

# RADIATION THERAPY ONCOLOGY GROUP

## RTOG 0234

### A PHASE II RANDOMIZED TRIAL OF SURGERY FOLLOWED BY CHEMORADIOTHERAPY PLUS C225 (CETUXIMAB) FOR ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

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**Activation Date: April 20, 2004**

**Update Date: October 15, 2004**

**Version Date: August 27, 2004 (Broadcast 9/20/04)**

**Includes Revision 1**

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**RADIATION THERAPY ONCOLOGY GROUP**

**RTOG 0234**

**A PHASE II RANDOMIZED TRIAL OF SURGERY FOLLOWED BY CHEMORADIOTHERAPY PLUS C225 (CETUXIMAB) FOR ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK**

**SCHEMA (8/27/04)**

<b>P O S T O P  P A T I E N T S</b>	<b>S T R A T I F Y</b>	<p><b>Zubrod Score</b></p> <p>1. 0 2. 1</p> <p><b>Risk Category<sup>b</sup></b></p> <p>1. Positive margins 2. High risk (≥ 2 positive nodes or extranodal capsular spread)</p>	<b>R A N D O M I Z E</b>	<p><b>Arm 1<sup>c</sup></b></p> <p><u>Week 1:</u> Cetuximab (C225) loading dose</p> <p><u>Weeks 2-7:</u> 60 Gy (2 Gy/day) plus weekly cisplatin plus weekly C225</p> <p><b>Arm 2<sup>c</sup></b></p> <p><u>Week 1:</u> Cetuximab (C225) loading dose</p> <p><u>Weeks 2-7:</u> 60 Gy (2 Gy/day) plus weekly docetaxel plus weekly C225</p>
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- a. Gross total resection must be completed within 7 weeks of randomization.
- b. If both risk factors are present, patient will be stratified as “positive margins”.
- c. It is strongly recommended that radiation therapy begin within 8 weeks after surgery; see Sections 6.0 and 7.0 for details.

**Patient Population** (See Section 3 for eligibility)

Pathologic stage III or IV (note that the preoperative clinical stage may be I-IV if nodes are not appreciated) squamous carcinoma of the head and neck (site of tumor origin oral cavity, oropharynx, larynx, or hypopharynx) following gross total resection and requiring postoperative XRT for high-risk features

**Required Sample Size: 230 patients**

Institution # \_\_\_\_\_

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**ELIGIBILITY CHECKLIST (8/27/04)**  
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RTOG Case# \_\_\_\_\_

- \_\_\_\_\_ (III/IV) 1. What is the pathologic tumor stage?
- \_\_\_\_\_ (Y) 2. Has histologically proven squamous cell cancer of the oral cavity, oropharynx, larynx, or hypopharynx (excluding lip, nasopharynx, or sinuses) been confirmed?
- \_\_\_\_\_ (Y) 3. Has a complete gross total resection been done within 7 weeks of randomization?
- \_\_\_\_\_ (Y) 4. Are one of the risk factors listed in Section 3.1.1.1 present?
- \_\_\_\_\_ (N) 5. Any evidence of distant metastasis?
- \_\_\_\_\_ (Y) 6. Were pre-treatment labs done within 4 weeks prior to study entry?
- \_\_\_\_\_ (Y) 7. Are the pre-treatment lab values within ranges specified in Section 3.1.4?
- \_\_\_\_\_ (Y) 8. Were pre-treatment radiographic studies done within 90 days prior to study entry?
- \_\_\_\_\_ (N) 9. Any symptomatic coronary artery disease (angina) or myocardial infarction within the last 6 months or  $\geq 3$  heart-related hospitalizations in the past year?
- \_\_\_\_\_ (N) 10. Any history of prior chemotherapy in the last three years?
- \_\_\_\_\_ (N) 11. Any prior anti-epidermal growth-factor receptor antibody therapy or therapy with a tyrosine-kinase inhibitor?
- \_\_\_\_\_ (N) 12. Any prior radiation to the head or neck area?
- \_\_\_\_\_ (N) 13. Was the patient hospitalized three or more times for COPD complications?
- \_\_\_\_\_ (N/NA) 14. If female, is patient pregnant or lactating?
- \_\_\_\_\_ (Y) 15. Is the patient willing to use effective contraception while on treatment and for at least 3 months after end of treatment?
- \_\_\_\_\_ (N) 16. Does the patient have  $\geq$  Grade 2 peripheral neuropathy?
- \_\_\_\_\_ (N) 17. Any uncontrolled seizure disorder, or active neurological disease?
- \_\_\_\_\_ (Y) 18. At least 18 years of age?
- \_\_\_\_\_ (N) 19. Any history of severe hypersensitivity reaction to docetaxel or other drugs formulated with polysorbate 80?
- \_\_\_\_\_ (N) 20. Did the patient require staged surgery?
- \_\_\_\_\_ (Y/N) 21. Is there any history of prior invasive malignancy?
- \_\_\_\_\_ (Y) 22. If yes, is it within parameters of Section 3.2.11?

