.7751	0.7584
0.6	0.6	0.7	0.67	0.7779	0.7645	0.7559	0.7366	0.7179
0.6	0.51	0.67	0.67	0.8519	0.8438	0.8353	0.8195	0.8026

Phase III component

The analysis reporting the treatment results will be carried out after 183 deaths have been observed, unless the criteria for early stopping are met. The usual components of this analysis are:

- Tabulation of all cases entered and any excluded from analysis with reasons for exclusion;
- Patient accrual rate;
- Institutional accrual;
- Distribution of important baseline prognostic variables;
- Frequency and severity of adverse events;
- Observed results with respect to the endpoints described in Sections 3.1-3.3.

The difference in overall survival (OS) distributions between the control arm and the experimental arm will be tested using the one-sided log-rank test at the significance level of 0.0287, given that the 3 interim analyses are carried out and show no statistical significance.

13.7 Statistical Design for Translational Research

As noted in Section 1.4, the proposed correlative studies in Sections 1.4, 10.3, and 13.7 of the protocol require the results of the parent study. Specifically, the number of events for the 2 clinical endpoints, DFS and OS, which are necessary to carry out a realistic statistical power justification cannot be ascertained until the parent study is completed. In addition, the projected timeline for the parent study is 7 years. The predictive and prognostic potential for these biomarkers may become scientifically obsolete or the assay technology may evolve over time making the technology outlined in the current protocol obsolete. As such, NO marker assays will be conducted (i.e., ERCC1, p53, and EGFR for correlative studies) on the collected specimens other than those required for patient stratification (i.e., p16, EGFR). When sufficient information is available from the parent study, a full correlative study document for the marker studies detailing

the scientific hypothesis, research plan, assay methods for each biomarker, and a complete statistical section (with adequate power justification and analysis plan) will be submitted to and reviewed by CTEP in accordance with the National Clinical Trials Network (NCTN) policies.

13.8 Statistical Design for Patient-Reported Outcomes (PROs) and Quality Adjusted Survival

For analysis of acute mucosal toxicity predicting long-term swallowing dysfunction and decreasing global QOL, we estimated statistical power based on 40-60% missing data at 1 or 2 years for dependent and independent variables. We also considered various partial correlations ranging from 0.1 to 0.9 between acute mucosal toxicities and swallowing dysfunction/QOL. Based on multiple linear regression and 245 patients, we will have 97% power for the 2 arms combined, if there is 60% missing data at 1 or 2 years.

Percent missing	Available patients	PCCOR=0.1	PCCOR=0.3	PCCOR=0.5	PCCOR=0.7	PCCOR=0.9
40%	245	34.7%	99.7%	99.9%	99.9%	99.9%
50%	205	29.9%	99.1%	99.9%	99.9%	99.9%
60%	164	24.9%	97.0%	99.9%	99.9%	99.9%

Overall, the mean summary score and standard deviation of acute mucosal toxicity, the FACT-H&N, MDASI-HN, MDADI, and the subscales including the swallowing domain will be determined. The effect of acute mucosal toxicity on swallowing dysfunction and global QOL will be modeled using general linear regression. Binary outcomes will be compared using Fisher's Exact test and modeled using logistic regression. Other potential covariates evaluated for the multivariate models would be assigned treatment, age, gender, race, Zubrod performance status, T-stage, N-stage, primary site, and smoking history. The mean change from completion of chemoradiation at each time point will be summarized using mean and standard deviations for each arm. Overall score and mean change from completion of chemoradiation will be compared between the arms using a two sample t test. If data normality assumptions are not met, the Wilcoxon rank sum test will be used to test the hypothesis. Mean change from completion of chemoradiation will be tested using an omnibus F test followed by individual comparisons of change scores at different time points within each treatment group. The same analysis will be conducted for between group comparisons at each time point. In addition to comparing the change scores, overall trends in these scores will be modeled using the general linear mixed-effect model. A logistic regression model will be used to summarize number of missing data and to test if the dropout process is missing completely at random (MCAR). Analyses of complete cases and cases with imputations will be considered as a sensitivity analysis. A pattern mixture or selection model may be used to assess treatment effect to see if it is dropout dependent. Quality-adjusted survival will be compared using a two-sample independent t test. If data normality assumptions are not met, the Wilcoxon rank sum test will be used to test the hypothesis. With a two-sided alpha of 0.05 and 408 patients, we will have 99% power to detect a difference of 0.5 (Mean/SD) for the 2 arms combined. Assuming various attrition rates during follow up based on previous head and neck trials, the table below summarizes results of a power analysis for detecting different effect sizes. Impact of late toxicity including dysphagia as well as other factors such as age, gender, race, Zubrod performance status, T-stage, N-stage, primary site, and smoking history will be modeled using general linear regression for the comparison between 2 arms.

