RTOG FOUNDATION

RTOG 3501

(ClinicalTrials.gov NCT #: 01711658)

TRYHARD: A PHASE II, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED STUDY OF LAPATINIB (TYKERB®) FOR NON-HPV LOCALLY ADVANCED HEAD AND NECK CANCER WITH CONCURRENT CHEMORADIATION

Amendment 8: September 27, 2016

RTOG Foundation Collaboration with Novartis

RTOG Foundation Study 3501

A Limited Participation Study

TRYHARD: A PHASE II, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED STUDY OF LAPATINIB (TYKERB®) FOR NON-HPV LOCALLY ADVANCED HEAD AND NECK CANCER WITH CONCURRENT CHEMORADIATION

Closure Date: April 18, 2017
Protocol Version Date: September 27, 2016
Amendment Number 8

Sponsor: RTOG Foundation

Principal Investigator/ Medical Oncology	Stuart Wong, MD

Study Co-Chairs

Medical Oncology	Nabil F. Saba, MD
Radiation Oncology	George Shenouda, MD
Surgical Oncology	Jeffrey M. Bumpous, MD
Medical Physics	Robert E. Wallace, PhD, DABR
Translational Research	Christine Chung, MD
Translational Research	Quynh-Thu Le, MD
Pathology	Adel El-Naggar, MD, PhD
Quality of Life	Clement K. Gwede, PhD, RN
Senior Statistician	Qiang Zhang, PhD

Protocol Acceptance
On behalf of the RTOG Foundation, Inc.

Walter J. Curran, Jr., MD
RTOG Foundation Chairman

April 18, 2017

RTOG FOUNDATION STUDY 3501

TRYHARD: A PHASE II, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED STUDY OF LAPATINIB (TYKERB®) FOR NON-HPV LOCALLY ADVANCED HEAD AND NECK CANCER WITH CONCURRENT CHEMORADIATION

Limited Participation Study

Study Chairs (8/13/15)

Principal Investigator/Medical Oncology
Stuart Wong, MD
Medical College of Wisconsin
9200 W. Wisconsin Avenue
Milwaukee, WI 53226
414-805-4603/FAX 414-805-4606
swong@mcw.edu

Medical Oncology Co-Chair
Nabil F. Saba, MD
Emory University/Winship Cancer Institute
1365 Clifton Road, C2110
Atlanta, GA 30322
404-778-3126/FAX 404-778-5676
NFSABA@emory.edu

Radiation Oncology Co-Chair
George Shenouda, MD
McGill University Health Center
Montreal General Hospital
1650 Cedar Avenue, D5-400
Montreal, CA H3G 1A4
514-934-8040/FAX 514-934-8450
george.shenouda@muhc.mcgill.ca

Surgical Oncology Co-Chair
Jeffrey M. Bumpous, MD
Univ. of Louisville School of Medicine
James Graham Brown Cancer Center, U of L HSC
529 South Jackson Street
Louisville, KY 40202
502-583-8303/FAX 502-561-7280
Jeffrey.bumpous@louisville.edu

Medical Physics Co-Chair
Robert E. Wallace, PhD, DABR
Samuel Oschin Cancer Center/Cedars-Sinai Health System
8700 Beverly Blvd.
Los Angeles, CA 90048
310-423-0648/FAX 310-659-3332
robert.wallace@cshs.org

Translational Research Co-Chair
Christine Chung, MD
Moffitt Cancer Center
12902 USF Magnolia Drive
Tampa, FL 33612
813-745-4673/FAX 813-449-8210
Christine.Chung@Moffitt.Org

Translational Research Co-Chair
Quynh-Thu Le, MD
Stanford University
875 Blake Wilbur Drive, MC 5847
650-498-5032/FAX 650-725-8231
qle@stanford.edu

Pathology Co-Chair
Adel El-Naggar, MD, PhD
MD Anderson Cancer Center
1515 Holcombe Blvd., Unit 085
Houston, TX 77030
713-792-3109/ FAX 713-792-5532
anaggar@mdanderson.org

Quality of Life Co-Chair
Clement K. Gwede, PhD, RN
H. Lee Moffitt Cancer Center
12902 Magnolia Drive MRC-CANCONT
Tampa, FL 33612
813-745-3052/FAX 813-745-6525
clement.gwede@moffitt.org

Senior Statistician
Qiang Zhang, PhD
RTOG Foundation
1818 Market Street, Suite 1720
Philadelphia, PA 19103
215-574-3197/FAX 215-928-0153
ezhang@acr.org

TRYHARD: A PHASE II, RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED STUDY OF LAPATINIB (TYKERB®) FOR NON-HPV LOCALLY ADVANCED HEAD AND NECK CANCER WITH CONCURRENT CHEMORADIATION

RTOG Headquarters Contact Information (9/27/16)	
Data Managers: For questions concerning eligibility or data submission	Vanita Patel, 215-574-3170, vpatel@acr.org or Janelle Robinson, 215-717-0837, jrobinson@acr.org
ACR Core Laboratory/RTQA: For questions concerning RT data submission	Nancy Linnemann, 215-717-0853, nlinnemann@acr.org Marsha Radden, 215-717-2757, mradden@acr.org
ACR Core Laboratory/RTQA: For questions concerning data submission to Triad	Triad-Support@acr.org
Serious Adverse Event Coordinator For questions concerning serious adverse event reporting procedures, timelines, and queries	Sara McCartney, 267-940-9404, smccartney@acr.org
Project Manager: For questions concerning regulatory documentation, HPV testing status and notification of testing results, drug supply, and/or drug shipment issues.	Treena Davis-Trotman, 215-574-3205, ttrotman@acr.org
Clinical Trials Administration: For questions concerning contracts and reimbursement	Sharon Hartson Stine, shartson@acr.org
For Code Breaks, 8:30 a.m. to 5 p.m. ET	215-574-3150, ask for the Supporting Statistician
For Code Breaks after business hours or on weekends or holidays	215-459-3576

Protocol Agents

Agent	Supply	IND #
Lapatinib	Novartis	115409
Cisplatin	Commercial	N/A

Document History

	Version/Update Date	Broadcast Date
Closure	September 27, 2016	April 18, 2017
Amendment 8	**September 27, 2016**	**November 30, 2016**
Amendment 7	March 22, 2016	March 31, 2016
Amendment 6	February 2, 2016	March 31, 2016
Amendment 5	August 13, 2015	August 19, 2015
Amendment 4	August 5, 2014	September 22, 2014
Amendment 3	January 16, 2014	February 4, 2014
Amendment 2	October 3, 2013	October 23, 2013
Activation	September 27, 2012	October 18, 2012
Amendment 1	September 27, 2012	October 3, 2012

INDEX

RTOG FOUNDATION STUDY 3501

TryHard: A Phase II, Randomized, Double Blind, Placebo-Controlled Study of Lapatinib (Tykerb®) for Non-HPV Locally Advanced Head and Neck Cancer with Concurrent Chemoradiation

SCHEMA (9/27/16)

			Age		
R		**S**	1. ≤ 65	**R**	Week 1: lapatinib/placebo
E	***For**	**T**	2. > 65	**A**	
G	**oropharyngeal**	**R**		**N**	Weeks 2-7: AFX RT + cisplatin
I	**cancer**	**A**	**T Stage**	**D**	+ lapatinib/placebo
S	**patients:**	**T**	1. T1-3	**O**	
T	Mandatory	**I**	2. T4	**M**	Followed by maintenance lapatinib/placebo
E	analysis for	**F**		**I**	for 3 months
R	p16 status	**Y**	**Nodal Status**	**Z**	
			1. N0-N2a	**E**	
			2. N2b-N3		

*Oropharyngeal cancer patients must be negative for p16, prior to Step 2 registration (randomization); these patients must consent to use of the submitted tissue for required HPV analysis. Analysis results are expected in approximately 7-10 business days. At that time, patients with oropharyngeal carcinoma can be randomized. See Section 5.3 for details. **Note**: If a specimen was previously submitted to the Biospecimen Bank at UCSF for determination of HPV status for another RTOG trial and found to be p16 negative, investigators can forward a Specimen Transmittal (ST) Form to the Biospecimen Bank at UCSF requesting that the specimen be sent to Dr. El-Naggar for central lab confirmation of p16 negativity.

Intensity Modulated Radiation Therapy (IMRT) is mandatory for this study. Image-Guided radiation therapy (IGRT) is mandatory when using a PTV margin of < 5 mm.

Patient Population: (See Section 3.0 for Eligibility)
Pathologically (histologically or cytologically) proven (from primary lesion and/or lymph nodes) diagnosis of Stage III or IV squamous cell carcinoma of the oropharynx, hypopharynx, or larynx; for patients with an oropharynx primary site, the tumor must be negative for p16 by immunohistochemistry.

Required Sample Size: 142

_____(Y) 1. Does the patient have pathologically (histologically or cytologically) proven diagnosis (from primary lesion and/or lymph nodes) of squamous cell carcinoma of the oropharynx, hypopharynx, or larynx? (**Note**: Patients with oral cavity, nasopharynx, sinuses and salivary gland primary tumors are excluded.)

_____(Y/N) 2. Does this patient have oropharynx primary? If yes, the patient must agree to consent for mandatory submission of tissue required for central review.

_____(Y) 3. Does the patient have selected stage III or IV disease: any anatomic site T2 N2-3 M0, T3-4 any N M0; p16 negative oropharynx cancer with T1 N2b, N2c, or N3; or hypopharynx T1-2 any N+?

_____(Y) 4. Was a history and physical examination done within 28 calendar days prior to registration, including assessment of patient's weight?

_____(Y) 5. Was the patient examined by a Medical Oncologist and a Radiation Oncologist within 28 calendar days prior to registration?

_____(Y) 6. Was the patient examined by an ENT or Head and Neck Surgeon (including laryngopharyngoscopy) within 42 days prior to registration?

_____(Y) 7. Was a Chest CT scan or PET/CT done within 42 calendar days prior to registration ?

_____(Y) 8. Was a contrast enhanced CT scan or MRI or PET/CT scan of the tumor site and neck nodes done within 42 calendar days prior to registration?

_____(N) 9. Does the patient have distant metastases?

_____(Y) 10. Was an EKG and ECHO or MUGA scan done within 84 calendar days prior to registration?

_____(Y) 11. Was the Zubrod Performance Status 0-1 within 14 calendar days prior to registration?

_____(Y) 12. Is the patient ≥ 18 years of age?

_____(Y) 13. Does the patient have adequate bone marrow, hepatic and renal function as specified in Section 3.1?

_____(Y) 14. Were magnesium, calcium, glucose, potassium and sodium done within 14 calendar days prior to registration with results within the parameters required in Section 3.1?

___(Y/NA) 15. For women of child bearing potential, was a serum pregnancy test completed within 14 calendar days prior to registration?

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

___(Y/NA) 16. If the patient is a woman of child bearing potential or a sexually active male, is the patient willing to use effective contraception during treatment and for at least 60 calendar days following the last study treatment?

_____(Y) 17. Will the patient be compliant with treatment plan and follow-up schedule?

Continued on next page

_____(Y) 18. Did the patient provide specific informed consent prior to study entry?

_____(N) 19. Does the patient have T1N1 or T1N2a oropharynx cancer or T1N1, T1N2a or T2 N1 non-hypopharynx tumors?

_____(N) 20. Does the patient have simultaneous primary or bilateral tumors?

_____(N) 21. Has the patient had initial surgical treatment (excluding diagnostic biopsy of the primary site or nodal sampling of neck disease); radical or modified neck dissection or gross total excision of the primary site (e.g. by tonsillectomy)?

_____(N/Y) 22. Did the patient have a prior invasive malignancy?

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

_____(N) 23. Has the patient had any prior systemic chemotherapy for the study cancer?

_____(N) 24. Has the patient had any prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields?

_____(N) 25. Is the primary site of tumor oral cavity, nasopharynx, sinuses or salivary gland?

_____(N) 26. Does the patient have prior allergic reaction to the study drugs involved in this trial?

_____(N) 27. Has the patient had any prior therapy that specifically and directly targets the EGFR/HER2 pathway?

_____(N) 28. Does the patient have current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, or stable chronic liver disease per investigator assessment)?

_____(N) 29. Does the patient have severe, active co-morbidity, as defined in section 3.2?

The following questions will be asked at Study Registration:
CREDENTIALING for IMRT (and IGRT if using reduced margins) 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 (First Middle Last)

_____ 6. Verifying Physician

_____ 7. Patient ID

Continued on next page

_____ 8. Date of Birth

_____ 9. Race

_____ 10. Ethnicity

_____ 11. Gender

_____ 12. Country of Residence

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

_____ 14. Method of Payment

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

_____ 16. Calendar Base Date

_____ 17. Randomization 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?

_____(Y/N) 24. Did the patient agree to participate in the quality of life component?"

_____ If no, please specify the reason from the following:

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_____

Continued on next page

_____ 25. Specify the patient's age (≤ 65 vs. > 65)

_____ 26. Specify T stage (T1-3 vs. T4)

_____ 27. Specify nodal status (N0-N2a vs. N2b-N3)

_____ 28. Specify primary site (hypopharynx, larynx, oropharynx)

_____(Y/N) 29. Will IGRT be used for patient positioning (< 5mm PTV expansion)?

_____(Y/N) 30. Will IGRT be used for patient positioning and margin reduction?

_____(Y) If yes, is the institution credentialed for head and neck IGRT?

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 RTOG audit.

Completed by _____ Date _____

Institution #
RTOG Foundation 3501 **ELIGIBILITY CHECKLIST– STEP 2 (2/2/16)**
Case # **(page 5 of 5)**
(assigned for Step 1)

Note: Sites will complete Step 2 for **all** patients. For patients with hypopharyngeal and laryngeal cancer, the site can proceed to Step 2 (randomization) immediately after completing Step 1 (registration). Patients with oropharyngeal cancer must have a mandatory p16 analysis prior to the site completing Step 2.

_____ 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 refusal;
4) physician preference;
5) failure to submit tissue assay;
6) other

_____ If response is "6) Other", specify the reason the patient cannot continue to Step 2.

_____ 4. Patient's Initials

_____ 5. Verifying Physician

_____ 6. Patient's ID number

_____ 7. Calendar Base Date (for Step 2)

_____ 8. Registration/randomization date: (for Step 2)

_____(Y/N) 9. If the primary site is oropharynx, is the patient negative for p16 (determined by Dr. El-Naggar's lab)?

_____ 10. Patient height

_____ 11. Patient weight

_____ 12. BSA

1.0 INTRODUCTION

1.1 Treatment of Locally Advanced Head and Neck Squamous Cell Carcinoma (HNSCC)

Over 40,000 new cases of HNSCC are diagnosed each year in the United States (American Cancer Society 2010) The majority of these patients present with locally advanced, non-metastatic disease in which multi-modality therapy may be appropriate. An accepted standard of care treatment for locally advanced squamous cell cancer of the head and neck (LA-HNSCC) is concurrent cisplatin-based chemotherapy with radiation (chemoRT). The updated MACH-NC meta-analysis, demonstrated that concomitant chemotherapy plus radiation was associated with significant reduction in risk of death compared to radiation alone (Pignon 2009). Several phase III studies comparing radiation alone versus concurrent chemoRT for LA-HNSCC also demonstrated this effect (Adelstein 2003; Al-Sarraf 1998; Forastiere 2003; Denis 2004).

Altered fractionated radiation has been studied as a way to enhance the efficacy of the concurrent chemoRT. RTOG 90-03 was a phase III study that showed improved disease free survival with accelerated fractionated radiation with concomitant boost compared to standard fractionated radiation (Fu 2000). RTOG 0129 was launched to compare 2 concurrent cisplatin chemoradiation regimens comprised of accelerated fractionated radiation versus standard fractionated radiation. The analysis of the phase III randomized RTOG 0129 trial showed that patients randomized to receive either accelerated fractionation radiotherapy (70 Gy in 35 fractions over 6 weeks) with 2 cycles of high-dose cisplatin or standard fractionation radiotherapy (70 Gy in 35 fractions over 7 weeks) with 3 cycles of high-dose cisplatin had similar overall and progression-free survival. In the standard fractionation schedule, 31% of the patients were unable to receive the last and 3rd dose of cisplatin during the 7th week of conventional radiotherapy because of toxicity. On the other hand, 88% of patients treated with the accelerated fractionation schedule received the 2 planned cisplatin cycles. Although there were no differences in overall high-grade acute or late toxicities, the cisplatin-related toxicities were significantly lower in the accelerated fractionation arm patients. Based on these results of RTOG 0129, current RTOG head and neck protocols have adopted the accelerated fractionation schedule as the standard treatment.

Based upon evidence that EGFR inhibition enhances the cellular response of radiation and cytotoxic chemotherapy, RTOG 0522 tested whether the anti-EGFR antibody, cetuximab, improves disease-free survival over radiation plus concurrent cisplatin. Initial report of the results of this study showed that the addition of cetuximab to radiation-cisplatin did not improve progression-free survival (PFS) or overall survival (OS) (Ang 2011). Failure of cetuximab to improved outcome may be due to insufficient synergistic effect of cetuximab or possibly due to inadequate duration of anti-EGFR therapy. No differential effect was observed based upon p16 status; however, testing was not possible for nearly half of oropharynx patients.

While the importance of EGFR in HNSCC has been well established, a direct role of HER2 in tumorigenesis and treatment resistance of HNSCC is not clear and poorly understood. HER2 is expressed in the range of 0-47% in HNSCC depending on the antibodies used, staining conditions, and scoring systems of immunohistochemistry (IHC) [Kearsley 1991; Beckhardt 1995; Field 1992; Craven 1992; Ibrahim 1997; Khan 200;Cavalot 2007]. Hou, et al. has shown that HER2 expression progressively increased as oral disease progresses from normal mucosa, pre-malignant lesions to invasive oral SCC (Hou 1992); however, its association with tumor stage, locoregional control, and survival as a prognostic marker varies depending on the sample size and evaluation methods (Craven 1992; Ibrahim 1997; Khan 2002; Cavalot 2007). In a recent study by Cavalot, et al. (2007), a high membranous HER2 protein expression was an independent prognostic factor for disease free survival. To date, HER2 expression has never been evaluated as a predictive biomarker of HER2-specific inhibitor therapy in HNSCC.

In addition, there is a strong rationale of dual-targeting of EGFR and HER2. There is evidence that heterodimers containing HER2 as a partner is the most potent combination for the receptor activity compared to other dimers formed by 4 family members of HER receptors (Arteaga 2003). Inhibitory effects of one receptor have shown to be negated by heterodimers formed by the rest of uninhibited HER receptor family members (Diermeier 2005; Motoyama 2002). The extent of EGFR-HER2 and HER2-HER3 heterodimerization in HNSCC is not known; however, potentially

heterodimerization may occur and contribute to resistance given EGFR-specific tyrosine kinase inhibitors. Therefore, a dual inhibition using lapatinib warrants further investigation.

The current proposed trial is a randomized study to examine whether the inhibitory effect of lapatinib upon the EGFR and HER2 signaling pathways enhances the cytotoxicity of a concurrent cisplatin-radiation regimen as determined by improvement in PFS. Selection of the experimental arm of the present study builds upon the RTOG experience, summarized above, and will utilize a backbone of accelerated fractionated radiation with 2 concurrent cycles of cisplatin.

1.2 Importance of a Non-HPV-Specific LA-HNSCC Trial

A recently published retrospective analysis of oropharyngeal cancer patients from RTOG 0129 identified factors associated with prognosis (survival outcome) [Ang 2010]. Tumor HPV status, as determined by expression of p16, was a strong independent predictor of survival. p16 positive patients had the most favorable survival outcome (3-year OS rates of 82.4%), while p16 negative patients had the worse outcome (3-year survival rates of 57.1%). An intermediate prognostic group also was identified that was p16 positive but had a significant smoking history. Implicit from this analysis is that p16 negative (non-HPV) oropharyngeal cancer patients behave much like the p16 negative, non-oropharyngeal, head and neck cancer population. Epidemiologic studies indicate that HPV positive population is a growing subset of HNSCC (Sturgis 2007). Nonetheless, the non-HPV population still represents the majority of HNSCC cases. It can be estimated that roughly 75% of non-HPV HNSCC cases will have aberrant p16, and therefore, carry a poor prognosis (Reed 1996; Gruttgen 2001; Bova 1999).

A clinical trial specifically designed for this poor prognostic population has not been conducted in the cooperative oncology group setting but is appropriate for several reasons. First, the molecular pathogenesis of disease of this group is quite distinct from the HPV population. In HPV-related oropharyngeal HNSCC, expression of viral E6 and E7 oncoproteins that inactivate p53 and pRb is the known mechanism of carcinogenesis (Rampias 2009). In contrast, non-HPV HNSCC is thought to occur as a result of a cumulative multistep process of genetic and epigenetic events due to chronic exposure to environmental carcinogens. Second, cooperative group oncology clinical trials specifically designed for HPV oropharyngeal cancer are active. Finally, the prognosis is unacceptably poor for this non-HPV HNSCC population; significant effort is necessary in order to improve their outcome. For all these reasons, a specific study for HPV negative patients is necessary in order to make overall progress in the treatment of HNSCC.

As discussed in the following section, lapatinib appears to enhance the effects of chemoradiation. Pilot data suggests that this effect may be more pronounced in p16 negative HNSCC patients. This study will, therefore, test a proof of biologic principle that a potent inhibitor of the EGFR and HER2 signaling pathways can enhance the efficacy of a chemoradiation regimen. In addition, there has never been a study evaluating the HER2 status as a predictive marker of HER2 inhibitors in HNSCC; the proposed study will allow us to evaluate this question, which can only be answered in a clinical trial setting with a control arm. The results of this study also are pertinent to the design of a future phase III clinical trial and development of novel therapeutic regimens and biomarkers.

1.3 EGFR Expression

EGFR expression by tumor cells has been linked with aggressive tumor growth, disease progression, poor survival, and poor response to therapy. Over-expression of EGFR has been reported in a number of epithelium-derived carcinomas including head and neck, colorectal, lung, esophageal, gastric, and breast carcinoma. Ang, et al. have demonstrated the prognostic value of epidermal growth factor receptor (EGFR) expression in predicting survival and patterns of relapse for LA-HNSCC patients treated with radiation therapy (2002). Recently, Chung, et al. have published a validation of EGFR as a predictive biomarker using an IHC quantitative image analysis assay (2010). These observations confirm a body of preclinical tumor biology studies that have examined the role of EGFR in modulating radiation response.