**(Continued on next page)**

Institution # \_\_\_\_\_

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**ELIGIBILITY CHECKLIST (4/20/04)**  
**(Page 2 of 3)**

RTOG Case# \_\_\_\_\_

\_\_\_\_\_ (N) 23. Any synchronous or concurrent head and neck primary tumors?

\_\_\_\_\_ (Y) 24. Has the patient signed a study-specific consent form?

**The following questions will be asked at study registration:**

- \_\_\_\_\_ 1. Name of institutional person registering this case?
- \_\_\_\_\_ (Y) 2. Has the Eligibility Checklist (above) been completed?
- \_\_\_\_\_ (Y) 3. Is the patient eligible for this study?
- \_\_\_\_\_ 4. Date the study-specific Consent Form was signed? (must be prior to study entry)
- \_\_\_\_\_ 5. Patient's Initials (First Middle Last) [May 2003. If no middle initial, use hyphen]
- \_\_\_\_\_ 6. Verifying Physician
- \_\_\_\_\_ 7. Patient's ID number
- \_\_\_\_\_ 8. Date of Birth
- \_\_\_\_\_ 9. Race
- \_\_\_\_\_ 10. Ethnic Category (Hispanic or Latino, Not Hispanic or Latino)
- \_\_\_\_\_ 11. Gender
- \_\_\_\_\_ 12. Patient's Country of Residence
- \_\_\_\_\_ 13. Zip Code
- \_\_\_\_\_ 14. Patient's Insurance Status
- \_\_\_\_\_ 15. Will any component of the patient's care be given at a military or VA facility?
- \_\_\_\_\_ 16. Tissue/blood used for research in current study?
- \_\_\_\_\_ 17. Tissue/blood kept for cancer research?
- \_\_\_\_\_ 18. Tissue/blood kept for medical research?
- \_\_\_\_\_ 19. Allow contact for future research

**(Continued on next page)**

Institution # \_\_\_\_\_

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**ELIGIBILITY CHECKLIST (8/27/04, 10/15/04)**  
(Page 3 of 3)

RTOG Case# \_\_\_\_\_

\_\_\_\_\_

20. Medical Oncologist

\_\_\_\_\_

21. Specify Zubrod Performance Status (0 vs. 1)

\_\_\_\_\_

22. Specify Risk Category (Positive margins vs. High risk [ $\geq$  2 positive nodes or extranodal capsular spread])

\_\_\_\_\_

24. Treatment Assignment

\_\_\_\_\_

25. Treatment Start Date

\_\_\_\_\_

26. For ACOSOG Investigators only: Name of the radiation treatment facility (RTF) at which the patient will receive treatment and the RTF number of that facility.

\_\_\_\_\_ RTF number

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

Completed by \_\_\_\_\_

Date \_\_\_\_\_

## **1.0 INTRODUCTION**

### **1.1 Background**

There are approximately 43,000 cases of head and neck squamous cell carcinoma diagnosed annually in the United States. Approximately two thirds of these patients present with advanced disease (Stage III or IV).<sup>1,2</sup> Successful nonoperative treatment strategies have advanced considerably over recent years through the refinement of intensified radiation fractionation schedules and/or the use of combination chemoradiation approaches.<sup>3-6</sup> Nonetheless, for many patients with advanced but resectable squamous cell carcinoma of the head and neck, surgical resection followed by postoperative radiation therapy remains a common treatment approach.<sup>7-11</sup> Despite aggressive surgery and adjuvant radiation, many patients still succumb to locoregional disease recurrence. Distant metastases (most commonly to the lungs) can also occur in advanced head and neck cancer patients, and the frequency of this event is increased in patients who suffer locoregional disease recurrence following definitive therapy.

Published reports suggest that approximately one quarter to one third of advanced head and neck cancer patients treated with surgery and postoperative radiation therapy experience locoregional disease recurrence. Efforts to diminish these recurrence rates have focused primarily on combined chemoradiation in the postoperative setting. Two recent Phase III cooperative group studies have addressed this precise question. Both studies (RTOG 95-01<sup>12</sup> and EORTC 22931) randomized postoperative head and neck cancer patients to radiation alone or radiation in combination with cisplatin chemotherapy.<sup>13, 14</sup> Paradoxically, preliminary reports from these two randomized trials provided contrasting results. The EORTC trial enrolled 334 patients and identified a clear benefit in locoregional disease control and survival for those patients receiving cisplatin chemotherapy concurrent with radiation, whereas the RTOG trial enrolled 459 patients and identified no survival advantage with the addition of cisplatin. However, as follow up for the RTOG trial has matured, an enhancement in locoregional disease control and disease free survival is emerging for the cisplatin arm. Both trials confirmed greater acute and overall toxicity with the addition of cisplatin chemotherapy. Therefore, it remains somewhat unclear whether the addition of cisplatin chemotherapy to postoperative radiotherapy for advanced head and neck cancer patients is routinely warranted. Further data maturation for both trials is ongoing.