Percent missing	Available patients	Effect Size = 0.5	Effect Size = 0.375
40%	245	97%	83%
50%	205	94%	75%
60%	164	88%	66%

13.9 Gender and Minorities

Randomized Phase II Component: Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	1	4	5
Not Hispanic or Latino	49	146	195
Ethnic Category: Total of all subjects	50	150	**200**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	0	1	1
Asian	1	2	3
Black or African American	1	9	10
Native Hawaiian or other Pacific Islander	0	0	0
White	48	138	186
Racial Category: Total of all subjects	50	150	**200**

Phase III Component: Projected Distribution of Gender and Minorities

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	2	10	12
Not Hispanic or Latino	116	347	463
Ethnic Category: Total of all subjects	118	357	**475**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	0	2	2
Asian	2	4	6
Black or African American	2	21	23
Native Hawaiian or other Pacific Islander	0	0	0
White	114	330	444
Racial Category: Total of all subjects	118	357	**475**

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(3/5/15) APPENDIX I, STUDY PARAMETER TABLE: PRE-TREATMENT ASSESSMENTS

*See Section 11.2 for details and exceptions

Assessments	Prior to Registration (calendar days)	Prior to Treatment (calendar days)
General H&P by Rad Onc or Med Onc	84 days	
ENT/Surgeon Exam*	Prior to surgery	
Pre-op Imaging of H&N: CT (with contrast) of neck or CT/PET (with contrast) and/or MRI of neck (T1 with Gadolinium and T2) with report*	84 days prior to surgery	
Chest CT or CT/PET of chest +/- contrast	Either 84 days prior to surgery or 120 days prior to registration; see Section 11.2.1 for further details	
Gross total resection/path assessment	63 days	
Performance status	14 days	
CBC, Diff, & AGC	14 days	
Bilirubin, AST or ALT	14 days	
Serum creatinine or creatinine clearance	14 days	
Serum pregnancy test (if applicable)	14 days	
Na, K, Cl, glucose, Ca, Mg, albumin	14 days	
Audiogram		Highly recommended: 84 days (12 weeks)
Dental eval		Recommended: 84 days (12 weeks)
Eval for G-tube placement		Recommended: Pre-tx
Tissue collection for EGFR analysis	Required for all patients pre-treatment	
Tissue collection for HPV/p16 analysis	Required for patients with oropharyngeal cancer pre-treatment	
MDASI-HN	Patients are required to complete at baseline.	
†PRO/QOL: FACT-H&N;; MDADI; EQ-5D	If the patient consents to participate in the patient-reported outcomes (PROs) and quality adjusted survival component of the study, sites are required to administer these baseline assessments prior to the start of protocol treatment	
†FFPE collection for banking	Recommended at pre-treatment	
†Serum, plasma, & whole blood collection for banking	Recommended at pre-treatment	

†For patients who consent to participate in this component of the study

(9/2/14) APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS DURING TREATMENT

*See Section 11.2 for details and exceptions

Assessments	**During RT**		
	Weekly	q3 weeks	As clinically indicated
General H&N exam by Rad Onc and/or Med Onc	X		
CT with contrast or CT/PET (with contrast) and/or MRI of H & N			X
Chest CT or CT/PET of chest +/- contrast			X
Biopsy			If suspicion of tumor recurrence
Performance status	X		
CBC, Diff, & AGC	X		
Bilirubin, AST or ALT, albumin		X	
Serum creatinine or creatinine clearance, BUN	X		
Serum pregnancy test (if applicable)			
Na, K, Cl, glucose, Ca, Mg,	X		
Eval for G-tube placement			X
Adverse event eval	X		
PRO/QOL: MDASI-HN	q 2 weeks (see Section 11.4.2 for details)		

