RADIATION THERAPY ONCOLOGY GROUP

RTOG 1016

PHASE III TRIAL OF RADIOTHERAPY PLUS CETUXIMAB VERSUS CHEMORADIOTHERAPY IN HPV-ASSOCIATED OROPHARYNX CANCER

Study Chairs

Co-Principal Investigator/Radiation Oncology

Study Chairs (Continued)

Quality of Life Co-Chair

ECOG Co-Chair/Medical Oncology

INDEX (6/9/11)

RTOG Institution #
RTOG 1016
Case #

ELIGIBILITY CHECKLIST – STEP 1 (6/9/11)
(page 1 of 5)

____ (Y) 1. Is there pathologically (histologically or cytologically) proven diagnosis of squamous cell carcinoma

_____(N) 17. Does the patient have Stage T1-2, N0-1 cancer?

_____(N) 18. Does the patient have distant metastasis or adenopathy below the clavicles?

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

_____ 14. Method of Payment

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

_____

RTOG Institution #
RTOG 1016 **ELIGIBILITY CHECKLISt –STEP 1 (6/9/11)**

1.0 INTRODUCTION

1.1 Background

1.1.1 Orophddddddrynx Candddcedddr T: Cudddrrent State of

(Pignon 2009). There is an estimated 6.5% absolute benefit in survival at 5-years with concomitant chemotherapy, and the benefit appears superior for platinum monotherapy when compared to other chemotherapy regimens.

1.1.3 Epidermal Signaling, Head and Neck Cancer. and Radiation Response

EGFR is expressed at very high levels in the majority of human head and neck squamous cell carcinoma (SCC). Furthermore, pre-clinical data indicate that it is not merely a 'bystander' but is intimately associated with the malignant phenoty pe of SCCHN. EGFR activation in response to

Table 1; Summary of Endpoints from the Phase III Trial of Radiation +/- Cetuximab

	Cetuximab + Radiation (n = 211)	Radiation Alone (n = 213)	Hazard Ratio (95% CI[3])	Stratified Log-rank p-value
Locoregional control				
Median Duration	24.4 mo	14.0 mo	0.68 (0.52-0.89)	0.005
Overall Survival				
Median duration	49.0 mo	29.3 mo	0.74 (0.57-0.97)	0.03

a CI = confidence interval

These data lead to FDA approval of the combination of cetuximab and radiation therapy for initial therapy of patients with local-regio

accelerated RT (70 Gy in 6 weeks) plus weekly cetuximab, as used in the Bonner and RTOG 0522 trials, which included 8 doses of cetuximab.

This is a head-to-head comparison of concurrent chemoradiation and + CDDx) versus nd plus a molecular targeting agent acetuximab) that hasbeen approved by the FDA for frontline therapy in loco-regionally advanced head and neck cancer. The prevailing global practice (per NCCN and

related outcomes is vitally important to future decision-making and treatment selection for this patient population.

Protocol-specific Toxicity Assessments are defined as evaluations (critical to the primary trial analysis) performed by the clinical team (doctor, nurse and research associate) and will include clinician-reporting and grading of CTCAE (v. 4)

Assuming the primary endpoint (non-inferior survival) is met and both of these toxicity o(r)(tcome)4.9( )]TJ-
less toxic alternative to concurrent cisplatin, in locally advanced1h ciated carcinoma of h
oropharynx.

1.5.2 Clinician-reported Toxicity Assessment Tools

Toxicity-related tools will be collected and reported by clinical staff at 11 assessments on the standard RTOG schedule: baseline, end of treatment, and at 1, 3, 6, 12, 15, 18, 21, and 24 months from the end of treatment.

Traditional clinician-reported endpoints will be captured by "hard-coding" data capture on case report forms. Collectively, completion of these forms requires < 30 minutes for the patient-clinician-research associate interaction.

- Hard-coded CTCAE events (10-15 minutes);
- Nutrition/feeding tube (5 minutes);
- Dental status (< 5 minutes).

Based on comparative review of these data, detectable reductions are anticipated in 10

Figure from Trotti 2007

RTOG 1016 will utilize accelerated radiation in both arms (70 Gy in 6 weeks, 6 fractions/week, weeks 2-6),and will co

1.5.8.8 *Work Status*
The ability of a patient who is gai

to cisplatin. eRTOGehaseused decisionemodels informedewith actualeclinicaletrial data to perform economiceanalysis ofeclinicaletrials in the past

prior to or after completion of therapy (Meyer 2008). A history of smoking has been associated with reduced response to platinum-based induction chemotherapy (Fountzilas 1997) and also with lower rates of complete response to radiation therapy (Browman 1993).