Other tyrosine kinase receptors in the ErbB family, besides EGFR, may play a role in HNSCC tumor progression as well as prognosis--specifically human epidermal growth factor receptor-2 (HER2/neu) (Khan 2002; Xia 1999; Rait 2003). In a similar manner, ErbB2 has been reported to

be over-expressed in 15-30% of invasive ductal breast cancer and has been associated with increased proliferation, poor clinical outcome, and altered responsiveness to various adjuvant therapies (Nahta 2003). Activation of either EGFR or ErbB2 initiates a series of signaling cascades that includes mitogen-activated protein kinase (MAPK), phosphoinositide 3-kinase (PI3K), Akt, and p70S6K. Dual inhibition of EGFR and HER2/neu may be attractive strategy to examine for treatment of LA-HNSCC.

1.4 Lapatinib

. Lapatinib acts as a dual inhibitor of both EGFR and ErbB2 tyrosine kinase activity. As a member of the 4-anilinoquinazoline class of kinase inhibitors, lapatinib is thought to react with the ATP binding site of EGFR/ErbB2, resulting in inhibition of autophosphorylation and subsequent proliferative signaling (Rusnak 2001). The ErbB family consists of 4 closely related growth factor receptor tyrosine kinases: ErbB1 (EGFR/HER), ErbB2 (HER2/neu), ErbB3 (HER3), and ErbB4 (HER4). All members of the ErbB family share a common extracellular ligand-binding domain, a single membrane-spanning region, and a cytoplasmic tyrosine kinase domain (Yarden 2001; Atalay 2003). A ligand for ErbB2 has not been identified, while ErbB3 lacks tyrosine kinase activity. Ligand binding to EGFR, ErbB3 or ErbB4 induces these inactive monomers to undergo an array of homo- or heterodimerization with other members of the ErbB family. ErbB2 is the preferred heterodimeric partner for all ErbB receptors, resulting in a complex that is endocytosed at one half to one third the rate of other EGFR dimers (Alroy 2000; Hendriks 2003). ErbB dimerization leads to receptor autophosphorylation and subsequent activation of the tyrosine kinase domain. The signaling characteristics of the ErbB family are thought to be strongly interdependent.

1.4.1 Lapatinib in Combination Chemoradiotherapy for LA-HNSCC

By virtue of its dual pathway inhibition of EGFR and HER2 signaling, lapatinib may have a greater inhibitory effect on downstream signaling and on cell growth than an anti-EGFR monoclonal antibody. A large randomized, placebo- controlled multicenter trial of post-operative lapatinib or placebo and chemoRT for high risk HNSCC is active and currently accruing patients (NCT00424255). Harrington, et al. recently reported the results of a multi-center randomized phase II study that examined concurrent chemoRT with or without concurrent and maintenance lapatinib for LA-HNSCC (2010). Complete clinical response at 6 months appeared to favor the lapatinib arm compared to the placebo arm (53% vs. 36%, odds ratio =2.2 (0.7, 7,0); p value= 0.1858). Although also not statistically significant, PFS and OS aligned similarly to demonstrate a trend towards favoring the lapatinib arm. Thus, a positive signal that lapatinib enhances the effects of chemoRT was observed in this pilot study. A retrospective analysis of patients on this study for whom p16 status could be determined (n=46), demonstrated that among p16 negative patients (n=33), those who received lapatinib plus chemoRT appeared to have improved PFS compared to those who received chemoRT alone (HR=0.626 (0.261, 1.506); log rank p value 0.2963). Unfortunately, definitive conclusions cannot be drawn from this analysis due to the small size of the subgroup in addition to the retrospective nature of the analysis. However, these findings are sufficiently compelling to warrant further examination of this question using a larger sampling of this high-risk patient population. Based upon these observations, we hypothesize that, due to the disruptive effect of lapatinib upon EGFR and HER2 signaling pathways, the addition of concurrent and maintenance lapatinib to a concurrent radiation-cisplatin regimen will enhance the cytotoxic effect, resulting in an improvement of PFS in high-risk (non-HPV) LA-HNSCC patients.

1.4.2 Mechanism of Action

Lapatinib has been shown to be a potent and selective dual inhibitor of EGFR and ErbB2 tyrosine kinase activity with IC50 values of 10.2 and 9.8 nM, respectively (Rusnak 2001). Lapatinib has demonstrated selective growth inhibition of human cell lines (head and neck, breast, and gastric) in vitro (IC90 values <2.26 μM or 1313 ng/mL) with no outgrowth observed up to 18 days following cessation of treatment. Growth inhibition corresponded with the ability of lapatinib to inhibit phosphorylation of Akt. These studies suggested that inhibition of EGFR by lapatinib resulted preferentially in cell growth arrest, while inhibition of ErbB2 led to cell growth arrest and apoptosis after 72 hours. Treatment with lapatinib leads to arrest of tumor cell growth and/or apoptosis, even in the presence of saturating concentrations of epidermal growth factor (EGF). Treatment of tumor xenografts resulted in inhibition of activation of EGFR, erbB2, Erk1/2, and Akt (Xia 2002).

1.4.3 Antitumor Activity

The ability of lapatinib to inhibit the growth of EGFR-over-expressing cell lines (IC50 <0.16 μM) was observed to be equal to that of other EGFR inhibitors being tested in clinical trials (e.g. gefitinib/IressaTM or erlotinib/TarcevaTM). With the exception of ErbB4, lapatinib was >300-fold more selective towards ErbB2 and EGFR kinase inhibition than to other kinases tested. Lapatinib demonstrated potent growth inhibition of human breast ductal (BT474) and head and neck (HN5) tumor xenografts in mice. A dose response inhibition was observed in both models receiving lapatinib (30 or 100 mg/kg twice daily orally for 21 days). Complete inhibition of tumor growth was seen in mice receiving 100 mg/kg (Rusnak 2001).

1.4.4 Signal Transduction

Lapatinib has been shown to inhibit Erk1/2 and Akt phosphorylation (pErk and pAkt) in both EGFR and erbB2-expressing cell lines (BT474 and HN5). The ability of lapatinib to inhibit pAkt was associated with a 23-fold increase in the percentage of cells undergoing apoptosis compared to control cells. Similarly, lapatinib treatment of BT474 and HN5 xenografts in mice also resulted in inhibition of Erk1/2 and Akt phosphorylation. These results suggested that lapatinib treatment of EGFR/erbB2 expressing tumors could lead to inhibition of downstream signaling events (Xia 2002).

A study of human breast cancer cell lines that over-express EGFR or erbB2 (SUM102, SUM149, SUM185, and SUM225) reported that treatment with lapatinib resulted in inhibition of cell proliferation that was associated with inhibition of Erk phosphorylation. Inhibition of Erk phosphorylation also correlated with radiosensitization of cell lines pretreated with lapatinib (Zhou 2003).

1.4.5 Toxicology

A range of toxicology studies has been conducted to support the oral administration of lapatinib to humans. Repeat oral dose toxicity studies have been completed in rats and dogs for up to 6 and 9 months, respectively. The effects of lapatinib on fertility in the rat and embryofetal development in the rat and rabbit have been investigated. A range of genetic toxicity studies has been performed in vitro and in vivo. The significant findings from the toxicology studies are summarized below.

- Following single oral administration, lapatinib was well-tolerated by both CD-1 mice and Wistar Han rats at doses up to 2000 mg/kg. Treatment-related findings consisted of reversible changes in body weight and body weight gain as well as reversible GI effects.
- A 13-week oral dose ranging pilot carcinogenicity study in mice showed that treatment with lapatinib at doses up to 200 mg/kg/day was generally well tolerated. Microscopic changes attributable to treatment with lapatinib were noted in the liver and preputial gland of males and large intestines (cecum and colon) of males and females.
- Administration of lapatinib to rats and dogs for up to 6 months or 9 months resulted primarily in exaggerated pharmacologic effects and organ toxicities generally associated with degenerative and/or inflammatory epithelial changes (GI tract and accessory digestive organs, skin, mammary gland, liver and prostate). Other treatment-related effects included clinical signs, decreased body weight and food consumption, organ weight changes and alterations in clinical pathology parameters. Following the recovery period, treatment-related changes were either significantly improved or completely reversed.
- There were no effects on male or female rat gonadal function, mating, fertility or pregnancy nor were there any increases in the number or incidence of any malformations when rats or rabbits were given lapatinib during the period of major organogenesis. At maternally toxic doses (≥ 60 mg/kg/day in rats and rabbits), lapatinib treatment was associated with growth retardation and developmental variations.
- In genetic toxicity studies, lapatinib was demonstrated to be non-mutagenic and non-clastogenic.

1.5 Quality of Life and Patient-Reported Outcomes

This study affords another unique opportunity: to prospectively explore quality of life (QOL) and patient-reported outcomes (PROs) in this disease. Most curative intent, multimodality treatment regimens in locally advanced head and neck cancer are associated with significant acute and late toxicities. Standard validated QOL measurements used in patients treated for squamous cell

carcinomas of the head and neck have demonstrated that a considerable proportion of patients report debilitating functional compromise and psychosocial morbidity (Bjordal 2000; Weymuller 2000; Ringash 2005; Martino 2008; Logemann 2008). There also is a growing body of literature supporting a relationship between better QOL with superior treatment outcomes (Siddiqui 2008; Karvonen-Gutierrez 2008). To our knowledge, data of this nature is nonexistent among patients treated with lapatinib with chemoradiation for non-HPV locally advanced head and neck cancer, and this trial would be an ideal mechanism to collect and analyze this subjective, patient-reported longitudinal data. Therefore, we will explore the impact of treatment assignment on QOL/PROs after initial therapy and during maintenance therapy using validated instruments: the Functional Assessment of Cancer Therapy (FACT) H&N subscale (12 items); the 15-item University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS) and the Performance Status Scale for Head and Neck Cancer (PSS-HN) [Ringash 2007; Ringash 2008; Murphy 2007; Henson 2001; Rodgers 2009; List 1996; 1999]. These outcomes will be assessed at baseline (pretreatment) and at 3, 12, and 24 months from completion of radiation treatment.

In this phase II trial, preliminary data will be obtained for assessing the extent to which quality of life, swallowing, and xerostomia are adversely affected by the addition of lapatinib in this setting. It is hypothesized that the above indicators, as measured by the FACT-H&N subscale, PSS-HN, and XeQOLS instruments, will be less favorable for patients undergoing chemoradiation with lapatinib relative to chemoradiation and placebo, at 3 months after completion of radiation treatment. The current investigation is exploratory, but allows us to explore the relative importance of these QOL/PROs in this setting. The goal of including an exploratory QOL/PROs correlative component is to generate estimates of effect sizes (means, standard deviations) that will guide the statistical power and effect size estimates for a subsequent phase III trial.

1.5.1 QOL and PRO Assessments

1.5.1.1 The FACT-HN is a multidimensional, patient self-report QOL instrument specifically designed and validated for use with head and neck cancer patients. The FACT-HN module consists of a 12-item head and neck subscale targeting head and neck related symptoms and side effects (Cella 2000; Ringash 2004; Ringash 2005; Ringash 2007; Ringash 2008), and can be administered independently from the general FACT-G instrument. High scores indicate better QOL and functioning. This tool takes approximately 5-10 minutes to complete.

1.5.1.2 The PSS-HN is a clinician/interviewer administered assessment that focuses on three functional areas: Normalcy of Diet, Eating in Public, and Understandability of Speech. The score on each of the three subscales ranges from 0-100, with higher scores indicating better performance (List 1996; List 1999; List 2000).

1.5.1.3 The XeQOLS instrument is patient self-report measure that consists of 15 items on a 5-point Likert-type scale covering mouth/throat dryness and its impact on four major domains of oral health-related quality of life: physical functioning, personal/psychological functioning, social functioning, and pain/discomfort issues [Murphy 2007; Henson 2001; Rodgers 2009]. The XeQOLS takes the patient approximately 5 minutes to complete.

1.6 Correlative Studies

While the importance of EGFR in HNSCC has been well established, a direct role of HER2 in tumorigenesis and treatment resistance of HNSCC is not clear and is poorly understood. HER2 is expressed in the range of 0-47% in HNSCC depending on the antibodies used, staining conditions and scoring systems of immunohistochemistry (IHC). Hou, et al. have shown that HER2 expression progressively increased as oral disease progresses from normal mucosa, pre-malignant lesions to invasive oral SCC; however, its association with tumor stage, locoregional control, and survival as a prognostic marker varies depending on the sample size and evaluation methods. In a recent study by Cavalot, et al., a high membranous HER2 protein expression was an independent prognostic factor for disease-free survival. To date, HER2 expression has never been evaluated as a predictive biomarker of HER2-specific inhibitor therapy in HNSCC. Biologic correlative studies of the TryHard study will address these important scientific questions as permitted by the study design that includes a randomized control arm.

Dual-targeting of EGFR and HER2 also provides a strong rationale for the use of lapatinib with chemoRT for LA-HNSCC. There is evidence that heterodimers containing HER2 as a partner is the most potent combination for the receptor activity compared to other dimers formed by 4 family

members of HER receptors. Inhibitory effects of 1 receptor have shown to be negated by heterodimers formed by the rest of uninhibited HER receptor family members. The extent of EGFR-HER2 and HER2- HER3 heterodimerization in HNSCC is not known; however, potentially heterodimerization may occur and contribute to resistance given EGFR-specific tyrosine kinase inhibitors. Therefore, a dual inhibition using lapatinib warrants further investigation and will be examined in the correlative studies.

1.6.1 HER2 Expression as a Predictive Biomarker of Lapatinib Response

Since lapatinib is a dual inhibitor of both EGFR and HER2, it is logical to evaluate HER2 protein expression and gene amplification in addition to the EGFR analysis and HPV assay (for oropharynx only). For this aim, we propose the following:

- HER2 protein expression determined by image-guided quantification of IHC staining (Cavalot 2007);
- HER2 gene amplification determined by FISH (Khan 2002).

1.6.2 EGFR-HER2 Heterodimer Expression as a Predictive Biomarker of Lapatinib Response

Activation of EGFR involves either homodimerization or heterodimerization between EGFR and HER2.The in situ proximity ligation assay (PLA) was developed to enable detection of individual proteins and protein–protein interactions in cell lines and tissues, specifically paraffin embedded tissues (Söderberg 2006; Weibrecht 2010). The approach uses oligonucleotides attached to the antibodies against the 2 target proteins, in this case, pEGFR and pHer2. The oligonucleotides on the proximity probes when brought into close proximity by protein dimerization, serve as templates for the circularization, which can then be amplified and visualized as bright fluorescent RCPs or colometric RCP dots (depending on the type of detection). Since each detected protein demierization gives rise to one RCP, the detected complexes can be easily enumerated and counted. Tissue PLA has been used to assay for HER-family dimerization in tissue samples using the Duolink Kit from Olink Bioscience (Uppsala, Sweden). We have also evaluated pEGFR dimerization in head and neck squamous cell carcinoma and found that this approach can be readily applied to tissue microarray of formalin-fixed, paraffin-embedded tumor tissues. We propose to use this assay to evaluate EGFR homodimerization and EGFR-HER2 heterodimerization on pretreatment tumor samples as a potential predictor for lapatinib efficacy.

1.6.3 EGFR Ligand Expression Levels in Tissue and Blood as a Predictive Biomarker of Lapatinib Response

mRNA expression of EGFR ligands such as TGFA, AREG, EREG, and HB-EGF have been shown to correlate with prognosis in HNSCC (Grandis 1998) and predict for efficacy of EGFR targeting, specifically cetuximab in colorectal cancer (Khambata-Ford 2007; Hatakeyama 2010). Based on this information, we propose to evaluate the following EGFR ligand expression levels as a biomarker predictor of lapatinib response: TGFA, AREG, EREG and HB-EGF mRNA levels determined by RT-PCR (Grandis 1998; Khambata-Ford 2007; Hatakeyama 2010). In addition, we will measure HB-EGF (one of the EGFR ligands) protein levels in plasma samples collected at pre-, end-of-radiation, and post-treatment (Hatakeyama 2010).

1.6.4 Variant EGFR 497 Arg Allele and EGFR Intron 1<20 CA Repeats as a Prognostic Biomarker of Poor Relapse-Free Survival and a Predictive Biomarker of Lapatinib Sensitivity

Variant EGFR 497 Arg allele and EGFR introl 1<20 CA repeats have been shown to be a prognostic biomarker of poor relapse-free survival (RFS) in HNSCC. However, its role in predicting lapatinib sensitivity in unknown in these patients. Since these polymorphisms can be readily measured from circulating WBC, we propose to evaluate these allelic variants in patients enrolled on this study, both to validate their prognostic significance as well as to determine their predictive effect of lapatinib response. The following assays will be performed:

- Assess EGFR gene polymorphism 497 arginine-to-lysine determined by PCR-RFLP using germline DNA collected from pre-treatment PBMC (Zhang 2005);
- Assess EGFR intron 1 CA repeat polymorphisms determined by PCR-RFLP using germline DNA collected from pre-treatment PBMC (Amador 2004).

1.6.5 Validation of Lysyl Oxidase (LOX) and Gli Family Zinc Finger (Gli1) as Biomarkers of Distant Metastasis

We have previously identified LOX and Gli1 as biomarkers for distant metastasis in HNSCC treated with radiation alone on RTOG 90-03 (Le 2009, Chung 2010). The role of these markers in HPV negative patients treated with chemoradiation has not been evaluated. We propose to validate the role of these biomarkers as predictors for distant metastasis by quantifying the level

of these proteins in pre-treatment tumor samples (as previously described in Le 2009 and Chung 2010).

1.6.6 Epithelial-to-Mesenchymal Transition (EMT) as a Prognostic Biomarker of Poor RFS and a Predictive Biomarker of Lapatinib Resistance

EMT is a well known process governing invasion and metastasis in epithelial cell tumors. Although several biomarkers have been suggested to reflect the EMT process, one common hallmark of EMT is increased vimentin expression in the tumor (Frederick 2007). Recently, certain microRNAs, including miR-212, miR-103 and miR-200 have been linked to the EMT process, and their expression levels have been correlated with poor outcomes (Hatakeyama 2010; Martello 2010). In this exploratory study, we proposed to measure EMT by the following 2 approaches and determine whether the levels of these EMT biomarkers correlate with poor RFS and/or lapatinib resistance in the treated patient population.

- Vimentin expression in pre-treatment tumors determined by automated quantitative analysis (AQUA) (Frederick 2007);
- miR-212, miR-103 and miR-200 expression in serum/plasma samples collected at pre-, end-of-radiation, and post-treatment (Hatakeyama 2010; Martello 2010).

2.0 OBJECTIVES

2.1 Primary Objective

2.1.1 To evaluate if the addition of lapatinib to concurrent cisplatin and radiation in this patient population sufficiently improves progression-free survival (PFS) to warrant a phase III trial

2.2 Secondary Objectives

2.2.1 To evaluate if the addition of lapatinib to concurrent cisplatin and radiation in this patient population improves overall survival (OS);

2.2.2 To evaluate if the addition of lapatinib to concurrent cisplatin and radiation in this patient population improves control of distant metastasis;

2.2.3 To evaluate toxicity and tolerability between treatment arms;

2.2.4 To evaluate if the addition of lapatinib to concurrent cisplatin and radiation in this patient population improves local regional control;

2.2.5 To investigate quality of life and patient-reported outcomes between treatment arms;

2.2.6 To explore HER2 expression, amplification and heterodimerization, EGFR ligand expression, EGFR polymorphisms, hypoxia, and EMT characteristics as biomarkers of lapatinib response, sensitivity, and resistance, PFS, and metastasis.

3.0 PATIENT SELECTION (10/3/13)

For questions concerning eligibility, contact the study Data Managers (see the title pages for contact information).