(9/2/14) APPENDIX I, STUDY PARAMETER TABLE: ASSESSMENTS IN FOLLOW UP

*See Section 11.2 for details and exceptions

Assessments	Follow Up			
	At 1 mo. post-RT	At 3 mos. post-RT	q3 mos. x 2 yrs; q6 mos. x 3 years; then annually	As clinically indicated
General H&P by Rad Onc or Med Onc	See Section 11.2 for details of assessments			
CT (with contrast) or CT/PET (with contrast) and/or MRI (T1 with Gadolinium and T2) of H & N with report				X*
Chest CT or CT/PET of chest +/- contrast				X
Biopsy				If suspicion of tumor recurrence
Performance status	X	X	X	
CBC, Diff, & AGC	X			
Bilirubin, AST or ALT	X			
Audiogram			Highly recommended: 6 mos. post-RT	
Adverse event eval	X	X	X	
† FACT-H&N	At end of RT		12 mos. from end of RT	
MDASI-HN	At end of RT (at fractions 30 or 33 +/- a 1-week window)	X	6, 12, and 24 mos. from end of RT	
†MDADI		X	6, 12, and 24 mos. from end of RT	
†EQ-5D			12 and 24 mos. from end of RT	

†For patients who consent to participate in this component of the study

APPENDIX II: ZUBROD PERFORMANCE SCALE

0 Fully active, able to carry on all predisease activities without restriction

1 Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours

4 Completely disabled. Cannot carry on self-care. Totally confined to bed

5 Death

APPENDIX III: AJCC STAGING SYSTEM

Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

HEAD & NECK

STAGING-PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*

LIP and ORAL CAVITY

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	Moderately advanced local disease*
	(lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose)
	(oral cavity) Tumor invades adjacent structures only (eg, through cortical bone [mandible or maxilla] into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)
T4b	Very advanced disease
	Tumor invades masticator space, pterygoid plates or skull base and/or encases internal carotid artery

*Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4.

APPENDIX III (Continued)

AJCC STAGING SYSTEM

Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

HEAD & NECK

NASAL CAVITY and PARANASAL SINUSES

Maxillary Sinus

T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
T3	Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Moderately advanced local disease
	Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
T4b	Very advanced local disease
	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V_2), nasopharynx or clivus

Nasal Cavity and Ethmoid Sinus

T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a	Moderately advanced local disease
	Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	Very advanced local disease
	Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V_2, nasopharynx, or clivus

APPENDIX III (Continued)

AJCC STAGING SYSTEM

Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

HEAD & NECK

PHARYNX

Nasopharynx

T1	Tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity with out parapharyngeal extension*
T2	Tumor with parapharyngeal extension*
T3	Tumor involves bony structures of skull base and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space

*Note: Parapharyngeal extension denotes posterolateral infiltration of tumor.

Oropharynx

T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4a	Moderately advanced local disease
	Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible*
T4b	Very advanced local disease
	Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

*Note: Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx.

Hypopharynx

T1	Tumor limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension
T2	Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest diameter without fixation of hemilarynx
T3	Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus
T4a	Moderately advanced local disease
	Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus or central compartment soft tissue.*
T4b	Very advanced local disease
	Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

*Note: Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.

AJCC STAGING SYSTEM

Edge, SB, ed. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2010.