This protocol is therefore designed to examine the addition of a promising new class of molecular growth inhibitor (C225: cetuximab) delivered in conjunction with adjuvant chemoradiation therapy for advanced head and neck cancer patients. In this Phase II setting, C225 will be combined with radiation in conjunction with either cisplatin or docetaxel at relatively low weekly doses in an effort to enhance locoregional disease control.

### **1.2 EGFR Signal Inhibition**

The epidermal growth factor receptor (EGFR) represents a particularly promising molecular target for modulation regarding the growth and spread of squamous cell carcinomas of the head and neck.<sup>15-17</sup> In fact, among human solid tumors, the highest frequency of EGFR overexpression is found in squamous cell carcinomas of the head and neck.<sup>18</sup> The knowledge that some 85%-100% of head and neck squamous cell carcinomas robustly express EGFR has justified the rationale for not performing a priori testing of EGFR expression for patient selection in head and neck cancer trials which incorporate the use of EGFR inhibitors. A series of high precision molecular agents have been designed to target the EGFR for growth inhibition in recent years.<sup>19,20</sup> C225 is a monoclonal antibody directed against the extracellular domain of the EGFR and represents a lead investigational agent in this arena.<sup>21</sup> Preclinical studies show that EGFR inhibition with C225 has the capacity to augment the effectiveness of radiation as well as that of a variety of cytotoxic chemotherapy agents.<sup>22-28</sup> These combinations may therefore facilitate therapeutic gains for the advanced head and neck cancer patient.<sup>29, 30</sup>

There is an established experience for the use of C225 in advanced head and neck cancer patients both in the definitive and in the metastatic/recurrent treatment setting. In a Phase III trial, 424 locoregionally advanced head and neck cancer patients were treated with high-dose radiation with or without weekly infusions of C225.<sup>31</sup> Results from this recently completed trial will likely become available in 2004. In another Phase III trial, metastatic or recurrent head and neck cancer patients were treated with cisplatin plus C225 or cisplatin plus placebo.<sup>32</sup> Results from this trial identified a higher response rate for patients receiving C225, although no overall survival advantage was identified. These randomized Phase III studies have provided considerable

information regarding the toxicity profile of C225 in head and neck cancer patients, delivered either concurrently with radiation or concurrently with cisplatin chemotherapy. In general, the toxicity profile for C225 has been considerably less than that observed with conventional cytotoxic chemotherapeutic agents. The most frequent adverse event is the development of skin rash (folliculitis, acne-like reaction), which occurs in approximately two thirds of patients treated with C225 (similar to other EGFR inhibitory agents). The spectrum of adverse events for C225 is more fully delineated in Section 7.2. To date, there is no clear evidence that C225 significantly augments the toxicity profile for radiation or cisplatin chemotherapy in head and neck cancer patients. Nevertheless, caution with regard to multimodality therapy remains warranted as suggested by a recently published abstract.<sup>33</sup> This study combined high dose radiation and high dose cisplatin chemotherapy with weekly C225 in 22 advanced head and neck cancer patients. Despite very impressive two-year survival rates, there were 2 deaths on treatment (one pneumonia and one unknown cause) prompting early study closure. Although this study employed a 17% higher radiation doses given with a more aggressive fractionation schedule, and several-fold higher doses of cisplatin chemotherapy than in the current postoperative trial, careful monitoring of toxicity profiles with combination studies remains important.

### **1.3 Cisplatin**

More clinical experience exists for the use of cisplatin chemotherapy in head and neck cancer patients than for any other single cytotoxic agent.<sup>34-37</sup> Cisplatin has been studied in head and neck patients in the neoadjuvant setting, the concurrent setting with radiation, and in the adjuvant setting following completion of surgery or radiation. Several dose/delivery schedules of administration have been used for cisplatin in head and neck cancer patients. The most common of these include 100 mg/m<sup>2</sup> delivered every three weeks, 30-40 mg/m<sup>2</sup> delivered weekly and 5-8 mg/m<sup>2</sup> delivered daily, all as IV doses. Cisplatin is a known radiosensitizer and for the current protocol, cisplatin will be delivered weekly at a dose of 30 mg/m<sup>2</sup> to optimize radiosensitization potential during a six-week course of adjuvant radiation. This low dose weekly cisplatin schedule is considerably less toxic than the 100mg/m<sup>2</sup> schedule. This delivery schedule will also best match the weekly administration of C225 and/or docetaxel.

### **1.4 Docetaxel**

Docetaxel as a single agent has established activity in patients with squamous cell carcinoma of the head and neck.<sup>38-40</sup> Studies have also been carried out combining docetaxel with cisplatin and with radiation in both head and neck as well as lung cancer populations. Preclinical data suggests that docetaxel serves as a potent radiosensitizer, which has prompted Phase I and Phase II studies combining docetaxel with radiation and cisplatin in head and neck cancer patients. A Phase I study recently completed evaluated docetaxel, cisplatin, and high dose radiation in locally advanced head and neck cancer patients and confirmed activity and feasibility of this regimen.<sup>41</sup> Doses between 15 and 40 mg/m<sup>2</sup> of docetaxel were used in conjunction with doses of cisplatin ranging from 20 to 60 mg/m<sup>2</sup> weekly. For the current study, the docetaxel dose will be maintained at 15 mg/m<sup>2</sup> in light of the triple combination of radiation, C225 and docetaxel following major head and neck surgery.