Epidemiological data indicate that tobacco smoking is not a strong co-factor for HPV-positive head and neck cancer (Gillison 2008; Applebaum 2007). With regard to survival outcomes, the independent effects of tobacco exposure and tumor HPV status on patient survival have been unclear, given the strong inverse correlation between the two. However, there is growing evidence that the biological behavior and treatment response of HPV-positive head and neck cancer may be modified by tobacco exposure. In a single-institution case-series of patients with tonsillar cancer, pat

Our data from RTOG 0129 further underscores the importance of measurement of tobacco

Factor	% HPV-positive with factor

Predictors of response or resistance to cetuximab therapy: Activation of the EGFR signaling pathway is frequently observed in head and neck squamous cell carcinoma, and elevated expression of EGFR is associated with poor su

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1.13 Patients who are HIV positive but have no prior AIDS-defining illness and have CD4 cells of at least 350/mm^3 are eligible. Patient HIV status must be known prior to registration. Patients must

to receive either prophylactic weekly infusion of magnesium and/or oral magnesium supplementation (e.g. magnesium oxide) at the investigator's discretion.

4.1.2 Protocol-specific dental assessment (see Appendices VIII and IX) by a physician or designee (such as a physician's assistant, nurse or nurse practitioner, or a dentist/hygienist) to assess number of teeth and overall dental health within 8 weeks prior to the start of treatment with management according to the guidelines in Appendix V;

4.1.3 Audiogram within 12 weeks prior to start of treatment;

4.1.4 Protocol-specific assessment of swallowing by clinical staff via CTCAE, v. 4 (dysphagia) within 4 weeks prior to the start of treatment;

4.1.5 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 functional assessments prior to the start of protocol treatment: QLQ-C30, QLQH&N35, EQ-5D, PRO-CTCAE-H&N, HHIA-S, and Work Status Questionnaire (baseline);

4.1.6 If the patient consents to complete the entire head and neck risk factor survey via the computer-assisted self interview (CASI), sites are required to provide it prior to start of treatment.

4.2 Highly Recommended Evaluations/Management

International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to

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 t he patient has been successfully

structures may become significant when repeated IGRT procedures are performed for

Contralateral submandibular gland

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.

Overnight hydration should address any dehydration with fluid/electrolyte imbalance. Concurrent Cetuximab and Radiation

7.1.2 Arm 2: Cetuximab with Radiation

7.1.2.1 *Cetuximab*

3. Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
4. Administration must be through a low protein binding 0.22-micrometer in-line filter

	Abdominal pain	***Abdominal pain***
	Cheilitis	***Cheilitis***
	Constipation	

Note: Cetuximab in combination with other agents could cause an exacerbation of any

7.4.6 Mucositis: Significant mucositis from both the radiation and the cisplatin is expected and will not

- Rash Occurring **Inside**

Adverse Event Reporting Requirements. January 2005;
http://ctep.cancer.gov/reporting/adeers.html]

The following guidelines for reporting adverse events (AEs) apply to **all** NCI/RTOG research protocols. 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 Ses a **Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Se.tion 7.X also must be reported via AdEERS.**

NOTE: If the event is a Ses-6.3(rious Adv)11.6(e)-0.3(rse Ev)11.6(ent (SAE) [see nes a7(xt)6(sectio)6.

7.7.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a non-CTEP-IND:

9.2 Non-permitted Supportive Therapy

10.5.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The RTOG Biospecimen Resour

regional biopsy, neck dissection, or salvage surgery. CT or MRI (of head and neck region, with CXR or Chest CT), or PET/CT (including chest anatomy) may.18. neck dissection, or salvage su

CASI iPAD and/or online systems should remain available to patients to assist them if necessary. Versions of the surveys are available on the RTOG web site for submission to site's IRBs.

11.7.1 The EORTC QLQ-C30

The EORTC QLQ-C30, v. 3.0 is a 30-item self-reporting questionnaire grouped into 5 functional subscales (role, physical, cogn

13.0 STATISTICAL CONSIDERATIONS

13.1 Primary Endpoint

analyzed and reported separately. The cohort of HIV+ patients will be assessed in a preliminary observational manner to gain insight into the feasibility of enrolling and treating this

between the 2 treatment arms. Overall acute toxicity burden scores will be compared using two sample t test.

13.6 Statistical Considerations for Translational Research

13.6.1 Sample Size and Power

REFERENCES

Abdel-Wahab M, Abitbol A, Lewin A, et al. Quality-of-life assessment after hyperfractionated radiation therapy and 5-fluorouracil, cisplatin, and paclitaxel (Taxol) in inoperable and/or unresectable head and neck squamous cell carcinoma. *Am J Clin Oncol*. 28: 359-366, 2005.