3.1 Conditions for Patient Eligibility (9/27/16)

3.1.1 Pathologically (histologically or cytologically) proven diagnosis (from primary lesion and/or lymph nodes) diagnosis of squamous cell carcinoma of the oropharynx, hypopharynx, or larynx;

3.1.2 For patients with an oropharynx primary, the tumor must be negative for p16 by immunohistochemistry;

3.1.3 Selected stage III or IV disease: patients with T2 N2-3 M0, T3-4 any N M0 are eligible; in addition, p16 negative oropharynx cancer T1 N2b, N2c, or N3; and hypopharynx cancer patients with T1-2 any N+ are eligible, including no distant metastases, based upon the following minimum diagnostic workup:

3.1.3.1 History/physical examination within 28 calendar days prior to registration, including an examination by a Medical Oncologist and Radiation Oncologist and documentation of the patient's weight;

3.1.3.2 Examination by an ENT or Head & Neck Surgeon, including laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) within 42 days prior to registration;

3.1.3.3 Chest CT scan, or PET/CT scan within 42 calendar days prior to registration to rule out metastatic disease;

3.1.3.4 Contrast enhanced CT scan or MRI or PET/CT scan of the tumor site and neck nodes within 42 calendar days prior to registration;

3.1.3.5 EKG and ECHO or MUGA scan within 84 calendar days prior to registration;

3.1.4 Zubrod Performance Status 0-1 within 14 calendar days prior to registration;
3.1.5 Age ≥ 18;
3.1.6 CBC/differential obtained within 14 calendar days prior to registration, with adequate bone marrow function defined as follows:
3.1.6.1 Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3;
3.1.6.2 Platelets ≥ 100,000 cells/mm^3;
3.1.6.3 Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.);
3.1.7 Adequate renal and hepatic function within 14 calendar days prior to registration, defined as follows:
3.1.7.1 Serum creatinine < 1.5 mg/dl or creatinine clearance (CC) ≥ 50 ml/min within 14 calendar days prior to registration, determined by 24-hour collection or estimated by Cockcroft-Gault formula:
CCr male = [(140 – age) x (wt in kg)]
[(Serum Cr mg/dl) x (72)]
CCr female = 0.85 x (CrCl male)
3.1.7.2 Total bilirubin < 2 x the institutional ULN;
3.1.7.3 AST or ALT $\leq$ 3 x the institutional ULN;
3.1.8 Magnesium, calcium, glucose, potassium, and sodium within 14 calendar days prior to registration, with the following required parameters:
3.1.8.1 Magnesium: > 0.9 mg/dl or < 3 mg/dl;
3.1.8.2 Calcium: > 7 mg/dl or < 12.5 mg/dl;
3.1.8.3 Glucose: > 40 mg/dl or < 250 mg/dl;
3.1.8.4 Potassium: > 3 mmol/L or < 6 mmol/L;
3.1.8.5 Sodium: > 130 mmol/L or < 155 mmol/L.
3.1.9 Negative serum pregnancy test within 14 calendar days prior to registration for women of childbearing potential;
3.1.10 Women of childbearing potential and men who are sexually active must practice adequate contraception during treatment and for at least 60 calendar days following treatment.
3.1.11 Patients must be deemed able to comply with the treatment plan and follow-up schedule.
3.1.12 Patients must provide study specific informed consent prior to study entry, <u>including, for oropharyngeal cancer patients, consent for mandatory submission of tissue for required, central p16 review.</u>

<u>3.2 Conditions for Patient Ineligibility</u> (9/27/16)

3.2.1 Patients with T1 any N or with T2 N1 are ineligible except for specific oropharynx or hypopharynx patients as described in Section 3.1.3;
3.2.2 Patients with simultaneous primaries or bilateral tumors;
3.2.3 Gross total excision (e.g., by tonsillectomy) of the primary tumor; however, partial removal of the tumor to alleviate an impending airway obstruction does not make the patient ineligible.
3.2.4 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 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;
3.2.5 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable;
3.2.6 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
3.2.7 Primary site of tumor of oral cavity, nasopharynx, sinuses, or salivary glands;
3.2.8 Initial surgical treatment, excluding diagnostic biopsy of the primary site or nodal sampling of neck disease; radical or modified neck dissection is not permitted.
3.2.9 Prior allergic reaction to the study drugs;
3.2.10 Prior therapy that specifically and directly targets the EGFR/HER2 pathway;
3.2.11 Patients who have current active hepatic or biliary disease (with exception of patients with Gilbert's syndrome, asymptomatic gallstones, or stable chronic liver disease per investigator assessment);
3.2.12 Pregnant women or women of childbearing potential and men who are sexually active and not willing or able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.
3.2.13 Severe, active co-morbidity, defined as follows:

3.2.13.1 Uncontrolled cardiac disease, such as uncontrolled hypertension or unstable angina;
3.2.13.2 Transmural myocardial infarction within the last 6 months;
3.2.13.3 History of congestive heart failure and/or history of left ventricular ejection fraction < 50%;
3.2.13.4 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
3.2.13.5 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 calendar days prior to registration;
3.2.13.6 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.
3.2.13.7 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that 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.

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 If the patient consents to participate in the quality of life (QOL) component of the study, sites are required to administer the baseline QOL and PRO assessments prior to the start of protocol treatment: the PSS-HN, FACT-HN, and XeQOLS.

4.2 Highly Recommended Evaluations/Management

The following pre-treatment evaluations/interventions are not required but are highly recommended.

4.2.1 Dental evaluation and if applicable, prophylaxis, within 84 calendar days prior to the start of treatment (see Appendix VII, Dental Management);
4.2.2 Whole body PET/CT scan within 42 calendar days prior to the start of treatment;
4.2.3 Baseline audiogram within 84 calendar days prior to the start of treatment;
4.2.4 Assessment of swallowing (dysphagia) within 28 calendar days prior to the start of treatment;
4.2.5 Nutritional evaluation for a prophylactic gastrostomy (PEG) tube placement any time prior to the start of treatment; **note**: In RTOG 99-14, a completed phase II trial assessing the feasibility of combining accelerated fractionation by concomitant boost with cisplatin, 79% of patients who did not have prophylactic PEG placement prior to treatment required placement of PEG during treatment

5.0 REGISTRATION PROCEDURES (8/13/15)

Note: This is a limited institution study; see participating institutions on the RTOG web site.

IGRT is mandatory when using reduced PTV margins (<5 mm). If the institution is not head and neck IGRT credentialed, contact the ACR Core Laboratory/RTQA Credentialing at 215-574-3219.

5.1 Regulatory Pre-Registration Requirements (10/3/13)

5.1.1 Prior to the recruitment of a patient for this study, investigators at participating institutions must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI.

Each investigator or group of investigators at a participating site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the RTOG Headquarters (FAX 215-940-8919) or e-mail them to RTOG3501Regulatory@acr.org. The following study-related regulatory documentation is required:

- Institutional Qualifying Questionnaire with RTOG approval for participation;
- RT Credentialing for IMRT and IGRT;
- IRB/REB initial approval letter;

- IRB/REB approved consent (English and native language versions*); *Note: Institutions with a large number of patients whose primary language is not English must provide certification/verification of IRB/REB consent translation to RTOG Headquarters (described below in Section 5.1.1.1);
- IRB/REB assurance number including renewal information, as appropriate;
- Study Agent Shipment Form (SASF) [available on the RTOG web site, www.rtog.org, under protocol-specific materials/regulatory resources];
- All subsequent amendment and annual approvals;
- All Regulatory submissions must also include a completed IRB certification Form as a cover sheet.

Note: In the event of an amendment of this protocol, sites should submit their amended consent form to RTOG Regulatory for approval **prior** to IRB/REB submission. Sites can submit the consent form with tracked changes to RTOG3501Regulatory@acr.org.

5.1.1.1 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 RTOG 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.

5.1.2 Pre-Registration Requirements for the Initial Shipment of Lapatinib:

5.1.2.1 *Participating Institutions*:

All pre-registration requirements must be met before registering the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF), which is available on the RTOG web site, www.rtog.org, under protocol-specific materials/regulatory resources. Institutions must submit the SASF to RTOG Headquarters by FAX 215-940-8919 or e-mail: RTOG3501Regulatory@acr.org as soon as the individual responsible for the study agent has been identified.

5.2 Pre-Registration Requirement: Central Pathology Review

Central pathology review for eligibility is required prior to registration. Pathology materials and a pathology report must be submitted to the Central Pathology Reviewer. (See Section 10.2.)

5.3 Registration (9/27/16)

5.3.1 Summary of Procedures

This study incorporates a two-step registration process for oropharyngeal patients.

5.3.1.1 All patients can be registered after completing the Eligibility Checklist, Step 1 via online registration.

All patients, except patients with oropharyngeal cancer, then can be randomized after completing the Eligibility Checklist, Step 2 via online registration.

See Section 5.3.2 online for registration instructions.

5.3.1.2 Oropharyngeal carcinoma patients must consent to submit tissue for HPV analysis; see Section 10.2 for details of submission. The Biospecimen Bank at UCSF will process 4 unstained slides from the tissue block submitted and will send the slides to Dr. Adel El-Naggar for HPV analysis. The results of the HPV analysis are expected in approximately 7-10 business days, and RTOG Headquarters 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.

Note: If a specimen was previously submitted to the Biospecimen Bank at UCSF for determination of HPV status for another RTOG trial and found to be p16 negative, investigators can forward a Specimen Transmittal (ST) Form to the Biospecimen Bank at UCSF requesting that the specimen be sent to Dr. El-Naggar for central lab confirmation of p16 negativity.

5.3.2 General Online Registration Instructions

Patients can be registered only after eligibility criteria are met.

Each individual user must have an RTOG user name and password to register patients on the RTOG web site. To get a user name and password:

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via http://phrp.nihtraining.com/users/login.php).
- A representative from the institution must complete the Password Authorization Form (http://www.rtog.org/LinkClick.aspx?fileticket=-BXerpBu5AQ%3d&tabid=219) and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to institutions.

An institution can register the patient by logging onto the RTOG web site (http://www.rtog.org), going to "Data Center Logon" and selecting the link for new patient registrations. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

Institutions can contact RTOG web support for assistance with web registration: websupport@acr.org.

In the event that the RTOG web registration site is not accessible, participating sites can contact RTOG web support for assistance with web registration: websupport@acr.org or call RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET.

6.0 RADIATION THERAPY

Note: All participating institutions will be credentialed for IMRT prior to registering patients to the study. Rapid review of cases is not required prior to patient enrollment.

Intensity Modulated Radiation Therapy (IMRT) is mandatory for this study. Image-Guided Radiation Therapy (IGRT) is mandatory when using a PTV margin of < 5 mm. Only institutions that are credentialed for head and neck IGRT are allowed to use a PTV margin of less than 5 mm.

Protocol treatment must begin within 14 calendar days after randomization.

6.1 Dose Specifications (8/5/14)

IMRT will be given in 35 fractions over 42 calendar days, which requires delivery of 6 fractions per week during 5 of the 6 treatment weeks. The sixth fraction can be delivered either on Saturday or as a second daily fraction, with at least a 6-hour interfraction interval, on one of the weekdays.

Treatment must be delivered using one single plan; concomitant boost techniques using a separate IMRT plans are not allowed. Sites must have completed pre-registration requirements for IMRT (and IGRT, if using reduced margins) credentialing prior to enrolling patients on trial.

Missed treatments due to holidays or logistic reasons can be compensated by delivering additional BID fractions, with a minimum inter-fraction interval of 6 hours, or by treating on Saturday or Sunday.

6.1.1 The primary tumor and involved nodes will be encompassed by the PTV-High Dose (PTV_7000) and will receive a dose of 70 Gy in 2 Gy fractions (see Section 6.1.3 for details of the prescription for the PTV_7000).

6.1.1.1 Regional lymph nodes that are considered to be at high risk of microscopic disease, PTV Intermediary (PTV_5950-6300), may be treated to a dose in the range of 59.5 Gy to 63 Gy in 1.7 Gy to 1.8 Gy per fraction, respectively.

6.1.1.2 Lower-risk targets, such as neck nodal levels that are not first echelon nodes and are not adjacent to levels containing grossly involved nodes, will be encompassed by PTV-Elective Dose (PTV_5600) and will receive a dose of 56 Gy in 1.6 Gy per fraction.

6.1.2 Treatment of the Low Neck

See details in Section 6.5.1. In patients with non-involved low neck nodes, the preferred technique is to treat with isocentric matching AP or AP-PA fields with a larynx block, matched to the IMRT portals just above the arytenoids. The dose will be 2 Gy per fraction prescribed to 3 cm depth to a total dose of 50 Gy in 25 daily fractions. Whole-neck IMRT is allowed.

In cases of gross involvement of the vallecula or low neck nodes, whole-neck IMRT should be considered. Whole-neck IMRT may also be considered if level VI is considered to be at high risk due to gross involvement of level IV nodes.

6.1.3 Prescription for the PTV_7000

All plans must be normalized such that 95% of the volume of the PTV_7000 is covered with prescription dose of 70 Gy.

Additionally:

- At 1 cc PTV_7000 volume on the DVH curve, the dose should not be >110% of the prescribed dose of 70 Gy.
- No volume > 0.03 cc within the PTV_7000 volume on the DVH curve should receive a dose < 95% of the prescribed dose.
- No more than 1 cc of the tissue outside the PTVs should receive ≥105% of the prescribed dose to PTV_7000.

Dose should be reported with inhomogeneity corrections.

6.2 Technical Factors

6.2.1 Treatment Planning/Delivery

Megavoltage energy photon beam irradiation with a photon beam of > 4 MV is required. Any treatment planning and delivery system that has been credentialed for head and neck IMRT for previous RTOG trials is acceptable.

6.2.2 Image Guidance for IGRT When Using Reduced Margins

Daily image guidance of IMRT may be achieved using any one or more of the following techniques:

- Orthogonal kilovoltage (KV) images, e.g. ExacTrac;
- Linear-accelerator mounted kV and MV conebeam CT images;
- Linear-accelerator mounted MV CT images (e.g., Tomotherapy).

6.2.2.1 The institution's procedure for registering daily treatment imaging datasets with a reference dataset should comply with the following recommendations:

- Region-of-Interest (ROI) or "clip box" for fusion should be set to encompass the high dose PTV and adjacent spinal cord; if the supraclavicular region is a part of the target volume the ROI should extend to the C6 level;
- If the fusion software allows the user to create an irregular ROI (e.g. ExacTrac), treatment room objects seen on in-room x-rays should be excluded from the registration;

- Both manual (e.g. based on bony anatomy) and automatic (e.g. based on mutual information) types of registration can be used; the result of the fusion must be visually checked for the alignment of the bony anatomy, such as vertebral bodies and applicable soft tissue structures (e.g. optic nerves and/or optic chiasm).
- Following the registration, the translational and (if the appropriate technology is available) rotational corrections should be applied to the treatment couch. If all the variances are <2.5 mm (this typically corresponds to one half of the usual PRV margin), the treatment can proceed without correction (however, the physician/team may elect to perform adjustments even for a variance <2.5 mm). If one or more corrections are 2.5 to 5 mm, adjustment is necessary prior to treatment; however, re-imaging is not mandatory. If one or more of the corrections are >5 mm, the imaging must be repeated in addition to performing table/positioning adjustments. However, the use of numerous repeat IGRT studies should be avoided (see next section).

6.2.2.2 Management of Radiation Dose to the Patient from IGRT

Estimates of patient doses per imaging study for various imaging systems vary considerably. The doses are in the range of 1 mGy for Cyberknife's and BrainLab's ExacTrac planar kV-systems. The doses from helical MV CT scan on a Tomotherapy unit were estimated to be in range from 1 to 3 cGy for head and neck studies, similar to doses reported for kV cone beam CT on the Varian OBI™ and Elekta Synergy™ machine. The doses for MV cone beam CT are in the range of 10 cGy for a pelvis study to 6 cGy for a head and neck study. Thus, the doses for 3D imaging systems are in the range from 1 to 6 cGy for head and neck imaging and can contribute from 0.5 to 3% to the daily dose of 2.0 Gy. These are small enough dose contributions that if there is only one imaging study done per treatment session, the dose is not expected to have any clinical relevance to the patient. However, the imaging dose to the patient may become significant if repeated studies are done for patients with severe set up problems (e.g., requiring frequent corrections of more than 5 mm). It is recommended that patients demonstrating severe set up problems during the first 7 calendar days of treatment be moved to a treatment with larger margins.

6.3 Localization, Simulation, and Immobilization

6.3.1 Immobilization

The use of a thermoplastic head and shoulder mask is mandatory for head and neck IMRT. Patients will be planned in the supine position with their arms at their sides.

6.3.2 Planning CT scan

The treatment planning CT scan is mandatory for defining target volumes and normal organ at risk. The "planning" CT scan will be done with and without contrast, the one with no contrast is intended for use in heterogeneity corrected IMRT planning. The "structuring" scan with contrast is fused to the planning scan for the purposes of structure definition and so that the major vessels of the neck are easily visualized. An institution may elect to use the "structuring" scan as the "planning" scan. CT scan thickness should be 0.3 cm, and the CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment. All tissues receiving irradiation should be included in the CT scan limits. The scanning limits should at least encompass the orbits superiorly, and 1 cm below the supra-sternal notch inferiorly. For more accurate contouring, diagnostic CT scans and/or MRI may be fused with the planning CT scan.

6.4 Treatment Planning/Target Volumes (8/13/15)

The primary tumor and involved nodes will be encompassed by the PTV_7000 and will receive 2 Gy per fractions, while subclinical disease sites will be encompassed by PTV_5600 which will receive 1.6 Gy per fraction. The total doses will thus be 70 Gy and 56 Gy in 35 fractions, respectively. Regional lymph node areas considered to be at high risk for microscopic disease, PTV_5950-6300, may be treated to dose in the range of 59.5 - 63 Gy at 1.7-1.8 Gy per fractions.

The treatment plan used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the PTV (CTV with a 5 mm margin) and critical normal structures.

An "inverse" planning with computerized optimization should be used.

Structures marked “required” in the table below **must** be contoured and submitted for review. **Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name as listed.**

All submitted treatment plans must strictly adhere to the structure names listed below:

GTV	Primary tumor and involved nodes **Required**
CTV_7000	GTV + 1cm margin **Required**
PTV_7000	CTV-PTV 5mm margin without IGRT; 3mm with daily IGRT **Required**
CTV_5600	CTV 7000 + 1cm margin and nodal regions **Required when applicable**
PTV_5600	CTV-PTV 5mm margin without IGRT; 3mm with daily IGRT **Required when applicable**
CTV_5950	Volume slightly larger than CTV 7000 **Required when applicable**
CTV_6000	Volume slightly larger than CTV 7000 **Required when applicable**
CTV_6300	Volume slightly larger than CTV 7000 **Required when applicable**
PTV_5950	CTV-PTV 5mm margin without IGRT;3mm with daily IGRT **Required when applicable**
PTV_6000	CTV-PTV 5mm margin without IGRT;3mm with daily IGRT **Required when applicable**
PTV_6300	CTV-PTV 5mm margin without IGRT;3mm with daily IGRT **Required when applicable**
SpinalCord	Spinal Cord **Required**
SpinalCord_05	Planning Risk Volume of 5mm **Required**
BrainStem	Brain Stem **Required**
BrainStem_05	Planning Risk Volume of 5mm **Required**
Parotid_L	Left Parotid **Required**
Parotid_R	Right Parotid **Required**
OralCavity	Oral Cavity **Required**
Lips	Lips **Required**
Mandible	Mandible **Required**
Pharynx	Uninvolved posterior pharyngeal wall plus adjacent constrictor muscles **Required**
Esophagus_Up	Cervical Esophagus **Required**
LarynxGSL	Glottic/Supraglottic (GSL) **Required**

Submandibula_L	Left Submandibular Salivary Gland **Required**
Submandibula_R	Right Submandibular Salivary Gland **Required**
External	External border of patient used to define Unspecified Tissue **Required**
PTV_7000_m08	Minimum dose(cold spot within PTV_7000 not including portion of PTV near (<8mm) skin) defined for a point that is 0.03cc in size **Required**
NonPTV	External minus PTVs **Required**

6.4.1 Gross Tumor Volume (GTV) represents the region judged to contain gross primary tumor or involved node(s) based on clinical and endoscopic examinations, CT scan, and, when applicable, other imaging techniques. Grossly positive lymph nodes are defined as any lymph nodes > 1 cm or nodes with a necrotic center.

6.4.2 Clinical Target Volume (CTV) is defined as the GTV plus areas considered at risk for containing microscopic disease delineated by the treating physician. CTV_7000 represents GTV plus a margin of generally 1 cm, and CTV_5600 represents CTV_7000 with a margin of 1 cm and nodal regions to receive elective irradiation.

When the tumor is infiltrative (endophytic) or when the border is ill defined, it might be desirable to deliver an intermediate dose (e.g. 59.5-63 Gy) to a volume (CTV_5950-6300) that is slightly larger than CTV_7000. The CTV margins can be narrower when GTV is in the proximity of the spinal cord or critical normal tissues. CTV should be limited by potential anatomical barriers to tumor spread such as air cavities and bones, and external body contours.

The guidelines for CT based delineation of lymph node levels for node negative patients can be found at the RTOG web site: http://www.rtog.org/CoreLab/ContouringAtlases/HNAtlases.aspx. For patients with positive neck nodes, the proposal by Gregoire (2006) for the delineation of the nodal CTV in the node-positive neck, may be used.

6.4.3 Planning Target Volume (PTV 7000, PTV 5950-6300, and PTV 5600) represents an additional margin around CTV_7000, CTV_5950-6300, and CTV_5600 to compensate for the variability of treatment set-up and internal organ motion. A minimum margin of 0.5 cm around the CTV is required in all directions to define each respective PTV, except for situations in which the CTV is adjacent to spinal cord or other critical normal tissues. In such situations, the margin can be reduced judiciously.

For those institutions using daily IGRT and that are credentialed to use IGRT for margin reduction, a minimum of 3 mm may be used for the CTV to PTV expansion. If IGRT is used without margin reduction, a minimum of 5 mm margin is required for the expansion of CTV to PTV.

When expansion of a CTV results in a PTV that extends beyond the patient's body surface, the PTV should be constrained to 5 mm from within the external contour. A 3 mm constraint of the PTV may be used if disease is near the skin surface. The use of tissue equivalent bolus material is indicated in situations where the disease is at or just under the skin surface. The PTV does not need to be constrained underneath the bolus.

6.4.4 The density corrected dose distributions shall be calculated, and the dose prescription is to be based on a dose distribution corrected for heterogeneities.

6.5 Critical Structures (8/5/14)

6.5.1 Management of the Low Neck/Supraclavicular Region (Match versus No Match)

It is recognized that comprehensive head and neck irradiation incorporating IMRT can be done in several ways, any of which is permitted for this study. Patient-specific QA measurements are required for all IMRT treatments. When a field "match" technique is used for treating the lower

neck, patient-specific measurements should include a verification of the dose coverage in the gap region for each patient.

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. Matching 2 IMRT plans is allowed.
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), e.g., the cervical esophagus, is entirely achieved by inverse treatment planning via IMRT algorithms.

6.5.2 Definitions of Normal Tissues/Organs at Risk (OARs)

6.5.2.1 *Spinal Cord*: The cord begins at the cranial-cervical junction (i.e. 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 (i.e., 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 PRV cord = spinal cord + 5 mm in each dimension. **This is irrespective of the use of IGRT for margin reduction.**

6.5.2.2 *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 process. 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 PRV brainstem = brainstem + 5 mm in each dimension. **This is irrespective of the use IGRT for margin reduction.**

6.5.2.3 *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. The oral cavity will be defined as a composite structure consisting of the anterior one half to two thirds of the oral tongue/floor of mouth, buccal mucosa, and palate.

6.5.2.4 *Parotid Glands:* Parotid glands are defined based on the treatment planning CT scan.

6.5.2.5 *Pharynx:* This is 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).

6.5.2.6 *Cervical Esophagus:* This is defined as a tubular structure that starts at the bottom of pharynx and extends to the thoracic inlet.

6.5.2.7 *Glottic/Supraglottic Larynx (GSL)*: The GSL 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.

6.5.2.8 *Mandible:* The mandible includes the entire bony structure from TMJ through the symphysis.

6.5.2.9 *Unspecified Tissue Outside the Targets:* This tissue is located between the skull base and thoracic inlet that is not included in either the target volumes or the normal tissues described above.