## **1.5 Summary of Results of Investigational Program**

### **1.5.1 *Clinically Relevant Adverse Events Related to Cetuximab (C225) (8/27/04)***

Safety data is available for 1473 patients enrolled in 26 trials who have received C225 alone or in combination with chemotherapy or radiotherapy. The most common composite groupings of adverse events deemed related to C225 as reported by investigators in all C225 trials (N = 1473) include skin reaction (73%), acne-like rash (69%), fatigue/malaise (30%), nausea/vomiting (24%), fever/chills (23%), mucositis/stomatitis (15%), diarrhea (14%), and hypersensitivity reaction (5%).

The development of acute interstitial pneumonitis in patients treated with EGFR-targeted agents has recently been described (Investigator's Brochure; see Section 7.2.1 to obtain a copy).

A detailed list of Serious Adverse Events (SAE) is presented in the Investigator Brochure. Noteworthy are SAEs leading to death; one from allergic reaction/hypersensitivity, and one from interstitial pneumonitis as described in Section 10.3 of the Investigator Brochure.

The incidence of the most significant or common adverse events occurring in all C225 trials and by relationship to C225, are presented in the following table:

**Adverse Events in All Cetuximab (C225) Trials\*  
(n = 1473, as of November 30, 2002)**

	All Adverse Events				Related Adverse Events**			
	Grades 1 – 4		Grades 3 & 4		Grades 1 - 4		Grades 3 & 4	
	N	(%)	N	(%)	N	(%)	N	(%)
Asthenia	821	(56)	160	(11)	435	(30)	59	(4)
Nausea	651	(44)	56	(4)	301	(20)	24	(2)
Rash	643	(44)	96	(7)	493	(34)	64	(4)
Acne	617	(42)	100	(7)	603	(41)	100	(7)
Diarrhea	509	(35)	92	(6)	210	(14)	33	(2)
Vomiting	481	(33)	67	(5)	206	(14)	21	(1)
Fever	451	(31)	16	(1)	262	(18)	2	(< 1)
Anorexia	414	(28)	42	(3)	147	(10)	13	(1)
Weight Loss	382	(26)	31	(2)	87	(6)	3	(< 1)
Dry Skin	321	(22)	13	(1)	285	(19)	12	(1)
Dyspnea	282	(19)	74	(5)	67	(5)	11	(1)
Mucous Membrane Disorder	269	(18)	109	(7)	96	(7)	28	(2)
Headache	245	(17)	15	(1)	128	(9)	9	(1)
Stomatitis	242	(16)	23	(2)	116	(8)	9	(1)
Chills	165	(11)	1	(< 1)	116	(8)	0	(0)
Pruritus	136	(9)	6	(< 1)	111	(8)	3	(< 1)
Nail Disorder	123	(8)	5	(< 1)	97	(7)	5	(< 1)
Allergic Reaction	80	(5)	24	(2)	57	(4)	20	(1)
Anaphylactoid Reaction	14	(1)	13	(1)	14	(1)	13	(1)

\* Data from 1473 patients enrolled in 26 trials receiving C225 alone or in combination with chemotherapy and radiation. All adverse events reported by investigator and by relationship to C225.

\*\* Possible, probable, or definite relationship to C225 as reported by investigator.

The incidence of the most significant or common adverse events occurring in single-agent C225 trials and by relationship to C225, are presented in the following table:

**Adverse Events in Single-Agent Cetuximab (C225) Trials\*  
(n = 281, as of November 30, 2002)**

	All Adverse Events				Related Adverse Events**			
	Grades 1 – 4		Grades 3 & 4		Grades 1 - 4		Grades 3 & 4	
	N	(%)	N	(%)	N	(%)	N	(%)
Asthenia	127	(45)	21	(7)	71	(25)	8	(3)
Nausea	76	(27)	3	(1)	38	(14)	0	(0)
Rash	87	(31)	8	(3)	86	(31)	6	(2)
Acne	104	(37)	20	(7)	104	(37)	20	(7)
Diarrhea	53	(19)	3	(1)	26	(9)	3	(1)
Vomiting	66	(24)	9	(3)	26	(9)	2	(1)
Fever	99	(35)	2	(1)	75	(27)	0	(0)
Anorexia	53	(19)	8	(3)	13	(5)	1	(< 1)
Weight Loss	24	(9)	0	(0)	3	(1)	0	(0)
Dry Skin	35	(13)	2	(1)	33	(12)	2	(1)
Dyspnea	51	(18)	20	(7)	11	(4)	3	(1)
Mucous Membrane Disorder	17	(6)	3	(1)	9	(3)	1	(< 1)
Headache	64	(23)	3	(1)	40	(14)	2	(1)
Stomatitis	26	(9)	7	(3)	13	(5)	0	(0)
Chills	13	(5)	2	(1)	0	(0)	0	(0)
Pruritus	25	(9)	2	(1)	21	(8)	1	(< 1)
Nail Disorder	21	(8)	0	(0)	18	(6)	0	(0)
Allergic Reaction	24	(9)	8	(3)	18	(6)	8	(3)
Anaphylactoid Reaction	4	(1)	4	(1)	4	(1)	4	(1)