Adelstein DA, Ridge J. Head and neck squamous cell ca

Meyer M. Human papillomavirus-16 modifes the association between fruit consumption and head and neck squamous cell carcinoma. *Canc Epidem Biomarkers Prevent*. 17fu8): 3419, 2008.

Moir D, Rickert WS, Levasseur G, Larose Y, Maertens R, White P, Desjardins S. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. *Chem Res Toxicol.* 21(2): 494-5022008. [Epub 2007 Dec 7]

Murdoch-Kinch CA, Kim HM, Vineberg KA, et al. Dose-effect relationships for the submandibular salivary

Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. TAX 324 Study Group. *NEJM.* 357(17): 1705-15, 2007b.

Quintela-Fandino M, Hitt R, et al. DNA-repair gene polymorphisms predict favorable clinical outcome among patients with advanced squamous cell carcinoma of the head and neck treated with cisplatin-based induction chemotherapy. *J Clin Oncol.* 24(26): 4333-9, 2006.

Ragin CC, Taioli E. Survival of squamous cellrviof the head and neck in relation to human papillomavirus infection: review and meta-analysis. *Int J CancerT4 1 Tf2[(. 121: 1813)6(18)6(2)*

Yellen SB, Cella DF, Webster K et al. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. *J Pain Symptom Manage*. 13(2): 63-74, 1997.

Zhang ZF, Morgenstern H, Spitz MR, et al. Marijuana use and increased risk of squamous cell carcinoma

APPENDIX I

RTOG 1016

Phase III Trial of Radiotherapy Plus Cetuximab versus Chemoradiotherapy in HPV-Associated Oropharynx Cancer

Informed Consent Template for Cancer Treatment Trials
(English Language)

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discu health ca
If you have any questions, you can ask your study doctor for moexplanation.

You are being asked to take part in this study because you have head and neck cancer that may be posit12 06(v)3.2(s)-6(t)-6(a)-6(g)-6(e)]TJ

For all patients:

- Physical examination by several doctors
- Examination of the back of your throat and voice box (larynx) with a mirror and/or a flexible lighted tube inserted through your mouth by an ear, nose and thr

•

•
•

How long will I be in the study?

Group 1 patients will receive radiation therapy for about 6 weeks and cisplatin on days 1 and 22 during radiation.

Group 2 patients will receive a dose of cetuximab a week before radiation therapy, and if they tolerate cetuximab well, will receive cetuximab once a week during the 6 weeks of radiation therapy and once after radiation therapy, for a total of 8 weeks of treatment.

All patients will be asked to visit the office for follow up at 1 and 3 months from the end of treatment, then every 3 months through year 2, every 6 months for 3 years, then once a year for their lifetimes.

- Acne

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to tak0.0009 Tc0.003study, you may leave the study at any time. No matter what decision you make, there

Your doctor performed a biopsy to make a diagnosis of oropharynx cancer. That tissue will bi 4( )3748nbi, to determine

Making Your Choice

Please read each sentence below and think about your choice

APPENDIX IV

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

HEAD & NECK

STAGING-PRIMARY TUMOR (T)

T	X
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*

LIP and ORAL CAVITY

T	X
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

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 adced 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
T2	Tumor withsparapharyngeal extension*
T3	Tumor involves bony structures
T4	

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

APPENDIX V

MANAGEMENT OF DENTAL PROBLEMS IN IRRADIATED PATIENTS

Dental Care for Irradiated Patients

Goals for a dental care program include:

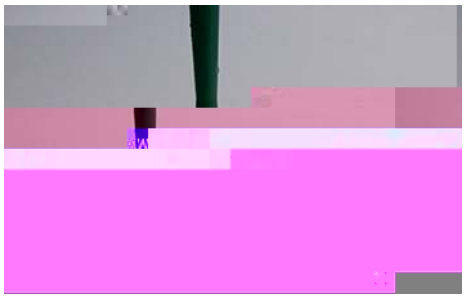
1. To reduce incidence of bone necrosis.
2. To reduce incidence of irradiation caries.
3. To allow proper fitting of dentures following treatment.

Pre-irradiatiopteooand PTEroceduionts

APPENDIX VI

RTOG FFPE SPECIMEN PLUG KIT INSTRUCTIONS

This Kit allows sub-sampling of an FFPE block for s



APPENDIX VII

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents: **For patient enrollments:** **Submit study da**

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and

DATA SUBMISSION AND RECONCILIATION

APPENDIX VIII (6/9/11)

RTOG 1016 DENTAL EFFECTS HEALTH SCALE

0 Normal: Edentulous, with no gingival disease; native teeth in place with gingiva in excellent condition.