6.5.3 In cases of weight loss >10%, or significant shrinkage of lymphadenopathy during therapy, it is recommended that the immobilization mask be adjusted or remade and a new plan be performed to assess the dose distributions with the current anatomy. Whether a new IMRT plan will be generated is at the discretion of the treating physician. If a new plan is made, the targets should be the same as those used for the initial plan. The new CT contour should be used for IGRT image registration with the new plan.

6.5.4 Doses to Normal Structures

6.5.4.1 *Spinal Cord:* The cord should not exceed 48 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). The PRV spinal cord should not exceed 50 Gy to any volume in excess of 0.03 cc. In treatment planning, the spinal cord PRV should be given the highest priority.

6.5.4.2 *Brainstem:* The PRV brainstem 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 PRV brainstem should be

given less priority than the PRVcord but more priority than the other critical structures listed below.

6.5.4.3 *Lips:* Reduce the dose as much as possible. The mean dose should be <20 Gy.

6.5.4.4 *Oral Cavity:* Reduce the dose as much as possible. The mean dose should be <30 Gy for the non-involved oral cavity. Efforts should also be made to avoid hot spots (>60 Gy) within the non-involved oral cavity.

6.5.4.5 *Parotid Glands:* In most cases, it will be easier to spare one parotid than the other. The treatment planning goal will be for this individual parotid gland to receive a mean dose of <26 Gy.

Contralateral submandibular gland: If contralateral level I is not a target, aim to reduce mean contralateral submandibular gland to <39 Gy.

6.5.4.6 *Pharynx:* Reduce the dose as much as possible. Some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the pharynx exceeds 50 Gy; 2) Mean dose <45 Gy; 3) No more than 15% of the pharynx exceeds 60 Gy.

6.5.4.7 *Cervical Esophagus:* Reduce the dose as much as possible. Some recommended (but treatment goals include: Mean dose <30 Gy.

6.5.4.8 *Glottic and Supraglottic larynx (GSL):* Reduce the dose as much as possible. The glottic larynx mean dose is recommended to be <20 Gy. If whole-neck IMRT is used, under-dosage of PTV_5950-6300 and PTV_5600 adjacent to the glottic larynx will be limited to <10% receiving <95% prescribed dose.

6.5.4.9 *Mandible:* Reduce the dose as much as possible. Hot spots within the mandible should be avoided. It is recommended that maximum dose within the mandible be <66 Gy.

6.5.4.10 *Unspecified Tissue Outside the Targets:* No more than 1cc of unspecified tissue outside the targets can receive 74 Gy or more.

6.5.5 Prioritization of IMRT Planning

1. Spinal Cord
2. Brainstem
3. PTV_7000
4. PTV_5950-6300(if applicable)
5. PTV_5600 (if applicable)
6. a. Pharynx
   b. Parotid gland contralateral to primary tumor site
7. a. GSL
   b. Esophagus
8. a. Lips
   b. Oral Cavity
9. a. Parotid gland ipsilateral to primary tumor site
   b. Mandible
10. Unspecified tissue outside the targets

6.6 Documentation Requirements for IMRT (9/27/12)

- Pre-treatment Radiation therapy planning CT scan (see Section 6.3.2);
- If IGRT is not used, then orthogonal images that localize the isocenter placement of IMRT are required. This information should be archived by the submitting institution, so it can be made available for possible future review.

6.7 Compliance Criteria (8/13/15)

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 5 treatment days at a time and 10 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 2 treatment days for reasons other than toxicity/illness will be considered a protocol deviation.

All treatment plans are to be normalized to provide exactly 95% volume coverage of the PTV_7000 with 70 Gy.

	Per Protocol	Variation Acceptable	Deviation Unacceptable
Total RT dose to PTV_7000 (to 95% of the PTV)	70 Gy	66.5Gy – 73.5Gy	Outside range of Variation Acceptable
Minimum dose (“cold spot” within PTV_7000, not including portion of PTV near (< 8 mm) skin) defined for a point that is 0.03 cc in size (PTV_7000_m08)	66.5 Gy (equals 95% of prescribed dose)	< 66.5 but > 63 Gy	≤ 63 Gy
Maximum dose (“hot spot” > 1cc) within PTV_7000 NonPTV	≤ 77 Gy	> 77 but ≤ 82 Gy	> 82 Gy
Maximum dose (“hot spot” > 1cc outside the PTVs)	< 74 Gy	74-77 Gy	> 77 Gy
Total dose to PTV_5950 or PTV_6000, or PTV_6300 (to 95% of the PTV_5950 or PTV_6000, or PTV_6300)	≥ 59.5 but < 63 Gy	-------	< 59.5 or ≥ 63 Gy
Total dose to PTV_5600 (to 95% of the PTV)	56 Gy	<56 Gy but >50.4 Gy	< 50.4 Gy
Total RT dose to SpinalCord_05 (0.03 cc)	≤ 50 Gy	≥ 50 but ≤ 52 Gy	> 52 Gy
Total RT dose to BrainStem_05 (0.03cc)	≤ 52 Gy	>52 Gy but ≤54 Gy	>54 Gy
Overall RT treatment time	< 45 days	46-50 days (without a medically appropriate indication for delay)	> 50 days (without a medically appropriate indication for delay).
Non-Medically Indicated Treatment Interruptions	0-2	2-4	> 4

Recommended dose acceptance criteria for other normal tissue, but not to be used for plan score.

Structure	Recommended dose acceptance criteria
SpinalCord	D0.03cc(Gy) < 48
BrainStem	D0.03cc(Gy) < 50
Lips	Dmean(Gy) < 20
OralCavity	Dmean(Gy) < 30 Dmax(Gy) < 60
Parotid_L	Dmean(Gy) < 26
Parotid_R	Dmean(Gy) < 26
Submandibula_L	Dmean(Gy) < 39
Submandibula_R	Dmean(Gy) < 39
Pharynx	V50Gy(%) ≤ 33 Dmean(Gy) < 45 V60Gy(%) ≤ 15
Esophagus_Up	Dmean(Gy) < 30

LarynxGSL	Dmean(Gy) < 20 V66.5Gy(%) < 10
Mandible	Dmax(Gy) < 66

6.8 R.T. Quality Assurance Reviews (8/13/15)

The Radiation Oncology Co-Chair, George Shenouda, MD, will perform RT Quality Assurance Reviews. These reviews will be ongoing and performed remotely. RT Quality Assurance reviews will be facilitated by the ACR Core Laboratory/RTQA.

6.9 Radiation Therapy Adverse Events

Grade 3-4 (CTCAE, v. 4) therapy-induced mucositis and/or dysphagia, which are enhanced by cisplatin, are expected to develop in about two thirds of patients. 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, and 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 VII), and cervical myelopathy (<1% with restriction of spinal cord dose to ≤ 45 Gy).

6.10 Radiation Therapy Adverse Event Reporting

See Section 7.10 for details.

7.0 DRUG THERAPY

Institutional participation in chemotherapy studies must be in accordance with the Medical Oncology Quality Control guidelines stated in the RTOG Procedures Manual.

Protocol treatment must begin within 14 calendar days after randomization.

7.1 Code Breaks

The decision to break the code must be based on a life-threatening event or extraordinary clinical circumstance for which knowledge of drug assignment will affect clinical judgment. One of these criteria must be met for RTOG to consider breaking the treatment code.

During business hours (8:30 AM to 5 PM ET), call RTOG Headquarters at 215-574-3150 and ask to speak to the Supporting Study Statistician. For after hours, weekends, and holidays, call 215-459-3576.

7.2 Treatment (2/2/16)

7.2.1 Cisplatin:

Weeks 2-7 with concurrent radiation therapy and lapatinib/placebo: Patients will receive cisplatin, 100 mg/m^2, administered intravenously on days 8 and 29 of the treatment course (Note: cisplatin given within 24 hours of days 8 and 29, e.g. due to holidays, is acceptable). Weekends count as days. Cisplatin can be given before or after the fraction of radiation that is given on the same day. If radiation is held for more than 2 days (for any reason), cisplatin may be held as well until radiation therapy resumes.

See Section 7.6.1 for dose modification for weight loss. Use the actual body weight for all patients. Dose modification for obesity is not recommended.

7.2.1.1 High dose cisplatin is a highly emetogenic regimen with significant incidence of delayed nausea and vomiting. Institutional guidelines for highly 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.. 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 or radiation oncologist. Delayed nausea and vomiting (greater than 24 hours after chemotherapy administration) may be managed by the addition of aprepitant concurrently or with metoclopramide and dexamethasone. Potential delayed nausea regimens include:
  1. The NK-1 antagonist, aprepitant (125 mg p.o.), may be added for prevention of delayed emesis on the day of cisplatin administration and for 2 consecutive days thereafter (80 mg, 80 mg p.o.), with a corticosteroid, such as dexamethasone on days 1, 2, and 3 after cisplatin. Dexamethasone should be reduced on day 1 to 12 mg and delivered at up to 8 mg total daily for up to 4 days total. 5HT3 antagonist (e.g. granisetron, ondansetron) may be given for 3 days, only if palonosetron was not given prior to chemotherapy. Fosaprepitant (115 mg iv. x 1) may be used instead of aprepitant on day 1, 30 minutes before cisplatin; if used, fosaprepitant may be used with or without aprepitant day 2 and 3, and dexamethasone will be given as described above.
  2. Delayed emesis also may be managed by the addition of dexamethasone 8 mg bid x 2 days, followed by dexamethasone 4 mg bid x 2 days, beginning day after chemotherapy; oral metoclopramide 0.5 mg/kg (usually 20-40 mg) in addition qid x 2-4 days; 5HT3 antagonist (e.g. granisetron, ondansetron) may be given for 3 days, only if palonosetron was not given prior to chemotherapy. Adjust dexamethasone downward if aprepitant was given in the preceding 4 days.

7.2.1.2 **Patients must receive vigorous hydration and diuresis.** A suggested regimen is pre-hydration with a 1 liter of D5N S over 2-4 hours and mannitol, 12.5 g iv. bolus immediately prior to cisplatin. Then cisplatin, 100 mg/m^2, in 500 ml NS is administered over 1-2 hours with an additional 1 to 1.5 liters of fluid given post-hydration. Any pre-existing dehydration must be corrected prior to cisplatin administration. Should extravasation occur, the treating physician should follow institutional guidelines for management.

Overnight hospitalization for hydration after cisplatin is strongly encouraged, if it is allowed by the patient's insurance company. Additional iv. hydration and BUN/creatinine check should be strongly considered later in the week after cisplatin administration, in order to prevent dehydration and severe fluid/electrolyte imbalance.

7.2.2 **Lapatinib/Placebo: (1/16/14)**

Note: See Section 7.2.2.1 for lapatinib/placebo feeding tube administration. See Section 7.6.2 for lapatinib/placebo dose modifications.

Week 1: Starting 7 calendar days prior to radiation, patients will take 6 lapatinib/placebo tablets (1500 mg) once daily, 7 days a week, by mouth or by feeding tube on an empty stomach (either 1 hour before or 1 hour after meals). Lapatinib/placebo tablets are **not** to be crushed.

Weeks 2-7: Concurrent with radiation and cisplatin, patients will take 6 lapatinib/placebo tablets (1500 mg) once daily, 7 days a week, by mouth or by feeding tube on an empty stomach (either 1 hour before or 1 hour after meals). Lapatinib/placebo tablets are **not** to be crushed.

After Concurrent Treatment (Maintenance): After completion of radiation, patients will continue lapatinib/placebo 6 tablets (1500 mg) once daily, 7 days a week, by mouth or by feeding tube on an empty stomach (either 1 hour before or 1 hour after meals) for 3 months.

Patient Diary: Patients will be asked to document daily lapatinib/placebo on a pill diary during concurrent treatment and maintenance, which will be collected by the institution as source documentation. Institutions will submit the DP form to RTOG at the end of concurrent treatment and every month during maintenance treatment (see Sections 11.2.3 and 12.1).

7.2.2.1 *Recommended Dosing Procedure for Slurry Preparation of Lapatinib/Placebo Water Suspension*

- Lapatinib tablets are NOT to be crushed.
- Place 120 mL (4 oz) of water in a glass container, then add 6 lapatinib/placebo tablets to the container. Cover the container, let it stand for 5 minutes, and then stir the

mixture intermittently for 10 minutes or until it is fully dispersed. Stir the mixture for 5 seconds then administer. Rinse the container with a 2 oz aliquot of water and repeat the administration process. This completes the administration process (total of 6 oz of liquid is dispensed).

7.2.2.2 *Recommended Dosing Procedure for Slurry Preparation of Lapatinib/Placebo Kool-Aid Suspension*

Prepare Lemonade or Tropical Punch Kool-Aid as directed on the package. Place 2 or 4 oz of Kool-Aid in a glass container, then add 6 lapatinib/placebo tablets to the container. Cover the container, let it stand for 5 minutes, and then stir the mixture intermittently for 10 minutes or until it is fully dispersed. Stir the mixture for 5 seconds then administer. Rinse the container with a 2 oz aliquot of water and repeat the administration process. This completes the administration process (total of 4-6 oz of liquid is dispensed).

7.3 Cisplatin (Cis-Diamminedichloroplatinum, DDP)

Refer to the package insert for additional 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 mechanism of action of DDP has not been clearly elucidated; however, preliminary studies have indicated that the most likely mechanism of antitumor action of this drug resides in its ability to inhibit DNA synthesis and to a lesser degree, RNA and protein synthesis. It has also been shown that DDP binds to DNA and produces inter-strand cross-links. Also DDP is not phase-sensitive and its cytotoxicity is similar in all phases of the cell cycle.

7.3.3 Administration: Intravenous

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: The following adverse events are anticipated:

- Hematologic: Myelosuppression, often with delayed erythrosuppression; rarely, acute leukemia;
- Gastrointestinal: Nausea, vomiting, anorexia, loss of taste;
- Dermatologic: Alopecia;
- Renal: Elevation of BUN, creatinine and impairment of endogenous creatinine clearance, as well as renal tubular damage which appears to be transient); hyperuricemia, much more severe and prolonged adverse events have been observed in patients with abnormal or obstructed urinary excretory tracts;
- Hepatic: Hypomagnesemia, hypokalemia, hypocalcemia;
- Neurologic: Restlessness, involuntary movements, loss of coordination, seizures, peripheral neuropathy;
- Allergic: Flushing, bronchoconstriction, tachycardia, hypotension;
- Other: Ototoxicity (with hearing loss which initially is in the high-frequency range, as well as tinnitus); muscle cramps; weakness.

7.3.6 Supply: Cisplatin is commercially available.

7.4 Lapatinib/Placebo (Tykerb®; GW572016) IND 115409 **(8/5/14)**

This study will be conducted under an IND to be held by RTOG and will require FDA submission and approval. Lapatinib and placebo will be supplied to patients on study free of charge. Participating institutions can access the Lapatinib Investigator Brochure on the RTOG web site (password protected).

7.4.1 Chemical Name: N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl]amino}methyl)-2 furyl]-4-quinazolinamine

7.4.2 Mode of Action: Dual inhibitor of epidermal growth factor receptor (EGFR or ErbB1) and ErbB2 tyrosine kinases.

7.4.3 How Supplied: Lapatinib and placebo are supplied as 250 mg oval, biconvex, orange film-coated tablets with one side plain and the opposite side debossed with FG HLS. The lapatinib

tablets contain 410 mg of lapatinib Ditosylate Monohydrate, equivalent to 250 mg lapatinib free base per tablet. The tablets are packaged into HDPE bottles with child-resistant closures. Excipients present in the tablet include: Microcrystalline cellulose, povidone, sodium starch glycolate, and magnesium stearate. The film-coat contains: Hydroxypropyl methylcellulose, titanium dioxide, triacetin/glycerol triacetate, and yellow iron oxide. Each bottle of lapatinib or placebo contains 90 tablets.

7.4.4 Administration: Oral on an empty stomach (either 1 hour before or 1 hour after meals).

7.4.4.1 *Prohibited Medications*
See Appendix VI.

7.4.5 Storage and Stability: The intact bottles should be stored at controlled room temperature (15°C-30°C). Shelf life surveillance studies of the intact bottle are on-going. Current data indicates lapatinib is stable for at least 2 years at controlled room temperature (15°C - 30°C).

7.4.6 Lapatinib Adverse Events

7.4.6.1 *Cardiac:* Cardiovascular events have been seen in patients taking other compounds that inhibit ErbB2 when used in combination with or following anthracyclines, and interstitial pneumonitis has been reported in patients taking compounds that inhibit ErbB1. See Sections 7.7.1 and 7.7.2 for management guidelines.

7.4.6.2 *Hepatotoxicity:* Hepatobiliary events have been seen in patients taking lapatinib and other tyrosine kinase inhibitors. See Section 7.7.3 for management guidelines.

7.4.6.3 *Dermatologic*
Significant skin adverse events (Grade 3 or more) resulting from lapatinib are rare (1-3%). For CTCAE, v. 4 Grade 4 rash manifested as toxic epidermal necrolysis (i.e. Stevens-Johnson's Syndrome etc) lapatinib must be permanently discontinued. See Section 7.7.4 for management guidelines.

7.4.6.4 *Gastrointestinal*
Experience thus far suggests that when lapatinib is used as monotherapy most diarrhea presents as uncomplicated CTCAE v. 4 grade 1 or 2 (G1 54%, G2 20%, G3 15%, G4<1%). In rare cases, diarrhea can be debilitating, and potentially life threatening if accompanied by dehydration, renal insufficiency, and/or electrolyte imbalances. Standardized and universal guidelines have been developed by an American Society of Clinical Oncology (ASCO) panel for treating chemotherapy-induced diarrhea (Benson, 2004). Early identification and intervention is critical for the optimal management of diarrhea. A patient's baseline bowel patterns should be established so that changes in patterns can be identified while the patient is on treatment. See Section 7.7.5 for management of nausea and/or vomiting and Appendix V for diarrhea management guidelines.

7.4.6.5 *Interstitial Lung Disease*
See Section 7.7.6 for management guidelines.

7.4.7 Supply: Lapatinib and matching placebo will be provided free of charge by Novartis and distributed by a vendor, Biologics, Inc., under contract to RTOG.

Each blinded, patient-specific bottle will be labeled with the following:

- The study number (i.e. RTOG 3501);
- The bottle number (i.e. Bottle 1 of 2 and Bottle 2 of 2);
- The number of capsules
- The patient ID number (e.g. 3501-YYY, where the study number and sequence number represents the unique patient identifier assigned by RTOG at registration);
- The patient's initials (i.e. first, middle, last);
- A blank line for the site pharmacist to enter the patient's name;
- Administration instructions (i.e. "Take xx tablets every day for xx days");
- Storage instructions (i.e. "Store at controlled room temperature, xx degrees");
- Emergency contact instructions.

7.4.8 Drug Ordering **(2/2/16)**
BLINDED (lapatinib or placebo) THERAPY

No blinded starter supplies will be available for this study. Blinded, patient-specific clinical supplies will be sent to the registering investigator at the time of randomization. This randomization will be performed by RTOG Headquarters. The patient ID number assigned by RTOG Headquarters must be recorded by the registering institution for proper study medication

dispersion. Once a patient has been registered, RTOG Headquarters will electronically transmit a clinical drug request for that patient to Biologics, Inc. This request will be entered and transmitted by RTOG Headquarters the day the patient is registered.

Upon receipt of patient randomization notification, Biologics will: 1) Check to confirm site has an active Study Agent Shipment Form (SASF): 2) Place a call to the study site confirming the order was received and arrange day and time of arrival for the study drug; 3) Ship the initial shipment of study drug as listed below:

7.4.8.1 *Initial Shipment:* 4 Bottles of study drug to be taken continuously beginning 1 week prior to RT (8 weeks at 1500 mg (6 tabs/250mg each) PO QD). Biologics will place a follow-up call at week 4 for subsequent shipment of maintenance therapy study drug. Subsequent shipments will be made as listed below.

7.4.8.2 *Subsequent Shipment*: 3 months for maintenance treatment (6 bottles: 3 months at 1500 mg (6 tabs/250 mg each) PO QD.

Drug requests received by Biologics prior to 2 PM ET Monday through Friday, will be processed and shipped that day. Drug requests received after 2PM ET Monday through Friday will be processed and shipped the next business day. See shipment schedule below.

RTOG 3501 Shipment Schedule				
Patient registered with RTOG	**E-order transmitted by RTOG**	**E-order Received by Biologics**	**Order shipped by Biologics**	**Order received at site**
Monday	Monday	Monday by 2PM ET	Monday	Tuesday
Tuesday	Tuesday	Monday after 2PM ET until Tuesday 2pm ET	Tuesday	Wednesday
Wednesday	Wednesday	Tuesday after 2PM ET until Wednesday 2pm ET	Wednesday	Thursday
Thursday	Thursday	Wednesday after 2PM ET until Thursday 2pm ET	Thursday	Friday
Friday	Friday	Thursday after 2PM ET until Friday 2pm ET	Friday	Monday
		Friday after 2PM ET	Monday	Tuesday

The SASF (available on the RTOG web site, www.rtog.org, under protocol-specific materials/regulatory resources) for U.S. and Canadian sites must be submitted to RTOG Headquarters (FAX 215-940-8919) or e-mail it to RTOG3501Regulatory@acr.org as soon as the individual responsible for the study agent has been identified.

All shipments will be sent by FedEx Priority Overnight delivery (delivery by 10:30AM to most US addresses. Packages will be tracked by Biologics until confirmed delivered and delivery exceptions are managed with the highest level of urgency to ensure therapy start date adherence. Packing slips with the shipment tracking number included will be faxed to the designated site coordinator for all shipments.

Questions about supply and delivery should be directed to:

Elliott Lee, Program Manager
Biologics, Inc.
Clinical Research Services

120 Weston Oaks Court
Cary, NC 27513-2256
(800) 693-4906
FAX (919) 256-0794
clinicalresearchservices@biologicsinc.com

7.4.9 Accountability

The Investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from Novartis. It is the responsibility of the Investigator to ensure that the agents are only dispensed to study patients. The agents must be dispensed only from official study sites by authorized personnel according to local regulations.