\* Data from 281 patients enrolled in 12 trials receiving single-agent C225. All adverse events reported by investigator and by relationship to C225.

\*\* Possible, probable, or definite relationship to C225 as reported by investigator

### 1.5.2 Acne-Like Rash

The most common adverse event associated with C225 administration is acne-like rash. Acne-like rash usually occurs on the face, upper chest, and back, but occasionally extends to the extremities and is characterized by multiple follicular- or pustular-appearing lesions characterized histologically as lymphocytic perifolliculitis or suppurative superficial folliculitis in subjects with metastatic carcinoma. The onset of the rash is generally within the first 3 weeks of therapy. In subjects who received C225 at doses less than 100 mg/m<sup>2</sup>, acne-like rash was reported infrequently and was restricted to Grades 1 or 2. A number of therapeutic interventions have been attempted, including oral and topical antibiotics, topical steroids, and rarely, oral steroids. The value of these measures is unknown since definitive clinical trials have not been performed. The etiology of the acne-like skin rash is believed to be the result of C225 binding to EGFR in the epidermis.

### 1.5.3 Nail Disorder

An uncommon adverse event reported is a nail disorder characterized as paronychia inflammation with associated swelling of the lateral nail folds of the toes and fingers. The most commonly affected digits are the great toes and thumbs. According to Investigators, the nail disorder may persist for up to 3 months after discontinuation of C225. Preliminary analysis in subjects treated at the doses to be administered in this trial (400 mg/m<sup>2</sup> initial dose, followed by 250 mg/m<sup>2</sup> weekly) revealed that incidence of nail disorder is greater in subjects who received > 6 C225 infusions (~10%) compared with subjects treated with ≤ 6 infusions (~3%).

### 1.5.4 Allergic Reactions

As C225 is a protein, the potential exists for allergic reaction to occur during or following C225 administration. In clinical trials, severe hypersensitivity reactions (including allergic and anaphylactic reactions), characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension, have been observed in approximately 3% of patients treated with C225. The large majority of these severe reactions occurred with the first infusion of C225 and were observed during or within one hour of the completion of dosing.

The approach to start giving a test dose was empirical, with the supposition that an allergic reaction was likely to be less severe with a test (small) amount of drug than with a full (large) amount of drug (the infusion rate of the test dose being only half that of the regular infusions). However, this has not proved to be the case.

The overall incidence of any Grade of hypersensitivity reaction or severe hypersensitivity reaction was similar in trials with or without a test dose. Counting test dose and loading dose as the 'first exposure' to C225, about 80% of all hypersensitivity reactions, including nearly 80% of severe hypersensitivity reactions, occurred upon 'first exposure' to C225. In addition, a negative test dose did not appear to be predictive of a lack of hypersensitivity reactions during the initial dose or in subsequent infusions. Approximately 15% of the patients experienced delayed severe hypersensitivity reactions during subsequent treatment (i.e., during infusions 2 - 7), irrespective of whether or not a test dose was administered. Further, there was no impact on the outcome of hypersensitivity reactions upon comparison of studies with or without a test dose. All patients completely recovered with adequate counteractive treatment.

In conclusion, based on previous clinical trials involving C225, the requirement for the administration of a test dose will be discontinued. There does not appear to be any advantage in administering a test dose with regard to identifying patients who would develop an allergic reaction. In addition, there does not appear to be any correlation between the severity or outcome of allergic reactions that occurred with a test dose versus those associated with a loading dose or full dose. However, caution must be exercised with every C225 infusion, as there are patients who experience their first severe hypersensitivity reaction during later infusions.

## 1.6 Rationale for this Proposed Phase II Trial

Locoregional disease recurrence following surgical resection and adjuvant radiation represents a dominant failure pattern for advanced head and neck cancer patients. Large scale randomized cooperative group studies have recently been completed examining the potential benefit of adding cisplatin chemotherapy during adjuvant radiation in the postoperative setting. These two randomized trials suggest that the addition of cisplatin to radiation in the postoperative setting for

high risk may improve overall outcome. However, both studies confirm significant enhancement of acute and overall toxicity from the addition of cisplatin. The current study is designed to incorporate one of the new molecular EGFR signaling inhibitors (C225) into the postoperative head and neck cancer treatment paradigm in an effort to improve outcome. The known radiosensitizing effects of cisplatin and docetaxel will also be examined in conjunction with C225 in this 2-arm Phase II study. Gaining experience regarding the feasibility, toxicity profile, and outcome for patients treated in this Phase II trial will provide a logical platform to consider future Phase III comparisons of one of these approaches against standard postoperative therapy with radiation plus cisplatin.