HEAD & NECK

LARYNX

Supraglottis

T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Moderately advanced local disease
	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease
	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Glottis

T1	Tumor limited to the vocal cord(s) [may involve anterior or posterior commissure] with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation, and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage
T4a	Moderately advanced local disease
	Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease
	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

Subglottis

T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Moderately advanced local disease
	Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease
	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

APPENDIX III (Continued)

AJCC STAGING SYSTEM

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HEAD & NECK

REGIONAL LYMPH NODES (N) Excluding Nasopharynx

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral node, more than 3 cm, but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none greater than 6 cm in greatest dimension, or bilateral or contralateral nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral node more than 3 cm, but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastases in a lymph node, more than 6 cm in greatest dimension

REGIONAL LYMPH NODES (N) Nasopharynx

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in lymph node(s), 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node, more than 6 cm in greatest dimension

DISTANT METASTASIS (M)

M0	No distant metastasis
M1	Distant metastasis

STAGE GROUPING, Excluding Nasopharynx

Stage 0	Tis, N0, M0
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T3, N0, M0 T1-3, N1, M0
Stage IVA	T4a, N0-1, M0 Any T, N2, M0
Stage IVB	T4b, Any N, MO Any T, N3, M0
Stage IVC	Any T, Any N, M1

STAGE GROUPING Nasopharynx

Stage 0	T*is*, N0, M0
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T1-T3, N1, M0 T3, N0, M0
Stage IVA	T4a, N0-2, M0 T1-3, N2, MO
Stage IVB	Any T, N3, M0 T4b, Any N, M0
Stage IVC	Any T, Any N, M1

APPENDIX IV: MANAGEMENT OF DENTAL PROBLEMS IN IRRADIATED PATIENTS

Dental Care for Irradiated Patients

Goals for a dental care program include:

1. To reduce incidence of bone necrosis.
2. To reduce incidence of irradiation caries.
3. To allow proper fitting of dentures following treatment.

Pre-irradiation Care and Procedures

The patients may be grouped into four groups in accordance with the problems they present prior to irradiation.

Group 1

Includes edentulous patients. They may require surgical removal of any symptomatic cysts, infected retained root tips, or alveolar hyperplasia. These patients require hygiene instruction and precautionary instruction about trauma with premature use of a prosthesis.

Group 2

Includes those with poor dental hygiene, including those patients whose teeth are beyond repair by ordinary dental procedure, those with generalized oral sepsis, those with generalized periodontal disease, and those with chronic periapical abscesses or granulomas.

Procedures performed on this group include removal of all remaining teeth prior to irradiation with primary closure and surgical preparation of the alveolar ridges to laterally support a prosthesis. There should be antibiotic coverage during the healing stage and adequate time prior to the start of radiation therapy. These patients need complete hygiene instruction and precautionary instruction about premature use of a prosthesis.

Group 3

Includes those in whom dental condition is fair, including those patients whose teeth are restored, ordinary dental procedures, periodontal pockets are less than 3 mm deep, carious lesions are not in proximity to the pulp, and no more than 20 restorable carious lesions are present. X-ray examinations show at least 1/2 of the bone still present around root surfaces. These patients require removal of any teeth that are non-salvageable in accordance with the above and restorations of the remaining teeth as required. The patients are instructed for dental prophylaxis and the patients utilize custom-made fluoride carriers.

Group 4

Includes those in whom dental hygiene is good. This includes patients who do not have severe malocclusion in whom few carious lesions are present. Carious lesions are not in close proximity to the pulp and are correctable by conventional methods. These patients require periodontal evaluation and dental prophylaxis training, restorations as needed, no extractions prior to radiation therapy, and fitting for custom carriers.

Extraction of Teeth

If extraction of teeth is necessary prior to radiation therapy, the bone must be contoured so that closure at the extraction site is possible. All loose spicules and sharp projections must be removed. The approximation of the gingival tissue must be such that the closure is neither too loose nor too tight. At least 10 days are required for adequate healing prior to initiation of therapy.

Causative Factors

The major causative factors appear to be the reduction of the amount of saliva and secondarily, reduced pH in the mouth. This occurs following high dose radiation to the major salivary glands using parallel opposed fields. The decay process usually occurs in the first year following radiation therapy. It tends to occur more quickly in teeth which have a large amount of root cementum exposed to those teeth with large amounts of plaque formation present. Doses of radiation in excess of 20 Gy to salivary tissue place the teeth at risk.