7.4.10 Drug Destruction

Opened bottles of lapatinib/placebo must be disposed of by incineration at the site as chemotherapy or biohazardous waste. At the completion of the study, all unused lapatinib/placebo also must be incinerated at the site. If the site is unable to dispose by incineration, opened bottles and/or unused lapatinib/placebo should be returned to Biologics, Inc. for destruction (see contact information above). It is the responsibility of the Investigator to ensure that a current record of agent disposition is maintained at each study site where agents are inventoried and disposed, including dates and quantities. Sites should complete the drug destruction form located on the RTOG web site, www.rtog.org , under protocol-specific materials/regulatory resources and send the form to Biologics (see above for contact information).

7.6 Dose Modifications (3/22/16)

7.6.1 Cisplatin Modifications, Day 29

7.6.1.1 *Neutropenia:* If on the day of scheduled treatment with cisplatin the absolute neutrophil count (ANC) is < 1200, hold treatment until ANC ≥ 1200, then treat at 100% dose. Neutropenic fever will require permanent 25% dose reduction. Per CTCAE, v. 4, febrile neutropenia is described as 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.

7.6.1.2 *Thrombocytopenia:* If on the day of scheduled treatment with cisplatin the platelet count is < 75,000, hold treatment until platelets are > 75,000, then treat at 100% dose. Thrombocytopenia that results in bleeding will require a 25% dose reduction.

7.6.1.3 *Neurotoxicity:* If any signs of grade 3 or greater neurotoxicity occur, discontinue cisplatin. Continue radiation therapy (RT) and lapatinib/placebo.

7.6.1.4 *Renal Adverse Events:* Cisplatin should be administered on the scheduled day of treatment using the following guidelines. **Note**: If creatinine is > 1.3 mg/dl, clearance must be calculated (Cockcroft-Gault) in order to make dose adjustment. If the calculated nomogram is 50 mL/min or above, a 24-hour urine collection is not needed, but if the calculation is less than 50 mL/min, a 24-hour urine collection is mandated and the cisplatin will be determined as follows:

Serum Creatinine		**Creatinine Clearance**	**Cisplatin Dose**
≤ 1.5 mg/dl	OR	> 50 ml/min.	100 mg/m^2
> 1.5 mg/dl	AND	40-50 ml/min.	50 mg/m^2
> 1.5 mg/dl	OR	< 40 ml/min.	Hold drug*

*Cisplatin should be held (but RT continued), and the creatinine measured weekly. If the serum creatinine is < 1.5 mg/dl or creatinine clearance is > 50 ml/min, then the second dose of cisplatin can be given at the reduced dose of 50 mg/m^2. Also see Section 7.6.1.6 below.

7.6.1.5 *Other Adverse Events*

- Mucositis: Significant mucositis from radiation and cisplatin is expected and will not be an indication for cisplatin dose modification. No cisplatin dose reductions will be made.

- Ototoxicity: For new clinical hearing loss not requiring a hearing aid or for tinnitus that interferes with activities of daily living, treat at 50% dose reduction. For hearing loss requiring a hearing aid, discontinue cisplatin. Continue RT and lapatinib/placebo.
- If the physician is unsure about the severity of the hearing loss, an audiogram is encouraged.

7.6.1.6 If the second dose of cisplatin is delayed more than 21 days because of hematologic or renal adverse events, that dose will be omitted.

7.6.2 Lapatinib/Placebo Modifications

Patients will be treated per protocol as described in Section 7.2.2 or until disease progression or withdrawal from treatment due to unacceptable adverse event or treatment consent withdrawal.

If lapatinib dose reduction is required the following general rules should be applied:

- Lapatinib/placebo dose should be reduced by increments of 250 mg at a time and only after all supportive care measures have been exhausted without an improvement of patient status.
- Lapatinib/placebo should not be used at doses below 1000 mg if given as monotherapy or below 750 mg concomitantly with cisplatin.

See the table below for a summary of dose holding/interruptions and dose de-escalation recommendations in case of lapatinib-related adverse events (graded according to CTCAE, v. 4). See Section 7.7 below for management guidelines of lapatinib adverse events.

Adverse Event (CTCAE, v. 4)	Action
Non-hematological, grade 1 or 2 (Not attributable to cisplatin or radiation)	Continue lapatinib therapy at full dose prescribed. Apply maximum supportive care recommendations. If prolonged duration of grade 2 adverse event is affecting quality of life a one-time decrease of dose by 250 mg is allowed.
Non-hematological, grade 3 or 4 (Not attributable to cisplatin or radiation)	Apply maximum supportive care recommendations. Hold lapatinib therapy until recovery to grade $\leq$ 1 (up to 14 days). In patients with symptomatic grade 3 or 4 left ventricular cardiac dysfunction, lapatinib must be permanently discontinued. For grade 3 or 4 interstitial pneumonitis or grade 4 rash manifested as toxic epidermal necrolysis (e.g. Stevens-Johnson Syndrome etc.), lapatinib must be permanently discontinued. If recurrence of adverse event after drug hold and/or interruptions is observed and maximum supportive care measures applied, a dose reduction by 250 mg is recommended. Lapatinib should not be used at doses below 1000 mg if given as monotherapy or 750 mg in combination with chemoRT. NOTE: The 750 mg dose should only be used after all supportive measures have been exhausted.
Non-hematological, grade 3 or 4 and adverse events NOT resolved to grade $\leq$ 2 within a maximum of 14 calendar days from last planned administration	Dose reductions by 250 mg (up to 2 reductions) will be considered after maximum supportive care recommendations are introduced.
Cardiac* *Severity corresponding to NYHA criteria; see Appendix II.	Lapatinib therapy to be discontinued permanently in the case of symptomatic NYHA class III and IV congestive heart failure OR decrease in LVEF by > 20% relative to baseline or less than the institution's lower limit of normal.

Abnormal Liver Function Tests	In the event of grade 3 or 4 abnormal ALT and/or bilirubin, lapatinib must be discontinued permanently. Refer to Section 7.7.4. For grade 1 or 2 abnormal ALT/bilirubin, lapatinib must be discontinued permanently for patients with: • BOTH bilirubin and ALT abnormalities being of grade 2 OR • EITHER bilirubin OR ALT abnormality is grade 2 and accompanied by signs or symptoms which, in the opinion of the treating physician, are related to liver injury caused by lapatinib. Such signs and symptoms may include abdominal pain, fever, jaundice, rash, eosinophilia or a PS drop of ≥ 1 point from baseline. Refer to Section 7.7.4.
In case of multiple short interruptions of dose due to either adverse events or drug supply or other reasons the sum of days without lapatinib treatment should not exceed 21 days in any 90 day treatment period.	

7.7 Management of Lapatinib/Placebo Adverse Events (8/5/14)

NOTE: SEE APPENDIX V FOR MANAGEMENT OF DIARRHEA.

7.7.1 Management of Non-Hematologic Adverse Events

If any of the following conditions occur, administration of lapatinib/placebo may be interrupted for a maximum of 14 days to allow the adverse event (AE) to resolve or decrease in severity:

- CTCAE, v. 4 grade 3 or 4 or unacceptable adverse events, e.g. cosmetic effect of grade 2 rash;
- No consideration and/or corroborative evidence that the AE is due to progressive disease;
- The AE is consistent with previously described lapatinib/placebo AEs. At a minimum, reassessment of AEs should be done weekly and more frequently if clinically indicated. When the AE decreases in severity to CTCAE, v. 4 grade 1, the patient may continue to take the assigned dose.

7.7.2 Management of Asymptomatic Cardiac Adverse Events

Refer to CTCAE v. 4 grading of left ventricular cardiac function. After the baseline ECHO or MUGA, repeat LVEF assessment is required at week 12. If a patient is found to have a ≥ 20% decrease in LVEF relative to baseline, or the ejection fraction is below the institution's lower limit of normal, then lapatinib/placebo should be permanently discontinued, and the patient should have a repeat evaluation of ejection fraction 28 calendar days later to confirm recovery.

7.7.3 Management of Symptomatic Cardiac Adverse Events

Study medication must be withdrawn if a patient develops symptoms of heart failure or test results indicating abnormal LVEF (see Section 7.7.2).

7.7.4 Management of Hepatoxicity

Liver chemistry stopping and follow up criteria have been designed to assure patient safety and evaluate liver event etiology. All patients who meet liver chemistry criteria requiring permanent discontinuation of investigational product must continue to be followed per the Liver Chemistry Follow-up Criteria below.

7.7.4.1 *Permanent Discontinuation Criteria*

If a patient experiences ALT > 3 × ULN and total bilirubin > 2.0 × ULN (> 35% direct; bilirubin fractionation required), then the following actions must be taken:

- Immediately and permanently discontinue investigational product;
- In addition to the liver event follow up assessments, the following are suggested: specialist or hepatology consultation; anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies; and liver imaging and/or liver biopsy to evaluate liver disease;
- Promptly report the event to Novartis within 24 hours of learning its occurrence;

- Monitor every 7 calendar days until liver chemistries resolve, stabilize or return to within baseline values;
- Do not re-challenge with investigational product.

NOTE: If bilirubin fractionation testing is unavailable and a patient meets the criterion of total bilirubin >2.0 × ULN, then the management of hepatotoxicity actions above must still be performed.

7.7.4.2 *Interruption Criteria*

If a patient experiences:

- ALT >8 × ULN or
- ALT >5 × ULN persisting for > 14 calendar days: retest within 3 days from the first occurrence and then every 7 calendar days to determine if ALT elevation persists or
- ALT >3 × ULN with signs or symptoms of hepatitis or hypersensitivity (the appearance or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia)

then hold investigational product for 14 calendar days, repeat liver chemistry testing in 14 calendar days, and then contact the Principal Investigator, Dr. Wong, to discuss the possibility of re-starting lapatinib. Liver chemistries and aforementioned signs and symptoms should be monitored at a minimum of every 14 calendar days until resolution, stabilization, or a return to baseline values, at which point monitoring should be continued per protocol.

7.7.4.3 *Continuation Criteria*

If a patient experiences ALT >3 × ULN but <5 × ULN and total bilirubin ≤2 × ULN, without signs or symptoms of hepatitis or hypersensitivity, and who can be monitored every 7 calendar days, then the following actions should be taken:

- Continue investigational product;
- Monitor every 7 calendar days until liver chemistries resolve, stabilize, or return to within baseline, then monitor liver chemistries as per protocol assessment schedule;
- If ALT >3 and < 5 × ULN persists for > 28 calendar days, discontinue treatment

7.7.4.4 *Liver Chemistry Follow-up Criteria*

For all patients who meet any of the liver chemistry criteria described above, make every attempt to carry out the liver event follow up assessments described below:

Viral hepatitis serology including:

- Hepatitis A IgM antibody;
- Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
- Hepatitis C RNA;
- Cytomegalovirus IgM antibody;
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Hepatitis E IgM antibody (if patient resides or has traveled outside USA or Canada in past 3 months).

Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH):

- Complete blood count with differential to assess eosinophilia;
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on an AE report form;
- Record use of concomitant medications, acetaminophen, herbal remedies, other over-the-counter medications, other putative hepatotoxins, and/or alcohol use.

7.7.5 Management of Dermatologic Adverse Events

Patients with poorly tolerated skin adverse events may be successfully managed by providing a brief (up to 14 days) therapy interruption; the daily dose of lapatinib should then be reinstated. However, the rash may improve without the need for interrupting therapy with lapatinib. Of note in current studies, many patients were able to resume lapatinib therapy at the same dose after resolution of rash, and they then had less extensive and/or severe rashes. A variety of agents can be used to manage skin rashes. These include mild-to-moderate strength steroid creams,

topical or systemic antibiotics, topical or systemic antihistamines, and occasionally, retinoid creams.

There is no standard, known, or established treatment proven effective for drug-related skin rashes or changes due to lapatinib. If the rash is severe (1-3%) then most commonly, a papular/pustular rash has been observed, which frequently improves even though the same dose of lapatinib therapy is continued uninterrupted. The need for oral or topical antibiotics is a clinical decision of the investigator and should be preceded by a culture of affected areas and, if indicated, a dermatology consultation. Oral retinoids should not be given because of theoretical concerns about negatively affecting the lapatinib mechanism of action. Oral steroids are also strongly discouraged. Other options for treatment of significant rashes may be determined upon consultation with dermatologist.

7.7.6 Management of Nausea and/or Vomiting

In patients who have emesis and are unable to retain lapatinib, every attempt should be made to obtain control of nausea and vomiting. A dose may be repeated if tablets can be visually found after the vomiting episode.

7.7.7 Management of Interstitial Lung Disease

If a patient develops symptoms suggestive of interstitial pneumonitis, adult respiratory distress syndrome (ARDS), or non-cardiogenic pulmonary edema, lapatinib therapy should be interrupted and a thorough evaluation performed. If CTCAE v. 4 grade 3 or 4 pneumonitis/fibrosis or pulmonary infiltrate is confirmed (and the relationship to lapatinib cannot be excluded), lapatinib must be permanently discontinued. All incidences of interstitial lung disease/ interstitial pneumonitis regardless of grade must be reported as serious adverse events (SAEs).

7.7.8 Management of Other Adverse Events

For any other CTCAE v. 4 grade 3 or 4 adverse events or any clinically significant, lower-grade adverse event, treatment with lapatinib should be interrupted for a maximum of 14 days until the patient recovers completely or the adverse event reverts to CTCAE v. 4 grade 1 or to baseline grade. If recurrence of an adverse event after drug holiday/interruptions is observed, then a dose reduction by 250 mg is recommended. Dose reduction should only be implemented when all supportive care measures have been exhausted without an improvement of patient status.

7.8 Modality Review

The Principal Investigator, Stuart Wong, 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 Principal Investigator, Stuart Wong, MD, will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Wong will perform the next review after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. 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 RTOG Headquarters, whichever occurs first.

7.9 Adverse Events (3/22/17)

All AE reporting on the study case report forms (CRFs) should follow grading criteria instructions on the specific CRF.

7.9.1 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).

AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1).

NOTE: If the event is a Serious Adverse Event (SAE) [see next section], further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

7.9.2 Serious Adverse Events (SAEs)

Definition of an SAE: An undesirable sign, symptom or medical condition which:

- is fatal or life-threatening;
- results in persistent or significant disability/incapacity;
- constitutes a congenital anomaly/birth defect;
- requires inpatient hospitalization or prolongation of existing hospitalization;

Note: Hospitalization for the following reasons does not require expedited reporting:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition;
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug;
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission;
- social reasons and respite care in the absence of any deterioration in the patient's general condition.

- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Any pregnancy, including a male patient's impregnation of his partner, occurring on study must be reported as a medically significant event.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements **as outlined in the previous AE reporting section.**

7.9.2.1 *Additions to SAE Definition*

- Cardiac dysfunction will be reported as an SAE and will be defined as any signs or symptoms of deterioration in left ventricular cardiac function that are grade 3 (CTCAE, v. 4) or a ≥ 20% decrease in left ventricular cardiac ejection fraction (LVEF) relative to baseline which is below the institution's lower limit of normal.
- Hepatobiliary events have been seen in subjects taking lapatinib and other tyrosine kinase inhibitors. As a precaution, the following will be reported as an SAE:• ALT > 3×ULN and total bilirubin > 2.0×ULN (>35% direct; bilirubin fractionation required). **Note**: If bilirubin fractionation testing is unavailable and a subject meets the criterion of total bilirubin > 2.0 × ULN, then the event should still be reported as an SAE. Other hepatic events should be documented as an AE or an SAE as appropriate.

7.10 Serious Adverse Event (SAE) Reporting Requirements (9/27/16)

The treating investigator has the obligation to report all serious adverse events to RTOG and per the local IRB per institutional policy. This study will utilize the RTOG SAE Report Form for reporting of SAEs. The SAE Report Form, SAE Reporting Guidelines, and SAE Report Form Instructions are available on the RTOG web site, www.RTOG.org.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after protocol-specified procedures begin and 30 days after the patient has stopped study treatment must be reported to RTOG within the timeframe detailed in the reporting table below. Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and **e-mail the completed form to RTOG at RTOG3501AE@acr.org.** RTOG will report applicable SAEs to Novartis within 24 hours of awareness.

It is the responsibility of the investigator to document all adverse events which occur during the study. It is the responsibility of the IND holder to comply with IND safety reporting of SAEs as set forth in the Code of Federal Regulations, Section 312.32 and as IND holder, RTOG will report applicable SAEs to FDA and Novartis within the requirement timeframe

7.10.1 Reporting SAEs

Any SAE regardless of relationship to protocol treatment must be reported by the investigator. All deaths during treatment or within 30 days following completion of protocol treatment must be reported within 5 working days.

Any SAEs experienced after this 30 days period should only be reported to RTOG if the investigator suspects a causal relationship to protocol treatment; see the reporting table below for timeframes. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow up to the original episode.

The SAE report should comprise a full written summary, detailing relevant aspects of the SAE in question. The SAE summary also must include the investigator's assessment of expectedness and relatedness to specific protocol treatment (e.g., radiation, cisplatin, or lapatinib). When applicable, information from relevant hospital case records and autopsy reports should be included. Initial and follow-up information, when it becomes available, should be e-mailed to RTOG3501AE@acr.org. In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the RTOG Operations Office by phone, (1-4189215-574-3191). An electronic report must be submitted immediately upon re-establish of the Internet connection. RTOG will report the SAE to the FDA and to Novartis.

SAEs brought to the attention of the investigator at any time after cessation of protocol treatment and considered by the investigator to be related or possibly related to protocol treatment also must be reported via the SAE Report Form, using the SAE Form instructions.

All SAEs must be e-mailed to RTOG3501AE@acr.org within the designated timeframe outlined in the table below as well as the SAE Form Instructions. RTOG will complete a preliminary review of the SAE details and may contact the site with queries. RTOG then will report the SAE to the FDA and Novartis. Note: The individual completing the SAE Report Form should remain vigilant for RTOG's review and be prepared to respond to queries expeditiously in order to ensure timely reporting to the FDA and Novartis.

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **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
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 within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes

<table>
<tr><td>Resulting in Hospitalization</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization</td><td>Not required</td><td>10 Calendar Days</td></tr>
<tr><td colspan="4"><u>Expedited AE reporting timelines are defined as:</u>
○ “24-Hour; 5 Calendar Days” - The AE must initially be reported within 24 hours; 5 Calendar Days; the AE must initially be reported 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.</td></tr>
<tr><td colspan="4">[1]Serious adverse events that occur more than 30 days after the last administration of protocol treatment 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</td></tr>
</table>

7.10.1.1 *Pregnancy* **(2/2/16)**

Patients who become pregnant during the study should discontinue the study immediately. Investigators should report any pregnancy, including a male patient's impregnation of his partner, as a grade 3 SAE and submit an SAE report to RTOG at RTOG3501AE@acr.org. Investigators should submit the pregnancy report form within 14 days of notification. RTOG will report the pregnancy to Novartis within 24 hours of awareness. Patients should be instructed to notify the investigator if it is determined after completion of the study that they become pregnant either during the treatment phase of the study or within five calendar days after the treatment period. Whenever possible a pregnancy should be followed to term, any premature termination reported, and the status of the mother and child should be reported after delivery to RTOG Headquarters. RTOG will report the status to Novartis.

7.10.2 Assessment of Causality and Expectedness

Every effort should be made by the investigator to explain each SAE and assess its expectedness and relationship, if any, to study drug treatment. Causality should be assessed using the following categories: no (not related), or yes (reasonable possibility).

The determination of expectedness and the degree of certainty with which a SAE is attributed to drug treatment (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of the following:

- Known pharmacology of the drug
- Reaction of similar nature being previously observed with this drug or class of drug
- The event having often been reported in literature for similar drugs as drug related (e.g. skin rashes, blood dyscrasia)
- The event being related by time to drug administration terminating with drug withdrawal (dechallenge) or reproduced on rechallenge.

The investigator may change his/her opinion of expectedness and/or causality in light of follow-up information, by amending the SAE Report Form. The expectedness and causality assessment is one of the criteria used when determining regulatory reporting requirements to the FDA.

8.0 SURGERY

8.1 Neck Dissection (8/13/15)

All patients will be assessed 3 months post-treatment with CT scan or MRI or PET/CT.

A neck dissection is required for patients with persistent nodal disease, any stage, if a palpable abnormality or worrisome radiographic abnormality persists in the neck 8-9 weeks after

completion of therapy. A neck dissection is optional for patients with multiple positive lymph nodes or with lymph nodes exceeding 3 cm in diameter at pre-treatment (N2a, N2b, N3) who achieve a complete clinical and radiographic response in the neck. Surgery will be performed within 2 weeks once the decision for neck dissection is made. The status of the primary tumor should be assessed thoroughly at the beginning of the surgical procedure before undertaking nodal dissection. Presence of persistent disease at the primary site, confirmed by frozen section, will be considered a failure of protocol treatment. Further treatment of such a patient will depend on the clinical situation and are at the discretion of the treating physicians.

8.1.1 *For Patients Undergoing a Neck Dissection*

Cervical lymphadenectomy will encompass the original levels of lymph node involvement, which should be removed en bloc. Preservation of the accessory nerve, jugular vein, and sternomastoid muscle is encouraged if consistent with complete removal of all residual nodal disease; however, the extent of the neck dissection will be at the discretion of the surgeon. A selective neck dissection should be performed when feasible. At no time will synchronous bilateral radical neck dissections be performed. If bilateral radical neck dissections are necessary the neck procedure must be staged at an interval of 6 weeks between lymphadenectomies.

The neck dissection specimens must be divided and oriented into discrete anatomic levels in the operating room by the supervising surgeon, and submitted for pathologic review in separate containers. Discrete groups of nodes that are matted or spaced too closely to be resolved as separate nodes under the microscope or by FDG-PET/CT (< 0.5 cm intervening distance) will be categorized as “nodal clusters.” These clusters will be considered equivalent to solitary nodes to allow for simpler and more accurate categorization of all sampled tissue. An attending pathologist should oversee evaluation of all neck dissection specimens according to Appendix IV.

8.1.2 Institutions must submit a Surgery Form (S1), a Surgical Operative Report (S2), and a Surgical Pathology Report (S5) for patients who have surgery to the primary site and/or to regional nodes post-treatment (see Section 12.1).