### **1.7 Molecular Biomarker Studies**

There is accumulating evidence that increased expression of EGFR correlates with poor clinical outcome in advanced head and neck cancer patients. Building upon recent RTOG biomarker studies from head and neck trial 90-03, quantitative evaluation of EGFR by immunohistochemistry emerged as the most promising marker for clinical outcome correlation. With the support of multivariate analysis, it was concluded that EGFR expression was a strong independent prognostic determinant for overall and disease-free survival and a strong predictor for locoregional relapse but not for distant metastasis.<sup>42</sup>

The current study will allow further opportunity to investigate the relationship between EGFR expression and clinical outcome in a surgically treated cohort of advanced head and neck cancer patients. In light of the larger tumor specimens that will be available from this surgical trial, evaluation of not only total EGFR expression, but also that of phosphorylated EGFR, phosphorylated MAPK, phosphorylated AKT and Stat-3 will be examined with respect to ultimate treatment outcome. These phosphorylated or “activated” forms of EGFR downstream signaling molecules may provide a more accurate reflection of the “activity state” of EGFR signaling status than simple measurement of total EGFR. In addition, Ki-67 will be examined as a proliferative marker that correlates well with tumor growth status. Further, to advance preliminary data from recent head and neck RTOG trials, this study will explore any correlation between COX-2 and Cyclin B1 expression with ultimate treatment outcome in advanced head and neck cancer patients treated with up front surgery. A preliminary study in patients with high-risk surgical-pathologic features receiving postoperative radiation revealed that cyclin B1 expression represents a strong prognostic factor. A subsequent study with specimens from patients enrolled into RTOG 90-03 demonstrated that COX-2 expression predicts for locoregional disease control, albeit to a lesser magnitude than EGFR. These preliminary data results will be further investigated with analysis of tissue specimens from the current study.

Finally, the fact that all patients will receive C225 (cetuximab) in the postoperative setting in the current trial will afford additional opportunities for correlative biomarker study. Specifically, it is hypothesized that patients with high EGFR tumor expression may be most likely to respond to EGFR inhibitory therapies such as C225 when combined with radiation or chemotherapy. This hypothesis will be further explored in the current study as a prelude to potential further examination in a subsequent Phase III study setting.

## **2.0 OBJECTIVES**

### **2.1 Primary Objective**

**2.1.1** To evaluate, using a random assignment phase II design, two treatment regimens that utilize the EGFR inhibitor C225 in combination with chemoradiation in high-risk postoperative head and neck patients. This trial is designed to determine if either regimen is promising enough to be pursued in a subsequent phase III study. This decision will be primarily based on whether there is improvement in disease-free survival relative to the RTOG database of similar patients treated with chemoradiation in the completed intergroup trial RTOG 9501.

### **2.2 Secondary Objectives**

**2.2.1** To determine whether each of the treatment regimens can be delivered safely and successfully following surgical resection for advanced head and neck cancer;

**2.2.2** To estimate the locoregional control and overall survival rates for patients treated with the each regimen;

**2.2.3** To examine the correlation between EGFR (total and phosphorylated), pMAPK, pAKT, Stat-3, Ki-67, COX-2, and cyclin B1 expression with the ultimate treatment outcome.

**3.0 PATIENT SELECTION**

**3.1 Eligibility (8/27/04)**

**3.1.1** AJCC pathological stage III or IV (note that the preoperative clinical stage may be I-IV) squamous cell carcinoma of the head and neck meeting the following criteria:

**3.1.1.1** Gross total resection must be completed within 7 weeks of randomization, with pathology demonstrating one or more of the following risk factors:

- Histologic extracapsular nodal extension;
- Histologic involvement of ≥ 2 regional lymph nodes;
- Mucosal margin of resection with invasive cancer (limited to microscopic detection only).

**3.1.2** Site of tumor origin in the oral cavity, oropharynx, larynx, or hypopharynx (excluding lip, nasopharynx, or sinuses);

**3.1.3** Zubrod performance status of 0-1;

**3.1.4** Pre-treatment evaluations required for eligibility include:

- History and physical examination within four weeks prior to study entry
- Dental evaluation with management according to the guidelines in Appendix IV prior to start of radiation
- Medical oncology examination to evaluate medical contraindications prior to start of chemotherapy
- Surgical evaluation and clearance prior to start of RT

Laboratory studies within four weeks prior to study entry: CBC with differential and platelet counts; serum chemistry tests to include sodium, potassium, glucose, calcium, magnesium, BUN, serum creatinine, total protein, albumin, alkaline phosphatase, total bilirubin, AST and ALT