Preventive Program

The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride concentration on the tooth surface and by the effect of fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by: 1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program, 2) construction of

fluoride carriers, custom-made mouth guards, which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is "Sta-Guard" plastic used in conjunction with vacutrole unit produced by Jelrus Technical Products, Corp., both of which are available through local dental supply. This material is molded to the cast impression and allowed to harden. A fluoride solution prepared at the M.D. Anderson Hospital is now available from the Emerson Laboratories, Inc., Dallas, Texas 75221. It has been used to coat the plastic carrier for use in the mouth. The patients are instructed to cleanse their teeth prior to placement of the carrier. It is then worn in place for 5 minutes each day. The patients are instructed to rinse their mouths thoroughly following the use of the carrier. This will be continued for an indefinite period of time. Close follow-up is necessary.

Results

In the 5-1/2 year program at the M.D. Anderson Hospital beginning in 1966, a study of 304 patients shows that the incidence of necrosis of the jaw was reduced to approximately 21% compared to 37% prior to initiation of the study. Groups 3 and 4 patients randomized with and without fluoride treatment showed reduction in radiation carries from 67% to 34% among Group 3 patients, and from 65% to 22% among Group 4 patients.

Failure to Control Decay

Management of failure to control radiation decay includes silver fillings with continued use of fluoride treatments. If the decay process is sufficiently advanced that a filling will no longer stay in place, these teeth are merely smoothed so that there will be no sharp, irritating edges. The mere existence of such a decayed tooth is not necessarily reason for extraction, for it must be remembered that extraction could lead to complications such as bone necrosis.

Pulp exposure resulting from the decay process can usually be handled by use of antibiotics and/or root-canal therapy.

Hypersensitivity of Teeth

Occasionally, a patient will exhibit extreme sensitivity of the teeth secondary to diminished amounts of saliva. This has been shown to be reduced in incidence with the fluoride treatments. Should this problem become manifest, increasing the fluoride treatment to 10 to 15 minutes 3 times a day is recommended.

Infections

Infections occurring in patients under or after radiation therapy are best managed conservatively with good oral hygiene, irrigation and flushing procedures, and systemic antibiotics.

Bone Necrosis

The patients receiving radiation therapy to a high dose to the head and neck region have increased susceptibility to bone necrosis for several reasons including: impairment of normal metabolism, increased susceptibility to infection and severely limited repair process. Bone necrosis occurs most often after dental or oral surgery in patients who have been previously radiated. Conservative management should be tried first, though in more aggressive lesions a more radical approach may ultimately be necessary.

APPENDIX V: BIOSPECIMEN COLLECTION (3/5/15)

FFPE Specimen Plug Kit Collection
Blood Collection Kit Instructions

Shipping Instructions:

U.S. Postal Service Mailing Address: For Non-urgent FFPE or Non-frozen Specimens Only
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
Campus Box 1800
2340 Sutter St, room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
2340 Sutter St, room S341
San Francisco, CA 94115

- ❑ Include all NRG Oncology paperwork in pocket of biohazard bag.
- ❑ Check that the Specimen Transmittal Form (STF) is complete and has the consent boxes checked off.
- ❑ Check that all samples are labeled with the NRG Oncology study and case number, and include date of collection as well as collection time point (eg, pretreatment, post-treatment).

❑ **FFPE Specimens:**
- o Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
- o FFPE Blocks can be wrapped with paper or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap or gauze. Place padding in top of container so that if you shake the container the blocks do not shake. If you can hear the block(s) shaking it is likely that they will break during shipping.
- o Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.

❑ **Frozen Specimens:**
- o Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
- o Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
- o Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
- o Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80° C until ready to ship.

❑ **For Questions regarding collection/shipping please contact the NRG Oncology Biospecimen Bank by e-mail: RTOG@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.**

APPENDIX V (Continued)

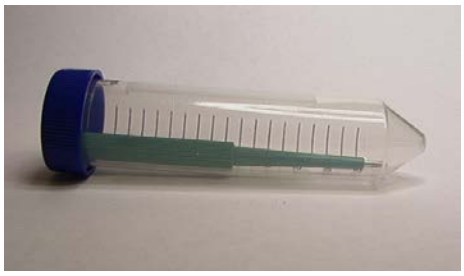
FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for submission to the NRG Oncology Biospecimen Bank. The plug kit contains a shipping tube and a punch tool.

Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample.

Step 2
Label the punch tool with the proper specimen and block ID. DON'T remove specimen from the punch.

Use a separate punch tool for every specimen. Call or e-mail us if you have any questions or need additional specimen plug kits.



Step 3
Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen and block ID.

***NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the NRG Oncology Biospecimen Bank and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block.
Ship specimen plug kit, specimen in punch tool, and all paperwork to the address below. For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the NRG Oncology Biospecimen Bank by e-mail: RTOG@ucsf.edu or call 415-476-7864/Fax 415-476-5271.

Shipping Instructions:

U.S. Postal Service Mailing Address: For Non-urgent FFPE or Non-frozen Specimens Only
NRG Oncology Biospecimen Bank-San Franciso
University of California San Francisco
Campus Box 1800
2340 Sutter St, room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen or Trackable Specimens
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
2340 Sutter St, room S341
San Francisco, CA 94115

APPENDIX V (Continued)

BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of <u>serum, plasma, or whole blood</u> *(as specified by the protocol)*:

<u>Kit contents</u>:

- One Red Top tube for serum (A)
- One Purple Top EDTA tube for plasma (B)
- One Purple Top EDTA tube for Whole Blood (C)
- Twenty-one (21) 1 ml cryovials
- Biohazard bags (3) and Absorbent shipping material (3)
- Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal Form (ST) and Kit Instructions

<u>PREPARATION AND PROCESSING OF PLASMA AND WHOLE BLOOD:</u>

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the STF.

(A) <u>Serum: Red Top Tube</u>

- ❑ Label as many 1ml cryovials (5 to 8) as necessary for the serum collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials "serum".

<u>Process</u>:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
3. Aliquot 0.5 ml serum into as many cryovials as are necessary for the serum collected (5 to 8) labeled with NRG Oncology study and case numbers, collection date/time, protocol time-point collected (eg pretreatment, post-treatment), and clearly mark specimen as "serum".
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

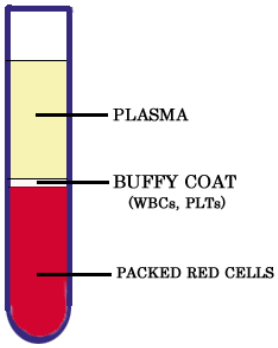
PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on the ST Form.

(B) <u>Plasma (If requested): Purple Top EDTA tube #1</u>

- ❑ Label as many 1ml cryovials (5 to 8) as necessary for the plasma collected. Label them with the NRG Oncology study and case number, collection date, time, and time point, and clearly mark cryovials "plasma".

<u>Process</u>:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the ST Form.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (5 to 8) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma". Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C.
6. Store frozen plasma until ready to ship on dry ice.
7. See below for storage conditions.



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(C) <u>Whole Blood for DNA (if requested): Purple Top EDTA tube #2</u>

- ❑ Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. Label them with the NRG Oncology study and case number, collection date/time, and time point, and clearly mark cryovials "blood".

<u>Process</u>:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot **1.0 ml blood** into as many cryovials as are necessary for the blood collected (3 to 5) labeled with NRG Oncology study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED and include collection time point on ST Form.

<u>Freezing and Storage</u>:

Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.

- ❑ Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  <u>OR</u>:
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

  <u>OR</u>:
  - Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- ❑ Please indicate on Specimen Transmittal (ST) Form the storage conditions used and time stored.

APPENDIX V (Continued)

BLOOD COLLECTION KIT INSTRUCTIONS

Shipping/Mailing:

- Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Include all NRG Oncology paperwork in a sealed plastic bag and tape to the outside top of the Styrofoam box.
- Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail RTOG@ucsf.edu or call (415) 476-7864.**

Shipping Address:

Courier Address (FedEx, UPS, etc.): For all Frozen Specimens
NRG Oncology Biospecimen Bank-San Francisco
University of California San Francisco
2340 Sutter Street, room S341
San Francisco, CA 94115
For questions, call 415-476-7864 or e-mail: RTOG@ucsf.edu