8.2 Surgical Removal (Salvage) of the Primary Tumor

Directed biopsies at the site of the index lesions will not be performed in the absence of suspicion for relapse. Criteria for biopsy after chemoradiation include a persistent mucosal abnormality or imaging studies that are suspicious for persistent or recurrent disease at 8-9 weeks after completion of therapy. Options for salvage therapy will depend upon the clinical situation and are at the discretion of the treating physicians. Surgical removal (salvage resection) of the primary tumor will be performed, if possible, when biopsy-proven cancer remains more than three months after completion of therapy. The nature of the surgical resection will be dictated by the extent of tumor at the initial evaluation. The operation will be conducted using accepted criteria for primary surgical treatment of the cancer.

Tissues for pathologic evaluation of margins must be taken from the patient (rather than the surgical specimen itself). However, the specimen itself should be marked at sites corresponding to the evaluated margins in order to assess sampling error in obtaining clear margins. If gross tumor remains or when no effort to remove tumor has been made, the patient will be considered to have "gross residual disease." In the absence of residual disease, if the cancer extends to within 5 mm of a surgical margin, the patient would be considered to have "close" margins.

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 medication.

9.2 Non-permitted Supportive Therapy

9.2.1 Hematopoietic Growth Factors

The routine use of erythropoietic growth factors (e.g. darbepoetin, erythropoietin) is strongly discouraged. Granulocytic growth factors (e.g. filgrastim) should not be used concurrently

during radiation therapy, unless radiation therapy has been stopped to allow for recovery of neutropenia and fever. Radiation therapy, lapatinib/placebo, and/or cisplatin should not be resumed within 48 hours of the last dose of filgrastim.

10.0 TISSUE/SPECIMEN SUBMISSION (8/13/15)

NOTE: **Patients must be offered the opportunity to participate in the correlative components of the study, such as tissue/specimen submission.** 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. Sites are not permitted to delete the tissue/specimen component from the protocol or from the sample consent.

10.1 Tissue/Specimen Submission

The Biospecimen Bank at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The Biospecimen Bank at UCSF 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. The Biospecimen Bank at UCSF also collects tissue for central pathology review. Central review of tissue can be for eligibility and/or analysis.

In this study, pre-treatment tissue will be submitted to the Biospecimen Bank at UCSF for the purpose of central review of pathology (mandatory for eligibility for oropharyngeal patients), for banking, and for translational research (highly recommended but optional). In addition, blood will be submitted pre-treatment, at the end of radiation treatment, and at 6 months from the end of treatment for translational research (highly recommended but optional).

If the patient consents to submission of tissue and blood for translational research, pre-treatment tissue will be used to test for predictive biomarkers of lapatinib response, lapatinib resistance, poor RFS, and metastasis. Blood will be used to test for prognostic biomarkers of poor RFS and predictive biomarkers of lapatinib sensitivity and resistance (see Section 1.6 for further details).

10.2 Specimen Collection For Central Review For Eligibility: Mandatory for Oropharyngeal Patients (9/27/16)

Patients with oropharyngeal carcinoma must consent to participate in use of submitted tissue for HPV analysis by p16 immunohistochemistry.

For patients with oropharyngeal carcinoma, the Biospecimen Bank at UCSF will process 2 unstained sections from the tissue block and will send the sections to Dr. Adel El-Naggar who will determine HPV status by p16 immunohistochemistry within 7-10 business days. **Note**: If a specimen was previously submitted to the Biospecimen Bank at UCSF for determination of HPV status for another RTOG trial and found to be p16 negative, investigators can forward a Specimen Transmittal (ST) Form to the Biospecimen Bank requesting that the specimen be sent to Dr. El-Naggar for central lab confirmation of p16 negativity.

The following material must be provided to the Biospecimen Bank at UCSF for Central Review:

10.2.1 One H & E stained slide per positive biopsy site (slide can be duplicate cut stained H&E; it does not have to be the diagnostic slide);

10.2.2 A corresponding paraffin-embedded tissue block of the tumor or three paraffin-embedded 2mm punches from the same block (with an H&E of the embedded punches); Institutions that are unable to submit a tissue block for the required HPV analysis of oropharyngeal cases may instead take 4 unstained sections from the block then obtain three 2 mm core punches of the block and re-embed the core punches into a recipient paraffin block for submission (or sites can send the punches to the Biospecimen Bank to be embedded). Institutions can request an FFPE specimen plug kit (see Appendix IV) from the Biospecimen Bank at UCSF free of charge for this purpose: 415-476-7864 (7864)/FAX 415-476-5271; RTOG@ucsf.edu.

If an institution is uncomfortable with obtaining the unstained sections and punches and wants to retain the tissue block, the site can send the entire block to the Biospecimen Bank at UCSF, and the Bank will obtain the unstained sections and the core punches from the block and return

the remaining block to the site. Please indicate this request (to obtain the sections, perform the core punch procedure, and return the block) on the submission form. **Note**: For oropharyngeal carcinoma patients, there is a 10-day turnaround needed for HPV assays, so institutions should send the block (or punches/slides) by overnight courier to the Biospecimen Bank as soon as possible with their request.

If an institution is not allowed to submit a tissue block or take punch biopsy cores from the paraffin block, the site may submit 15 unstained slides, but this is considered as an exception.

10.2.3 A Pathology Report documenting that the submitted block, core, or slides contain tumor; the report must include the RTOG 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. The block, unstained, or punches must all be from the same block as the H&E being submitted.

10.2.4 A Specimen Transmittal (ST) Form stating that the tissue is being submitted for Central Review. The Form must include the RTOG protocol number and the patient's case number.

10.2.5 Central Review will be performed for every oropharyngeal case by Adel El-Naggar, MD, PhD.

10.3 Specimen Collection for Tissue Banking and Translational Research: Highly Recommended but Optional (8/13/15)

For patients who have consented to participate in the tissue/blood component of the study

The following must be provided in order for the case to be evaluable for the Biospecimen Bank (**Note**: For patients with oropharyngeal cancer, the H&E slides and block must be submitted for required central review as described above in Section 10.2 and would not be submitted again as described below.):

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

10.3.2 A corresponding paraffin-embedded tissue block (the block must match the H&E being submitted) of the tumor or three 2 mm diameter core of tumor tissue, punched from the tissue block containing the tumor with a punch tool and embedded in paraffin along with a corresponding H&E slide. The new block made from the punches must be labeled with the surgical pathology number. **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 and block ID that corresponds to the Pathology Report. If sites are unable to submit tissue blocks, then an exception can be made to accept 15 unstained slides. The block, unstained, or punches must all be from the same block as the H&E being submitted (in Section 10.3.1).

10.3.3 A Pathology Report documenting that the submitted block or core contains tumor. The report must include the RTOG 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 Plasma and whole blood will be collected and stored for future translational studies. See Appendix IV for specimen processing and shipping information. Blood collection kits can be requested from the Biospecimen Bank free of charge at rtog@ucsf.edu or 415-476-7864.

10.3.5 A Specimen Transmittal (ST) Form clearly stating that tissue/plasma/blood is being submitted for the Biospecimen Bank at UCSF; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number.

The following materials must be provided to the Biospecimen Bank at UCSF with all specimens: A Specimen Transmittal (ST) Form documenting the date of collection of the biospecimen; the RTOG protocol number, the patient's case number, time point of study, and method of storage, for example, stored at -80° C, must be included.]

10.3.6 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 refrigerator preferred) for up to 7 calendar days (please ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in plenty of dry ice for up to 7 calendar days, 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.

10.3.7 Specimen Collection Summary **(8/13/15)**

Specimens for Central Review (mandatory for patients with oropharyngeal cancer) and Tissue Banking (highly recommended)			
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 corresponding paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or three 2 mm diameter cores of tissue, punched from the tissue block with a punch tool and embedded in paraffin with 4 unstained slides	Pre-treatment	Paraffin-embedded tissue block or block with 3 punch biopsies with 4 unstained slides **Note**: If site is not allowed to send blocks or punches, then 15 unstained slides will be allowed, but this is an exception.	Block or punch block shipped ambient; include a cold pack during warm weather.

Specimens for Banking and Translational Research (highly recommended)			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/ lavender top) and centrifuge	Pre-treatment, end of radiation therapy (or within 2 weeks of end of radiation therapy), and at 6 mos. from the end of 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 (If site missed this collection they can collect this specimen at any time point or at follow up but this must be noted on the ST)	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

10.3.8 **(8/13/15)** Submit materials for Tissue Banking, Central Review, Translational Research as follows:

U. S. Postal Service Mailing Address: For Non-urgent, Non-frozen Specimens Only
Biospecimen Bank at UCSF
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS): For Frozen Specimens and Urgent FFPE Samples
Biospecimen Bank at UCSF
2340 Sutter Street, Room S341 (Box 1800)
San Francisco, CA 94115

10.4 Reimbursement

The RTOG Foundation will reimburse institutions for submission of protocol-specified biospecimen materials sent to the Biospecimen Bank at UCSF. After confirmation from the Biospecimen Bank that appropriate materials have been received, ACR Clinical Trials Administration will authorize payment according to the schedule detailed in the study-specific contract.

10.5 Confidentiality/Storage

(See the RTOG 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 RTOG protocol number and the patient's case number only. The Biospecimen Bank at USCF 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 central review will be retained until the study is terminated. 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. See Section 11.2 below for details of assessments and exceptions.

11.2 Details of Assessments (8/13/15)

11.2.1 It is necessary to repeat the ECHO or MUGA at week 12 (4 weeks post-completion of radiation therapy); see Section 7.7.2.

11.2.2 A chest CT scan, or a PET/CT scan must be done within 42 calendar days prior to registration to rule out metastatic disease. In addition, a contrast enhanced CT scan or MRI or PET/CT scan of the tumor site and neck nodes must be done within 42 calendar days prior to registration. Note: The CT scan of the neck and/or PET/CT performed for radiation planning may serve as both staging and planning tools.

11.2.3 If the patient consents to submission of tissue and blood for translational research, primary tumor tissue will be submitted pre-treatment, and peripheral blood will be submitted pre-treatment, at the end of radiation therapy, and at 6 months from end of treatment.

11.2.4 Patients will be asked to document daily lapatinib/placebo on a pill diary during concurrent treatment and maintenance treatment, which will be collected by the institution as source documentation. Institutions will submit the **DP** form to RTOG at the end of concurrent treatment and every month during maintenance treatment (see Section 12.1).

11.2.5 Evaluation During Radiotherapy

- A brief history and physical by a Radiation Oncologist and/or Medical Oncologist must be done weekly.
- Bilirubin and AST/ALT must be done 4 weeks after start of lapatinib/placebo.

11.2.6 Evaluation in Follow Up

- Patients will be seen in long-term follow up every 3 months for years 1 and 2, every 6 months for years 3-5 and then annually until publication of study results.
- A brief history and physical by a Radiation Oncologist and/or Medical Oncologist and/or ENT or Head & Neck Surgeon must be done at 4 weeks and 3 months from the end of radiation treatment, then every 3 months through year 2, every 6 months for years 3-5, then annually. A laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) is recommended at these time points but is not required.
- Post-radiation imaging evaluation of the primary tumor and neck at 3 months from the end of radiotherapy is required. The post-radiation imaging can be contrast enhanced CT, MRI, or PET/CT of the head and neck or "whole body" PET/CT (minimum neck and chest),

based on the preference of the treating clinician. However, if a pre-treatment PET/CT was performed, it is highly recommended that a post-radiation PET/CT be used as the post-radiation imaging modality.

Post-radiation imaging evaluation (CT scan or MRI) of the primary tumor and neck also must be done at 6 and 12 months from end of treatment, then annually until year 5.

- A chest CT scan must be done at 6 and 12 months from end of treatment, then annually until year 5.

11.3 Measurement of Response/Progression

11.3.1 Response versus "Tumor Clearance" versus Cancer Progression

Response and confirmation of local (primary site) or regional (neck) "tumor clearance" are not endpoints in this study. Clinical or radiographic evidence of progressive local-regional disease beyond 20 weeks should be documented in the clinical record and ideally confirmed by local or regional biopsy, neck dissection, or salvage surgery. CT or MRI (of head and neck region, with Chest CT), or PET/CT (including chest anatomy) may be used as radiographic evaluation of overall cancer status. The primary, neck and chest portions of the scans should be evaluated and reported separately. The CT portion of a PET/CT may serve as sufficient radiographic evaluation of the chest. If CT or MRI is used for evaluation of the head and neck region, CT of chest will be needed to rule out distant disease or second primaries at the designated evaluation intervals as outlined above in Section 11.2.6 and Appendix I.

11.3.2 Local or Regional Progression

Local (primary site) or regional (neck) progression is defined as palpable residual disease or CT/MRI evidence of persistent disease at the primary site or neck. The location of progressive disease should be separately distinguished (local vs. neck) to document the precise pattern of failure if possible. Progression of local or regional disease should be confirmed by biopsy when possible but may be clinically assessed and documented in the clinical record at the judgment of the treating clinicians.

11.3.3 Distant Metastasis

Clear evidence of distant metastases (lung, bone, brain, etc.); biopsy is recommended where possible. A solitary, spiculated lung mass/nodule is considered a second primary neoplasm unless proven otherwise.

11.3.4 Second Primary Neoplasm

Tumor reappearing with the initial and immediate adjoining anatomical region of the primary will be considered local recurrence. Multiple lung nodules/masses are considered distant metastases from the index cancer unless proven otherwise.

11.4 Criteria for Discontinuation of Protocol Treatment

- Progression of disease;
- Unacceptable adverse events per the judgment of the treating physician(s);
- Patient refusal.

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

11.5 Quality of Life/Patient-Reported Outcomes Instruments

Note: 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 participate in the quality of life (QOL) component of the study, sites are required to administer the baseline QOL and PRO assessments prior to the start of protocol treatment: the PSS-HN, FACT-HN, and XeQOLS. Outcomes will be assessed at baseline (pretreatment) and at 3, 12, and 24 months from completion of radiation treatment.

11.5.1 *The Functional Assessment of Cancer Therapy-Head & Neck (FACT-H&N)* is a multidimensional, patient-self report quality of life (QOL) instrument specifically designed and validated for use with head and neck patients. The patient can complete the 12-item head and neck subscale in 5-10 minutes. The site research nurse or CRA is encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they can skip that question. Similarly, interviewers will give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break.

11.5.2 *The University of Michigan Xerostomia-Related Quality of Life Scale (XeQOLS)* consists of 15 items covering 4 major domains of oral health-related quality of life: physical functioning, personal/psychological functioning, social functioning, and pain/discomfort issues. The patient can respond to the 15 items in the scale in approximately 5 minutes. The Scale is only available in English.

11.5.3 *The Performance Status Scale for Head and Neck Cancer (PSS-HN)* consists of assessment of 3 functional areas (subscales): Normalcy of Diet, Eating in Public, and Understandability of Speech. The site research nurse or clinical research associate (CRA) will administer the PSS-HN. Interviewers are encouraged to be sensitive to each patient's demeanor. If patients appear particularly uncomfortable answering a question, they will be informed that they can skip that question. Similarly, interviewers will give patients a short break if the patient appears fatigued or otherwise in need of a few minutes break. The interviewer rates the patient on each scale based on the patient's responses to targeted questions. The PSS-HN takes approximately 5 minutes to complete.

12.0 DATA COLLECTION (9/27/16)

Data should be submitted to:

RTOG Headquarters*
1818 Market Street, Suite 1720
Philadelphia, PA 19103

***If a data form is available for web entry, it must be submitted electronically.**

Patients will be identified by initials only (first middle last); if there is no middle initial, a hyphen will be used (first-last). Last names with apostrophes will be identified by the first letter of the last name.

12.1 Summary of Data Submission (9/27/16)

Item	Due
Demographic Form **(A5)** Initial Evaluation Form **(I1)** Pathology Report **(P1)** Slides/Blocks **(P2)** PSS-HN **(QP)** FACT-HN **(FA)** Xe-QOL **(L4)**	Within 14 calendar days of study entry
Treatment Form **(TF)**	Within 7 calendar days of end of treatment
Pill Diary **(DP)**	End of concurrent treatment and every 30 calendar days during maintenance treatment
Surgery Form **(S1)** Surgical Operative Report **(S2)** Surgical Pathology Report **(S5)**	Only for patients who have surgery to the primary site and/or to regional nodes post-treatment
Radiotherapy Form **(T1)** Daily Treatment Record **(T5)**	Within 7 calendar days of RT end
PSS-HN **(QP)** FACT-HN **(FA)** Xe-QOL **(L4)**	At 3, 12, and 24 months from end of RT
Follow-up Form **(F1)**	q3 mos. for years 1-2, q6 mos. for years 3-5, then annually until publication of study results

12.2 Summary of Dosimetry Digital Data Submission (Submit to RTOG Headquarters; see Section 12.2.1)

Item	Due
Preliminary Dosimetry Information (DD) Digital Data Submission – Treatment Plan submitted in DICOM format to RTOG via TRIAD exported from treatment planning machine by Physicist Digital data submission includes the following: • DICOM CT data (non-contrast CT and CT with contrast; see Section 6.3.2) • DICOM STRUCTURE • DICOM RT PLAN • DICOM DOSE **NOTE: Sites must notify RTOG via e-mail RTOG-RTQA@acr.org after digital data is submitted. The e-mail must include both the study, "Foundation 3501", and case numbers.** **Digital Data Submission Form (DT)** - Web data entered (form is located on RTOG website: Foundation 3501 under Forms).	Within 7 calendar days of start of RT
Final Dosimetry Information Radiotherapy Form **(T1)** Daily Treatment Record **(T5)** Modified digital patient data as required by RTOG will be submitted via TRIAD	Within 7 calendar days of RT end

12.2.1 Digital Data Submission to RTOG Headquarters

Digital data will be submitted to RTOG via the site's TRIAD account.

12.2.2 Method of Plan Submission

RTOG will provide sites with the American College of Radiology Imaging Network's image acquisition and management software, TRIAD, via electronic installation. TRIAD offers a web-based, software solution allowing institutions to submit DICOM data securely through electronic transmission. Internal to the site, TRIAD allows the site to "DICOM push" from the site's Treatment Planning System (TPS), thus eliminating the need to burn physical media. Once the institution has transferred the RT data onto a TRIAD workstation, the software will anonymize, encrypt, and submit the DICOM RT data via secure internet to the RTOG image archive. For more information please visit the TRIAD web site at https://triad.acr.org.

Institutions initiate installation of TRIAD by e-mailing the name and e-mail address of the person(s) responsible at the site for submitting RT data for the trial (recommend the Physicist and/or Dosimetrist) to TRIAD-Support@acr.org. The site will then receive a TRIAD greeting letter, which describes how to prepare for the installation.

TRIAD technical assistance may be requested by e-mailing TRIAD-Support@acr.org. Please always include the institution name and trial number when requesting TRIAD technical assistance.

13.0 STATISTICAL CONSIDERATIONS

13.1 Primary Endpoint

13.1.1 Progression-free survival (PFS)

13.2 Secondary Endpoints

13.2.1 Overall survival;
13.2.2 Distant metastasis;
13.2.3 Adverse events;
13.2.4 Compliance with planned treatment;
13.2.5 Local-regional control;
13.2.6 Quality of life and patient-reported outcomes;
13.2.7 HER2 expression, amplification and heterodimerization, EGFR ligand expression, EGFR polymorphisms, hypoxia, and EMT characteristics as biomarkers of lapatinib response, sensitivity, and resistance, PFS, and metastasis.

13.3 Randomization and Stratification (10/3/13)

Patients will be randomized to 1 of 2 treatment arms. Additionally, patients will be stratified according to age (≤ 65 vs. > 65); T stage (T1-3 vs. T4); and N stage (N0-2a vs. N2b-3).

13.4 Definitions of Failure

The following table shows how each first event will be counted for progression-free survival, local-regional failure, and distant metastasis. Anything not explicitly in the table (e.g., second primary tumor) is not considered an event, and the patient will continue to be followed for failure. For overall survival, death from any cause will be considered a failure. All failure times will be measured from randomization to the date of failure, competing risk, or last follow-up.

First event	Progression-Free Survival	Local-Regional Failure	Distant Metastasis
None	Censored	Censored	Censored
Local-regional progression or recurrence	Failure	Failure	Competing risk
Distant metastasis	Failure	Competing risk	Failure
Death due to study cancer or from unknown causes	Failure	Failure	Competing risk
Death to due any other reason	Failure	Competing risk	Competing risk
Salvage surgery of primary with tumor present/unknown	Failure	Failure	Competing risk
Salvage neck dissection with tumor present/unknown, > 20 weeks from end of RT	Failure	Failure	Competing risk

13.5 Sample Size and Patient Accrual (9/27/16)

This study will be a randomized phase II screening trial as proposed by Rubinstein, et al (2005). Based on the accrual to RTOG 0129 in this population, it is expected that the monthly accrual will be 12 patients after the first 6 months post-activation (allowing for IRB approvals). In RTOG 0129, this group of patients treated on the accelerated fractionation arm had a 2-year progression-free survival (PFS) rate of 53.5%. Hazard rates for first and second years are 37% and 15%. Based on discussions with the study chair, a 35% reduction in the hazard rate is clinically meaningful. With statistical power 0.80 and significance level 0.20 (1-sided) and one interim efficacy and futility analysis, the Lan-Demets (OF) spending function boundary for efficacy and rho family spending function with parameter of 1.5 for futility were utilized to derive a nonbinding rule. A total of 69 PFS events are required. To observe the required number of events, a sample size of 158 accrued over 1.22 years with an additional 2.6 years of follow-up (total study duration 4.3 years including 6 months for IRB approvals) is required. Allowing for up to 10% of patients to be ineligible or not evaluable, **the total original required sample size is 176**.

Following activation of the study little accrual is anticipated initially. The date at which the first patient is accrued will be used as the baseline for monitoring accrual. If the total accrual during months 18 through 24 is less than 20% of the projected total for 6 months of accrual (15 patients), then the study statistician will recommend to the RTOG DMC and the sponsor that the protocol will be discontinued. If the total accrual is between 21-49%, then the protocol will continue to accrue subjects pending approval to remain open by the RTOG DMC and the study sponsor.

Revised Sample Size and Patient Accrual

As of September 2016, the observed accrual rate in this study is about 30 patients/year (2.5/month). To finish accrual within a reasonable timeframe and to maintain the same design parameters detailed above, we plan to accrue a total of 142 patients (128 analyzable), with a total accrual duration of 4.7 years instead of 5.9 years. According to this plan, we will finish accrual around March 2017.