- Serum pregnancy test, if applicable, within one week prior to study entry; urine dipstick test on the first day of treatment

Radiographic Studies:

- Pre-operative CT or MRI of the primary tumor and neck for clinical staging is required
- Chest x-ray or thoracic CT scan within 90 days prior to study entry

**3.1.5** ANC ≥ 2,000/mm<sup>3</sup>; platelets ≥ 100,000/mm<sup>3</sup>; hemoglobin > 8.0 g/dl; bilirubin ≤ 1.5 X the ULN; serum creatinine ≤ 1.5 mg/dl; AST **and** ALT **and** alkaline phosphatase must be within the range allowing for eligibility, as in the following table:

<b>AST or ALT:</b>				
<b>ALK PHOS:</b>	<b>≤ ULN</b>	<b>&gt;1x but ≤ 1.5x ULN</b>	<b>&gt;1.5x but ≤5x ULN</b>	<b>&gt;5x ULN</b>
<b>≤ ULN</b>	Eligible	Eligible	Eligible	Ineligible
<b>&gt;1x but ≤ 2.5x</b>	Eligible	Eligible	Ineligible	Ineligible
<b>&gt;2.5x but ≤ 5x</b>	Eligible	Ineligible	Ineligible	Ineligible
<b>&gt;5x ULN</b>	Ineligible	Ineligible	Ineligible	Ineligible

**3.1.6** Patients must be ≥ 18 years of age;

**3.1.7** Women of childbearing potential (WOCBP) and male participants must be willing to consent to using effective contraception while on treatment and for at least 3 months thereafter;

**3.1.8** Pregnant or lactating women are ineligible as treatment involves unforeseeable risks to the participant and to the embryo or fetus. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [hCG], or in accordance with local regulations, whichever is more sensitive);

**3.1.9** Patients must sign a study-specific informed consent form prior to registration.

**3.2 Conditions for Patient Ineligibility**

**3.2.1** Histology positive for other than squamous cell carcinoma or lymphoepithelioma;

**3.2.2** Evidence of distant metastases;

**3.2.3** Less than gross total resection or patients requiring staged surgery;

**3.2.4** Prior head and neck radiotherapy;

**3.2.5** Prior cytotoxic chemotherapy, unless disease free > 3 years;

**3.2.6** Active cardiac disease defined as unstable angina, uncontrolled hypertension, myocardial infarction in the last six months (unless successfully treated with CABG or PTCA), uncontrolled arrhythmia, or congestive heart failure; ≥ 3 heart-related hospitalizations in the past year;

**3.2.7** Severe COPD requiring ≥ 3 hospitalizations over the past year;

- 3.2.8 Women of childbearing potential (WOCBP) and male participants who are unwilling or unable to use an acceptable method to avoid pregnancy for the entire study period and for up to 3 months after the study;
- 3.2.9 Pre-existing  $\geq$  Grade 2 peripheral neuropathy;
- 3.2.10 Uncontrolled seizure disorder or active neurological disease;
- 3.2.11 Prior invasive malignancy (excluding non-melanoma skin cancer) within the previous 3 years;
- 3.2.12 Prior anti-epidermal growth factor receptor antibody therapy or therapy with a tyrosine kinase inhibitor;
- 3.2.13 Patients with a history of severe hypersensitivity reaction to docetaxel or other drugs formulated with polysorbate 80 must be excluded;
- 3.2.14 Presence of synchronous or concurrent head and neck primary tumors.
- 3.3 **(8/27/04) ACOSOG Investigators:** All questions regarding eligibility should be directed to the RTOG Coordinating Center at (215) 574-3189.

#### **4.0 RECOMMENDED PRETREATMENT EVALUATIONS**

(In addition to required evaluation in Section 3.0)

- 4.1 Prophylactic placement of a gastrostomy (PEG) tube is recommended only as per physician discretion.

#### **5.0 REGISTRATION PROCEDURES**

##### **5.1 Preregistration Requirements (8/27/04)**

- 5.1.1 **U.S. sites** must mail or send overnight the completed, signed, **original** study-specific FDA 1572 form to the CTSU Regulatory Office, Coalition of National Cancer Cooperative Groups, 1818 Market Street, Suite 1100, Philadelphia, PA 19103.

**U.S. sites** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206) prior to registration of the institution's first case:

- IRB approval letter;
- IRB approved consent form;
- IRB assurance number;
- CV for the PI and all sub PIs;
- Lab accreditation certificate and institutional normals.

Financial disclosure forms are not required.

- 5.1.2 **(8/27/04) Canadian sites** must mail or send overnight the completed, signed, **original** study-specific FDA 1572 form to RTOG Headquarters, 1818 Market Street, Suite 1600, Philadelphia, PA , 19103.

**Canadian sites** must fax copies of the documentation below to RTOG Headquarters (215-574-0300) prior to registration of the institution's first case:

- IRB approval letter;
- IRB approved consent form;
- IRB assurance number;
- CV for the PI and all sub PIs;
- Health Canada's TPD Forms
- Lab accreditation certificate and normals.