13.6 Analysis Plan (9/27/16)

Progression-free and overall survival rates will be estimated using the Kaplan-Meier method (1958) and rates of distant metastasis (DM) and local-regional control (LRC) by the cumulative incidence method (Kalbfleisch 1980) to account for competing risks (see Section 13.4). The distributions of the progression-free and overall survival times will be compared between treatment arms with a one sided log rank test (Mantel, 1966). Distant metastasis and local-regional control will be compared using cause-specific log rank test. If the resulting p-value for PFS is < 0.1803, the result will be interpreted as a significant indication of lapatinib improving progression-free survival of these patients to warrant a definitive phase III trial.

Only adverse events (AEs) assessed to be definitely, probably, or possibly related (if the relationship is missing, it will be assumed to be definitely, probably, or possibly) to protocol treatment will be considered. The rates of adverse events and treatment compliance will be estimated using a binomial distribution along with their associated 95% confidence intervals and will be compared using Fisher's exact test.

Comparison of change from baseline quality of life scores between the 2 arms will be done using a 2-sample independent t test. With 158 patients, we will have 87% power to detect an effect size of 0.5 with a two-sided type I error rate of 5% and the statistical power will be 79% and 66% to detect effect sizes of 0.5 with 126 and 94 patients. Analysis of the covariance model (ANCOVA) will be used to adjust for effects from other factors.

For analysis of local-regional control, distant metastasis, PFS, and OS, we will examine whether patients with normal baseline levels of biomarkers have a different prognosis than patients with abnormal baseline levels by calculating the product-limit estimates of the survival function and comparing those estimates using the log-rank statistic. The relationship between local-regional control, distant metastasis, PFS, OS, and abnormal baseline marker levels also will be explored by fitting Cox proportional hazards regression models, both adjusted for baseline disease and patient characteristics and unadjusted. Assuming usable baseline tissue/blood samples can be obtained from 118 eligible patients (~75%), this will provide at least modest power (>69%) to detect large differences (hazard ratios > 2.0) between patients with normal and abnormal marker levels, assuming 50% abnormal prevalence, with a two-sided 5% alpha, for the PFS endpoint.

13.6.1 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 AEs. The RTOG Data Monitoring Committee (DMC) will review this study twice a year in conjunction with the RTOG semiannual meetings with respect to patient accrual and morbidity. The DMC also will review this study on an "as needed" basis between meetings.

13.6.2 Significance Testing for Early Termination and Reporting

One interim treatment comparison will be performed when 50% (34 PFS failures) of the 69 required number of PFS failures are observed. Only the primary endpoint will be tested in the interim analysis. The efficacy will be tested using boundary of 0.0699 on the p value scale for the interim tests and 0.1803 for the final analysis to preserve an overall alpha level of 0.20 for the study. A single interim futility analysis will be conducted when one-half (34) of the requisite events for definitive analysis have been observed. If the p value is equal to or greater than 0.5827 favoring the control (i.e. in the wrong direction with respect to demonstrating that the lapatinib arm is more favorable), then early stopping will be considered. The results will be reported to the RTOG DMC with the treatment blinded. The responsible statistician may recommend early reporting of the results and/or stopping accrual (if applicable) of the trial if the treatment effect with respect to PFS is highly significant or if it is not likely to be.

13.6.3 Analysis for Reporting the Initial Treatment Results

The analysis to report the initial results of treatment will be undertaken when each patient has finished concurrent therapy, around July 2017. All randomized patients (ITT) will be included in the analysis. Eligible patients with both on-study and follow-up information will be considered for sensitivity analysis. The emphasis of this analysis will be on treatment compliance and adverse events. 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;
- Compliance rate for treatment delivery with respect to the protocol prescription;
- Observed results with respect to the endpoints described above.

Only adverse events (AEs) assessed to be definitely, probably, or possibly related (if the relationship is missing, it will be assumed to be definitely, probably, or possibly) to protocol treatment will be considered. The rates of adverse events, treatment compliance, will be estimated using a binomial distribution along with their associated 95% confidence intervals and will be compared using Fisher's exact test.

13.6.4 Analysis for Reporting the Final Treatment Results

The analysis to report the definitive results of treatment will be undertaken when 69 events (total from both arms) have been reported for the primary endpoint, PFS, unless the criteria for early stopping are met. The time from when accrual is finished to this analysis is projected to be approximately 2.7 years based on the observed accrual rate. All randomized patients (ITT) will be included in this analysis. Eligible patients with both on- study and follow-up information will be considered for sensitivity analysis. 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 above.

The difference in PFS between the control arm and the experimental arm will be tested using the one sided log-rank statistic at the significance level of 0.1803 given that the one interim analysis is carried out and shows no statistical significance. If the resulting p-value for efficacy is <0.1803, this result will be interpreted as an indication of lapatinib in improving progression-free survival in these patients.

A final analysis report will be prepared and provided for review by the co-investigators. Results for dissemination will be developed, and a manuscript drafted for review, approval, and submission. After manuscript acceptance, patient follow up will be discontinued and the trial terminated. It is anticipated that termination will occur approximately 3.9 years from when the accrual is finished. This time-frame may be extended depending on factors such as the observed accrual and event rates, in which case a new trial termination date will be established.

REFERENCES

Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol.* 21: 92-98, 2003.

Alroy I, Arden Y. Biochemistry of HER-2 oncogenesis in breast cancer. *Breast Disease*. 11: 31-48, 2000

Al-Sarraf M, LeBlance M, Shanker PG, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: Phase III randomized intergroup study 0099. *J Clin Oncol*. 16: 1310-1317, 1998.

Amador ML. An epidermal growth factor receptor intron 1 polymorphism mediates response to epidermal growth factor receptor inhibitors. *Cancer Res*. 64(24)9139-43, 2004.

American Cancer Society. Cancer Facts and Figures. 2010.

American Cancer Society. Caring for the patient with cancer at home: Diarrhea. http://www.cancer.org/Treatment/TreatmentsandSideEffects/PhysicalSideEffects/DealingwithSymptomsatHome/caring-for-the-patient-with-cancer-at-home-diarrhea

Ang KK, Berkey BA, Tu, X, et al. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. *Cancer Res*. 62(24): 7350-6, 2002.

Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *NEJM.* 363(1): 24-35, 2010. [Epub 2010 Jun 7]

Ang KK. A randomized phase III trial (RTOG 0522) of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III-IV head and neck squamous cell carcinomas. 2011 ASCO Annual Meeting. Abstract 5500.

Arteaga CL. ErbB-targeted therapeutic approaches in human cancer. *Exp Cell Res*. 284(1): 122-30, 2003.

Atalay G, Cardoso F, Awada A, et al. Novel therapeutic strategies targeting the EGFR family and it's downstream effectors in breast cancer. *Ann Oncol*. 14: 1346-1363, 2003.

Beckhardt RN. HER-2/neu oncogene characterization in head and neck squamous cell carcinoma. *Arch Otolaryngol HN Surg*. 121(11): 1265-70, 1995.

Benson A, Jaffer AA, Catalano RB, et al. Recommended Guidelines for the Treatment of Cancer Treatment-Inducted Diarrhea. J Clin Oncol. 22: 2918-2926, 2004.

Bjordal K, de Graeff A, Fayers PM, et al. A 12 country field study of the EORTC QLQ-C30 (version 3.0) and the head and neck cancer specific module (EORTC QLQ-H&N35) in head and neck patients. EORTC Quality of Life Group. *Eur J Cancer*. 36(14): 1796-807, 2000.

Bova RJ, Quinn DI, Nankervis JS, et al. Cyclin D1 and p16INK4a expression predict reduced survival in carcinoma of the anterior tongue. *Clin Cancer Res*. 5: 2810–9,1999.

Cavalot A. Prognostic impact of HER-2/neu expression on squamous head and neck carcinomas *Head & Neck*. 29(7): 655-64, 2007.

Cella DF, et al., The Functional Assessment of Cancer Therapy scale: Development and validation of chemoradiotherapy regimens. *Amer Soc of Clin Onc*. 412, 2000.

Charma R, Tobin P, Clarke SJ. Management of chemotherapy-induced nausea, vomiting, oral mucositis, and diarrhea. Lancet/Oncology. 6: 93-102, 2005.

Chung C. GLI family zinc finger 1 expression and metastasis in patients with head and neck squamous cell carcinoma treated with radiation therapy (RTOG 90-03). *J Clin Oncol*. In press.

Chung CH, Zhang Q, Hammond EM, et al. Integrating epidermal growth factor receptor assay with clinical parameters improves risk classification for relapse and survival in head-and-neck squamous cell carcinoma. *IJROBP.* [Epub 2010 Aug 21 ahead of print]

Cox DR. Regression models and life tables. *J Royal Stat Soc* (series B). 34:187-229, 1972.

Craven JM. Expression of c-erbB-2 gene in human head and neck carcinoma *Anticancer Res*. 12(6B): 2273-6, 1992.

Denis F, Garaud P, Bardet E, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol*. 22(1): 69-76, 2004. [Epub 2003 Dec 2]

Diermeier S. Epidermal growth factor receptor coexpression modulates susceptibility to Herceptin in HER2/neu overexpressing breast cancer cells via specific erbB-receptor interaction and activation. *Exp Cell Res*. 304(2): 604-19, 2005.

Dijkema T, Raaijmakers CP, Ten haken RK, et al. Parotid gland function after radiotherapy: The combined Michigan and Utrecht experience. *IJROBP*. [Epub ahead of press 2010].

Field JK. C-erbB-2 expression in squamous cell carcinoma of the head and neck. *Anticancer Res*. 12(3): 613-9, 1992.

Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. *NEJM*. 349: 2091-2098, 2003.

Frederick BA. Epithelial to mesenchymal transition predicts gefitinib resistance in cell lines of head and neck squamous cell carcinoma and non-small cell lung carcinoma. *Mol Cancer Ther*. 6(6):1683-91, 2007.

Fu KK, Pajak TF, Trotti A, et al. A radiation therapy oncology group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: First report of RTOG 9003. *IJROBP*. 48: 7-16, 2000.

Gregoire V, Eisburch A, Hamoir M, and Levendag P. Proposal for the delineation of the nodal CTV in the node-negative and the post-operative neck. *Radiotherapy and Oncology*. 79:15-20, 2006.

Gruttgen A, Reichenzeller M, Junger M, et al. Detailed gene expression analysis but not microsatellite marker analysis of 9p21 reveals differential defects in the INK4a gene locus in the majority of head and neck cancers. *J Pathol*. 194:311-7, 2001.

Harrington K. et al. Phase II study of oral Lapatinib, a dual-tyrosine kinase inhibitor, combined with chemoradiotherapy (CRT) in patients with advanced squamous cell carcinoma of the head and neck (SCCHN). *J Clin Oncol*. 28:15s, 2010 suppl. Abstract 5505. GSK study 884.

Hatakeyama H. Regulation of heparin-binding EGF-like growth factor by miR-212 and acquired cetuximab-resistance in head and neck squamous cell carcinoma. *PLoS ONE*. 5(9):e12702, 2010.

Hendriks BS, Opreskolk, Wiley HS, Lauffenburger,D .Quantitative analysis of HER-2-mediated effects on HER2 and EGFR Endocytosis. *J of Biol Chem.* 278 (26): 23343-23351, 2003.

Henson BS, Inglehart MR, Eisbruch A, Ship JA. Preserved salivary output and xerostomia-related quality of life in head and neck cancer patients receiving parotid-sparing radiotherapy. *Oral Oncol*. 37(1): 84-93, 2001.

Hou L. Oral cancer progression and c-erbB-2/neu proto-oncogene expression. *Cancer Letter*. 65(3): 215-20, 1992.

Ibrahim SO. Expression of c-erbB proto-oncogene family members in squamous cell carcinoma of the head and neck. *Anticancer Res*. 17(6D): 4539-46, 1997.

Kalbfleisch JD, Prentice RL. *The Statistical Analysis of Failure Time Data*. New York: Wiley; 1980.

Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Amer Stat Assoc. 53: 457-481, 1958.

Karvonen-Gutierrez CA, Ronis DL, Fowler KE, et al. Quality of life scores predict survival among patients with head and neck cancer. *J Clin Oncol*. 26(16): 2754-60, 2008.

Kearsley JH. A comparison of epidermal growth factor receptor (EGFR) and c-erbB-2 oncogene expression in head and neck squamous cell carcinomas. *Pathology*. 23(3): 189-94, 1991.

Khambata-Ford S. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. *J Clin Oncol*. 25(22): 3230-7, 2007.

Khan AJ, King BL, Smith BD, et al. Characterization of the HER-2/neu oncogene by immunohistochemical and fluorescence in situ hybridization analysis in oral and oropharyngeal squamous cell carcinoma. *Clin Cancer Res*. 8:540-8, 2002.

Le QT. Validation of lysyl oxidase as a prognostic marker for metastasis and survival in head and neck squamous cell carcinoma: Radiation Therapy Oncology Group trial 90-03. *JCO*. 27(26): 4281-6, 2009.

List MA, D'Antonio LL, Cella DF, et al. The performance status scale for head and neck cancer patients and the functional assessment of cancer therapy-head and neck scale: A study of utility and validity. *Cancer*. 77: 2294-301, 1996.

List MA, Siston A, Haraf D, et al. Quality of life and performance in advanced head and neck cancer (HNC: Comparison between paclitaxel-based (P-CT/XRT) and cisplatin-based (C-CT/XRT) concomitant chemoradiotherapy: A prospective examination. *J Clin Oncol*. 17: 1020-8, 1999.

List MA, Stracks J. Evaluation of quality of life in patients definitively treated for squamous carcinoma of the head and neck. *Curr Opin Oncol*. 12(3):215-20, 2000.

Logemann JA, Pauloski BR, Rademaker AW, et al. Swallowing disorders in the first year post-radiation and chemoradiation. Head & Neck. 30: 148-158, 2008.

Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemotherapy Reports*. 5: 163-170, 1966.

Martello G. A MicroRNA targeting dicer for metastasis control. *Cell*. 141:1195-1207, 2010.

Martino R, Ringash J. Evaluation of quality of life and organ function in head and neck squamous cell carcinoma. *Hematol Oncol Clin North Am*. 22(6):1239-56, 2008. Review.

Motoyama AB. The efficacy of ErbB receptor-targeted anticancer therapeutics is influenced by the availability of epidermal growth factor-related peptides. *Cancer Res*. 62(11): 3151-8, 2002.

Murphy BA, Ridner S, Wells N, Dietrich M. Quality of life research in head and neck cancer: A review of the current state of the science. *Crit Reviews Oncol/Hemat*. 62:251–267, 2007.

Nahta R, Esteva FJ. HER-2 targeted therapy: Lessons learned and future directions. *Clin Canc Res*. 9 (14): 5078-5084, 2003.

National Cancer Institute. Overview of nutrition in cancer care (PDQ®). http://www.cancer.gov/cancertopics/pdq/supportivecare/nutrition

Nguyen NP, Frank C, Moltz CC, et al. Impact of dysphagia on quality of life after treatment of head and neck cancer. *IJROBP*. 61:772–8, 2005.

Pignon JP, le Maître A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomized trials and 17,346 patients. MACH-NC Collaborative Group. *Radiother Oncol.* 92(1): 4-14, 2009. [Epub 2009 May 14]

Rait AS, Pirollo KF, Ulick D, et al. HER-2-targeted antisense oligonucleotide results in sensitization of head and neck cancer cells to chemotherapeutic agents. *Ann N Y Acad Sci*. 1002:78-89, 2003.

Rampias T, Sasaki C, Weinberger P, Psyrri A. E6 and E7 gene silencing and transformed phenotype of human papillomavirus 16-positive oropharyngeal cancer cells. *J Natl Cancer Inst*. 101:412-23, 2009.

Reed AL, Califano J, Cairns P, et al. High frequency of p16 (CDKN2/MTS-1/INK4A) inactivation in head and neck squamous cell carcinoma. *Cancer Res*. 1996;56:3630–3.

Ringash J, Bezjak A, O'Sullivan B, Redelmeier DA. Interpreting differences in quality of life: The FACT-H&N in laryngeal cancer patients. *Qual Life Res*. 13(4): 725-33, 2004.

Ringash J, Warde P, Lockwood G, O'Sullivan B, Waldron J, Cummings B.Postradiotherapy quality of life for head-and-neck cancer patients is independent of xerostomia. *IJROBP*. 61(5): 1403-7, 2005.

Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA. Interpreting clinically significant changes in patient-reported outcomes. *Cancer.* 110(1):196-202, 2007.

Ringash J, Lockwood G, O'Sullivan B, et al. Hyperfractionated, accelerated radiotherapy for locally advanced head and neck cancer: quality of life in a prospective phase I/II trial. *Radiother Oncol*. 87(2):181-7, 2008. Epub 2008 Jan 22.

Rogers SN, Johnson IA, Lowe D. Xerostomia after treatment for oral and oropharyngeal cancer using the University of Washington saliva domain and a Xerostomia-Related Quality-of-Life Scale. *IJROBP*. 77(1): 16-23, 2010. [Epub 2009 Aug 11]

Rubin Grandis J. Levels of TGF-alpha and EGFR protein in head and neck squamous cell carcinoma and patient survival *JNCI.* 90(11): 799-801, 1998.

Rubinstein LV, Korn EL, Freidlin B, et al. Design issues of randomized phase II trials and a proposal for phase II screening trials. J Clin Oncol. 23: 28, 7199-7206, 2005.

Rusnak DW, Lackey K, Afflek K, et al. The effects of the novel reversible, EGFR/ErbB2 tyrosine kinase inhibitor, GW 572016, on the growth of human normal and tumor derived cell lines in vitro and in vivo. *Mol Canc Therapeutics*. 1: 85-94, 2001

Saltz LB. Understanding and Managing Chemotherapy-Induced Diarrhea. *J Support Oncol*.1:35-46, 2003.

Siddiqui F, Pajak TF, Watkins-Bruner D et al. Pretreatment quality of life predicts for locoregional control in head and neck cancer patients: a radiation therapy oncology group analysis. *IJROBP*. 70(2): 353-60, 2008.

Söderberg O. Direct observation of individual endogenous protein complexes in situ by proximity ligation. *Nat Methods*. 3(12): 995-1000, 2006. Epub 2006 Oct 29.

Sturgis EM, Cinciripini PM. Trends in head and neck cancer incidence in relation to smoking prevalence: an emerging epidemic of human papillomavirus-associated cancers? *Cancer*. 110(7): 1429-35, 2007.

Webster GJ, Rowbottom CG, Ho KF, et al. Evaluation of larynx-sparing techniques with IMRT when treating the head and neck. *IJROBP*. 72:617-22, 2008.

Weibrecht I, Leuchowius KJ, Clausson CM, et al. Proximity ligation assays: A recent addition to the proteomics toolbox. *Expert Rev Proteomics*. 7(3): 401-9, 2010. Review.

Weymuller EA, Yueh B, Deleyiannis FW, et al. Quality of life in patients with head and neck cancer: Lessons learned from 549 prospectively evaluated patients. *Arch Otolaryngol Head Neck Surg*. 126(3): 329-35; discussion 335-6, 2000.

Xia W, Lau YK, Zhang HZ, et al. Combination of EGFR, HER-2/neu, and HER-3 is a stronger predictor for the outcome of oral squamous cell carcinoma than any individual family members. *Clin Cancer Res*. 5:4164-74, 1999.

Xia W, Mullin RJ, Keith BR et al. Anti-tumor activity of GW 572016: A dual tyrosine kinase inhibitor blocks EGF activation of EGFR/ErbB2 and downstream Erk 1 / 2 and AKT pathways. *Oncogene.* 21: 6255-6263, 2002.

Yarden Y. Biology of HER2 and its importance in breast cancer. *Oncology*. 61 (Suppl 2), 1-13, 2001.

Zhang W. Epidermal growth factor receptor gene polymorphisms predict pelvic recurrence in patients with rectal cancer treated with chemoradiation. *Clin Can Res*. 11:600-5, 2005.

Zhou Y, Brattain, MG. A novel strategy of colon cancer therapy: Targeting both EGFR and ErbB2 receptors. Proceedings AACR: 44, Abstract 5529, 2003.

(8/13/15) APPENDIX I: STUDY PARAMETER TABLE: *See Section 11.2 for details and exceptions

Assessments	Prior to Registration (calendar days)	Prior to Treatment (calendar days)	q7 days During Treatment	From End of Radiation Therapy (calendar days)					q 3 mos. in year 2; 6 mos. in years 3-5; then annually*
				4 weeks	3 mos.	6 mos.	9 mos.	12 mos.	
Complete history/physical	28 days		Brief H&P	X*	X*	X*	X*	X*	X*
Rad Oncology Exam				X*	X*	X*	X*	X*	
Med Oncology Exam	28 days			X*	X*	X*	X*	X*	
Zubrod	14 days		X		X	X	X	X	X
Weight	28 days		X		X	X	X	X	X
Chest CT or PET/CT	42 days					X*		X*	Annually until year 5
Contrast enhanced CT or MRI or PET/CT of tumor site and neck nodes	42 days				X*	X*		X*	Annually until year 5
EKG	84 days								
ECHO or MUGA	84 days			X*					
ENT or H&N Surgeon exam	42 days			See Sec. 11.2.5	See Section 11.2.6				
CBC, Diff, Platelets	14 days		X		X	X	X	X	
Na, K, glucose, Ca, Mg	14 days								
Na, K, Cl, glucose, Ca, Mg, albumin			X	X	X	X	X	X	
Bilirubin, AST/ALT	14 days		See Sec. 11.2.5		X	X	X	X	
Serum creatinine or creatinine clearance	14 days		X		X	X	X	X	
Serum pregnancy test, for women of childbearing potential	14 days								
Adverse Event Eval, including mucosal assessment			X	X	X	X	X	X	X
Dental assessment		Recommended at 84 days							
Whole body PET scan		Recommended at 42 days							
Audiogram		Recommended at 84 days							
Swallowing assessment		Recommended at 28 days							
Nutritional eval for PEG tube		Recommended prior to tx							
*Pill Diary			End of tx	q30 days. for 3 mos.					
QOL/PRO assessments, if patient consents		X			X			X	at 24 mos. from end of tx
Tissue/blood for research, if patient consents	Prior to treatment			End of RT		X			

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**

NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

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 (e.g., 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.

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

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.

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 (e.g., 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 (e.g., 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 (e.g., 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 (e.g., 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.

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 (8/13/15)

Biospecimen Bank at UCSF Instructions for
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
Biospecimen Bank at UCSF
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS): For Frozen or Urgent FFPE samples and Trackable Specimens
Biospecimen Bank at UCSF
2340 Sutter Street, Room S341 (Box 1800)
San Francisco, CA 94115

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

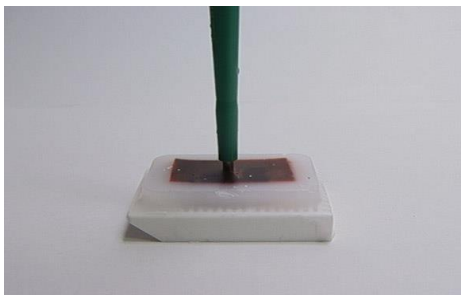
- ❑ **FFPE Specimens:**
  - ○ Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear the slides shaking it is likely that they will break during shipping.
  - ○ All specimens must be clearly labeled with pathology accession number and block ID. A corresponding H&E stained slide must be submitted with all blocks and unstained slides. Incomplete submissions without H&E slides will be returned to sites to correct before they can be processed.
  - ○ FFPE Blocks can be wrapped with paper towel, 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 are not shaking. If you can hear shaking, it is likely that they will break during shipping.
  - ○ 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:**
  - ○ Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and clearly identified.
  - ○ 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.
  - ○ Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
  - ○ 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.

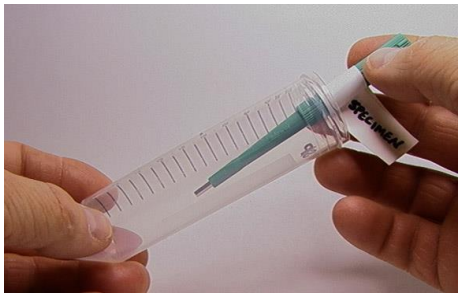
- ❑ **For Questions regarding collection/shipping please contact the Biospecimen Bank at UCSF by e-mail: RTOG@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.**

APPENDIX IV (Continued) (8/13/15)
FFPE SPECIMEN PLUG KIT INSTRUCTIONS

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

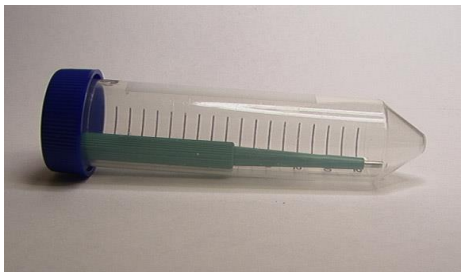


Step 1
If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate 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 ID (study number, case number, pathology accession, and block number). 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
Embed the punches into one block, and cut an H&E from it.
For sites unable to embed the punches, 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 ID.

***NOTE:** If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the Biospecimen Bank at UCSF, 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 and provide a return air bill.

Ship punch block or 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 Biospecimen Bank at UCSF by e-mail: RTOG@ucsf.edu or call 415-476-7864/Fax 415-476-5271.

U.S. Postal Service Mailing Address: For Non-urgent, Non-frozen Specimens Only
Biospecimen Bank at UCSF
University of California San Francisco
Campus Box 1800
2340 Sutter Street, Room S341
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS): For Frozen Specimens or Urgent, Trackable shipments
Biospecimen Bank at UCSF
2340 Sutter Street, Room S341 (Box 1800)
San Francisco, CA 94115

BLOOD COLLECTION KIT INSTRUCTIONS (8/13/15)

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

Kit contents:

- Twenty-nine (29) 1 ml cryovials for ALL TIME POINTS
- Biohazard bags (4) and Absorbent shipping material (4)
- 1 Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers
- Specimen Transmittal (ST) Form and Kit Instructions

PREPARATION AND PROCESSING OF SERUM, PLASMA AND WHOLE BLOOD:

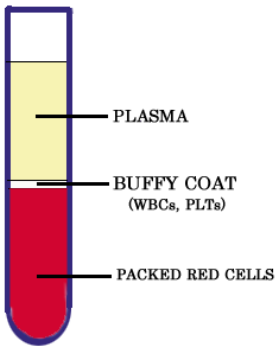
(A) Plasma : Purple Top EDTA tube #1

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

Process:

1. After collection, into an EDTA blood draw tube (not provided in kit unless requested) 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 RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "plasma". Avoid pipetting up the buffy coat layer. **If an aliquot has < 0.5 ml in the tube, please note the volume on the vial and also note it on the ST Form.**
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.

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



Continued on next page

(B) Whole Blood for DNA : Purple Top EDTA tube

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

Process:

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 RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood". **If an aliquot has < 1.0 ml in the tube, please note the volume on the vial and also note it on the ST Form.**
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.

Freezing and Storage:

- ☐ 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).

  OR:
  - 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).

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

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 RTOG 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): For all Frozen Specimens
Biospecimen Bank at UCSF
University of California San Francisco
2340 Sutter Street, Room S341 (Box 1800)
San Francisco, CA 94115
For questions, call 415-476-7864 or e-mail: RTOG@ucsf.edu

APPENDIX V

DIARRHEA MANAGEMENT GUIDELINES

Presented in the sections below are the recommended guidelines for the management of diarrhea in patients receiving lapatinib-based therapy; these guidelines were derived from the recommendations published by the ASCO panel (Benson, 2004).

Early identification and intervention is critical for the optimal management of diarrhea. A patient's baseline bowel patterns should be established so that changes in patterns can be identified while patient is on treatment.

It is strongly recommended to give patients receiving lapatinib-based therapy a prescription of loperamide with instructions to start loperamide at the onset of diarrhea as per the recommendations outlined below.

Patients should be instructed to first notify their physician/healthcare provider at onset of diarrhea of any severity.

An assessment of frequency, consistency and duration as well as knowledge of other symptoms such as fever, cramping, pain, nausea, vomiting, dizziness and thirst should be taken at baseline. Consequently patients at high risk of diarrhea can be identified. Patients should be educated on signs and symptoms of diarrhea with instructions to report any changes in bowel patterns to the physician.

It is recommended that patients keep a diary and record the number of diarrhea episodes and its characteristics. They should also include information on any dietary changes or other observations that may be useful in the evaluation of their diarrhea history.

If patients present with diarrhea of any Grade, check they are taking lapatinib correctly, i.e. single daily dose, rather than splitting it through the day. Obtain information on food (solid and liquid) and over the counter (OTC) medication, including herbal supplements, taken during the lapatinib treatment period.

Definitions

Define diarrhea compared to baseline (Table 1).

Table 1

Adverse Event Grade, CTCAE v. 4	Diarrhea
1	Increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4-6 stools/day over baseline; moderate increase in ostomy output compared to baseline;
3	Increase of ≥7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care activities of daily living (ADL)
4	Life-threatening consequences; urgent intervention indicated
5	Death

Uncomplicated diarrhea is considered mild-to-moderate and defined as CTCAE v. 4 grade 1 or 2 with no complicating signs or symptoms.

Complicated diarrhea is severe and defined as any CTCAE v. 4 grade 3 or 4 diarrhea, or grade 1 or 2 with one or more of the following signs or symptoms:

- Moderate to severe abdominal cramping
- Nausea/vomiting ≥Grade2
- Decreased performance status
- Fever
- Sepsis
- Neutropenia
- Frank bleeding (red blood in stool)
- Dehydration

Management Guidelines for Patients Receiving Lapatinib Alone or as Combination Therapy

A) Uncomplicated Diarrhea

I. CTCAE Grade 1

NOTE: Patient should be instructed to start supportive care immediately at the first episode of diarrhea (i.e., unformed stool) and call their physician.

1. Administer loperamide
   a. Initial dose 4mg followed by 2mg after every unformed stool. Re-evaluate after 24 hours, if:
      i. Diarrhea is resolving:
         - Continue loperamide treatment at 2mg dose after every unformed stool until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours.
         - If diarrhea recurs, re-initiate loperamide treatment as needed to maintain normal bowel patterns

      ii. Diarrhea is not resolving:
         - Administer loperamide at 2mg every 4 hours for the next 24 hour. Re-evaluate after 24 hours. If diarrhea is resolving, administer loperamide at 2mg after every unformed stool until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours. If diarrhea is not resolving continue loperamide treatment at 2mg every 4 hours and re-evaluate every 24 hours.

   b. If Grade 1 diarrhea persists for more than 1 week with loperamide treatment, consider treatment with second-line agents (octreotide, budesonide or tincture of opium).

2. Dietary modifications which are essential in the management of diarrhea include the following recommendations (American Cancer Society; National Cancer Institute):
   a. Stop all lactose containing products and eat small meals
   b. Avoid spicy, fried and fatty foods, raw vegetables and other foods high in fiber
      i. Eat foods low in fiber (i.e., lean meat, rice, skinless chicken or turkey, fish, eggs, canned or cooked skinless fruits, cooked/pureed vegetables)
   c. Avoid caffeine and alcohol as they can irritate the bowel and increase motility
   d. Hydration: Drink 8-10 large glasses of clear liquids a day (e.g., water, electrolyte drink).
      i. Avoid acidic drinks such as tomato juice and fizzy soft drinks
   e. Supplement diet to include foods rich in potassium (e.g., bananas, potatoes, and apricots) , evaluate their impact on diarrhea due to the fiber content (e.g., apricots)

3. Continue with study treatment (i.e. lapatinib-based treatment)
   Continue with supportive care until diarrhea has resolved (diarrhea free for 12 hours/bowel pattern return to baseline). Once diarrhea has resolved, the patient can begin to gradually re-introduce foods from their normal diet.

   If diarrhea recurs following stopping of loperamide treatment, resume loperamide treatment at the dose and schedule recommended above and re-introduce diet modifications. Continue with study treatment.

   If grade 1 diarrhea persists for ≥ 2 weeks, refer to the management guidelines for persistent grade 2 diarrhea.

II. CTCAE Grade 2
NOTE: Patient should be instructed to call physician at first episode of diarrhea and start supportive care immediately

1. Administer loperamide
   a. Initial dose 4mg followed by 2mg every 4 hours or after every unformed stool. Re-evaluate after 24 hours. If:
      i. Diarrhea is resolving, continue loperamide treatment at 2mg dose after every unformed stool until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 12 hours
         - If diarrhea recurs, re-initiate loperamide treatment as needed to maintain normal bowel patterns
      ii. Diarrhea is not resolving, consider loperamide dose of 2mg every 2 hours for 24 hours. If Grade 2 diarrhea persists after total of 48 hours of loperamide treatment, start second-line agents (octreotide, budesonide or tincture of opium).
         - Consider performing stool work-up, CBC, electrolytes and other tests as appropriate

2. Dietary modifications which are essential in the management of diarrhea include the following recommendations (American Cancer Society; National Cancer Institute):
   a. Stop all lactose containing products and eat small meals
   b. Avoid spicy, fried and fatty foods, bran, raw vegetables and other foods high in fiber
      i. Eat foods low in fiber (i.e., lean meat, rice, skinless chicken or turkey, fish, eggs, canned or cooked skinless fruits, cooked/pureed vegetables)
   c. Avoid caffeine and alcohol as they can irritate the bowel and increase motility
   d. Hydration: Drink 8-10 large glasses of clear liquids a day (e.g., water, electrolyte drink).
      i. Avoid acidic drinks such as tomato juice and fizzy soft drinks
   e. Supplement diet to include foods rich in potassium (e.g., bananas, potatoes, and apricots), evaluate their impact on diarrhea due to the fiber content (e.g., apricots)

3. Continue with study treatment (i.e., lapatinib-based treatment)
   Continue with supportive care until diarrhea has resolved (diarrhea free for 12 hours/bowel pattern return to baseline). Once diarrhea has resolved, the patient can begin to gradually re-introduce foods from their normal diet. Refer to Section IV “Recurrent Diarrhea” for study treatment guidelines.

   If diarrhea recurs following stopping of loperamide treatment, resume loperamide treatment at the dose and schedule recommended above and re-introduce diet modifications.

III. **Persistent (≥ 3days/72 hours) Grade 2 Diarrhea**: hold lapatinib and chemotherapy (if applicable) until diarrhea resolves (<Grade 1/return to baseline bowl pattern). If supportive care measures an
    1. If supportive care measures and the interruption of study treatment (i.e., lapatinib and if applicable chemotherapy) are ineffective in treating persistent Grade 1 or Grade 2 diarrhea, perform stool work-up, CBC, electrolytes and other tests as appropriate, consider consulting with a gastrointestinal (GI) specialist.
        a. After diarrhea resolves (≤Grade 1), resume treatment with lapatinib and chemotherapy (if applicable).

IV. **Recurrent Diarrhea (more than 1 occurrence of Grade 2 diarrhea):** once the 2nd occurrence of grade 2 diarrhea resolves to ≤ grade 1, consider reducing the dose of lapatinib by 250mg or 1 tablet, unless the lapatinib dose already had been reduced to 750mg. No further dose reduction is recommended for patients taking lapatinib at 750mg.
    1. Consider a dose reduction for chemotherapy (if applicable)

B) Complicated Diarrhea

I. CTCAE, v 4 grade 3 or Grade 1 or 2 with complicating features (severe cramping, severe nausea/vomiting, decreased performance status, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration)

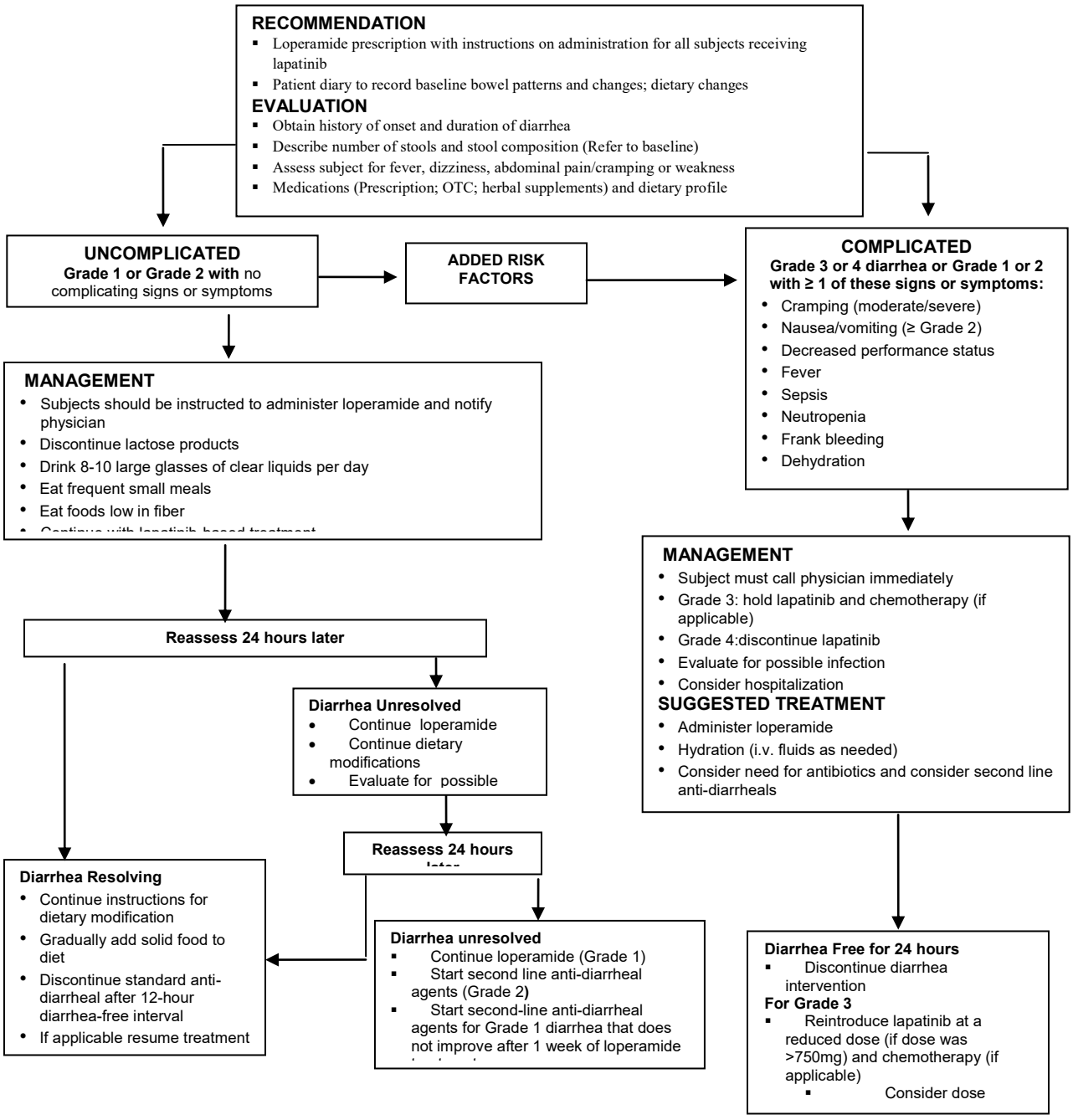
1. Patient **must** call physician immediately for any complicated severe diarrhea event
2. If loperamide has not been initiated, initiate loperamide immediately: Initial dose 4mg followed by 2mg every 2 hours or after every unformed stool
3. Refer to the dietary modification recommendations for Grade 1 and Grade 2 uncomplicated diarrhea
4. For dehydration use intravenous fluids as appropriate, if patient presents with severe dehydration administer octreotide
5. Perform stool work-up, CBC, electrolytes and other tests as appropriate
6. Administer antibiotics as needed (example fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3-4 neutropenia
7. Hold lapatinib and chemotherapy (if applicable) until symptoms resolve to ≤Grade 1 and reintroduce lapatinib at a reduced dose (unless dose had been reduced to 750mg, contact medical monitor for further guidance)
    a. Consider a dose reduction for chemotherapy (if applicable)
8. Supportive care and other interventions should be continued until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 24 hours
9. Intervention may require hospitalization for patients most at risk for life threatening complications

II. CTCAE v. 4 grade 4

1. Patient must call physician immediately for any Grade 4 diarrhea event
2. Discontinue treatment with lapatinib, hold chemotherapy (if applicable)
3. If loperamide has not been initiated, initiate loperamide immediately: Initial dose 4mg followed by 2mg every 2 hours or after every unformed stool
4. For dehydration use intravenous fluids as appropriate, if patient presents with severe dehydration administer octreotide
5. Perform stool work-up, CBC, electrolyte and other tests as appropriate
6. Recommend consulting with GI specialist
7. Administer antibiotics as needed (example fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3/4 neutropenia
8. Supportive care and other intervention should be continued until diarrhea free (i.e., <Grade 1/bowel patterns returned to baseline) for 24 hours
9. Intervention may require hospitalization for patients most at risk for life threatening complications

Refer to and follow the recommended supportive care guidelines in the previous sections and as depicted in Figure 1 (see next page).

Figure 1: Algorithm for the management of diarrhea in patients treated with lapatinib-based therapy



1. For Grade 1 diarrhea that persists for 2 weeks or longer, refer to Section III.
2. For Grade 2 diarrhea that persists longer than 3 days/72 hours, refer to Section III.
3. For recurrent diarrhea, refer to Section IV for further management guidelines.

APPENDIX VI (2/2/16)

PROHIBITED MEDICATIONS

Lapatinib is a substrate for CYP3A4. Inducers and inhibitors of CYP3A4 may alter the metabolism of lapatinib. The following list of CYP3A4 inducers and inhibitors are prohibited from screening through discontinuation from study.

Drug Class	Specific Agents	Wash-out[1]
CYP3A4 Inducers		
rifamycin antibiotics	rifampicin, rifabutin, rifapentine	2 weeks
anticonvulsants	phenytoin, carbamezepine, barbiturates (e.g., phenobarbital)	
antiretrovirals	efavirenz, nevirapine, tipranivir, etravirine	
glucocortical steroids (oral only) **Note**: Steroids are required as an anti-emetic for cisplatin. The short-term administration of steroids for this indication poses minimal risk related to CYP3A4.	cortisone (>50 mg), hydrocortisone (>40 mg), prednisone or prednisolone (>10 mg), methylprednisolone or triamcinolone (>8 mg), betamethasone or dexamethasone (>1.5 mg)[2]	
other	St. John's Wort, modafinil	
CYP3A4 Inhibitors		
antibiotics	clarithromycin, erythromycin, troleandomycin, flucloxacillin	1 week
antifungals	itraconazole, ketoconazole, fluconazole (>150 mg daily), voriconazole	
antiretrovirals	delaviridine, nelfinavir, amprenavir, ritonavir, indinavir, saquinavir, lopinavir, atazanavir	
calcium channel blockers	verapamil, diltiazem	
antidepressants	nefazodone, fluvoxamine	
gastrointestinal agents[3]	cimetidine	
fruit juices	grapefruit, star fruit, and papaw	
other	amiodarone	6 months
Miscellaneous		
antacids	Mylanta, Maalox, Tums, Rennies	1 hour before and after dosing
herbal supplements[4]	ginkgo biloba, kava, grape seed, valerian, ginseng, echinacea, evening primrose oil	2 weeks

1. Time period between last dose of listed drug and first dose of lapatinib, required to avoid drug-drug interaction potential for toxicity (inhibitors) or loss of efficacy (inducers) that could make the patient unevaluable. Clinically appropriate substitution of drugs not on the list is recommended.
2. A standard 3-5 day course of dexamethasone at a dose following the institutions standard of care for the prevention and/or treatment of platinum-induced nausea and vomiting is allowed. Glucocortical steroid oral dose equivalents (in parentheses) to dexamethasone 1.5 mg (or less) given daily are allowed. Intravenous dosing should be considered if clinically appropriate.
3. Emetogenic chemotherapy may require 3-4 daily doses of aprepitant. CYP3A4 inhibition by oral (not IV) aprepitant may require a concurrent dose reduction of 1-2 lapatinib tablets.
4. This list is not all-inclusive; therefore, for herbal supplements not listed, please contact a Novartis Medical Monitor or Clinical Scientist.

NOTE: If future changes are made to the list of prohibited medications, formal documentation will be created and stored with the study file. Any changes will be communicated to the investigative sites in the form of a letter.

APPENDIX VII

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.