Financial disclosure forms are not required.

- 5.1.3 **For the initial shipment of Cetuximab:**

**U.S. and Canadian institutions** must email the shipment form for this study (available at: <http://www.rtog.org/members/protocols/0234/0234shipmentform.doc>) to [RTOG\\_BMS@phila.acr.org](mailto:RTOG_BMS@phila.acr.org) as soon as the individual responsible for the study agent has been identified and prior to registration of the institution's first case. (Fax 215-574-0300 if unable to email). Allow adequate processing time (7-10 days) before calling to randomize your first patient. See Appendix V for the procedure for resupply requests.

##### **5.2 Registration**

##### **5.2.1 Online Registration (8/27/04)**

Patients can be registered only after eligibility criteria are met (and BMS approval and the SASF have been received and entered into the RTOG database).

Institutions 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 must have completed Human Subjects Training and been issued a certificate (Training is available via <http://69.5.4.33/c01>).
- The institution must complete the Password Authorization Form at [www.rtog.org/members/webreg.html](http://www.rtog.org/members/webreg.html) (bottom right corner of the screen), 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 ([www.rtog.org](http://www.rtog.org)), going to "Data Center Login" 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.

In the event that the RTOG Web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, as discussed in Section 5.2.2.

### 5.2.2 Dial-in Registration

Patients can be registered only after eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG Headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient's study file and will be evaluated during an institutional NCI/RTOG audit.

### 5.3 Pre-Registration Requirements for ACOSOG Investigators (8/27/04)

#### 5.3.1 **U.S. Investigators** must mail or send overnight the completed, signed, **original**, study-specific FDA 1572 form to Coalition of National Cancer Cooperative Groups, 1818 Market Street, Suite 1100, Philadelphia, PA 19103.

U.S. Investigators must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206) prior to registration of the institution's first case:

- IRB approval letter;
- IRB approved consent form;
- IRB assurance number;
- CV for the PI and all sub PIs;
- Lab accreditation certificate and institutional normals.

Financial disclosure forms are not required.

CTSU requires 24-72 hours to process and enter the regulatory documentation into the CTSU database. Then the regulatory documentation is forwarded to BMS for final approval; this process can require an additional 24 hours. BMS will notify RTOG via email of final approval of the regulatory documents received from CTSU. When notified, RTOG will note receipt of BMS approval in the RTOG Database.

**5.3.2** Simultaneously with the submission of regulatory documentation to CTSU, ACOSOG (U.S.) Investigators must email the study agent shipment form (SASF) for the initial shipment of Cetuximab (available at <http://www.rtog.org/members/protocols/0234/0234shipmentform.doc>) to [RTOG\\_BMS@phila.acr.org](mailto:RTOG_BMS@phila.acr.org). The SASF should be emailed as soon as the individual responsible for the study agent has been identified and prior to registration of the institution's first case. (Fax 215-547-0300 if unable to email). The SASF will be reviewed for completeness, processed, and entered as received in the RTOG database. Registration will not be possible unless both BMS approval and the SASF have been received and entered into the RTOG database. See Appendix V for the procedure for resupply requests.

**5.3.3** ACOSOG Investigators must provide the name of the radiation treatment facility (RTF) at which the patient will receive treatment and the RTF number of that facility at the time the patient is registered (Question 26, page 3 of the Eligibility Checklist). The radiation treatment facility must be monitored by the Radiological Physics Center (RPC) <http://rpc.mdanderson.org/rpc/> (See Section 6.1.6).

#### **5.4** Registration

##### **5.4.1** Online Registration

Patients can be registered only after eligibility criteria are met (and BMS approval and the SASF have been received and entered into the RTOG database).

ACOSOG physician groups 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 must have completed Human Subjects Training and been issued a certificate (Training is available via <http://69.5.4.33/c01>).
- The institution must complete the Password Authorization Form at [www.rtog.org/members/webreg.html](http://www.rtog.org/members/webreg.html) (bottom right corner of the screen), and fax it to 215-923-1737. RTOG Headquarters requires 3-4 days to process requests and issue user names/passwords to sites.

The ACOSOG physician group will register the patient by logging onto the RTOG web site (<http://www.rtog.org/>), going to "Data Center Login" 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 and to ACOSOG: 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.

In the event that the RTOG web registration site is not accessible, investigators can register a patient by calling RTOG Headquarters, (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET.

## **6.0** RADIATION THERAPY **Note: Intensity Modulated Radiation Therapy (IMRT) is not allowed.**

### **6.1** Radiation Dose (8/27/04)

**6.1.1** Patients will be randomized post-operatively, and it is strongly recommended that radiation therapy begin within 8 weeks after surgery. If there are wound complications after surgery, e.g., a major active fistula or wound dehiscence, and radiation therapy will be delayed, contact the Principal Investigator/Radiation Oncology Study Chair, Dr. Harari.

Once daily (2 Gy/d) radiation therapy is given to a total minimum dose of 58 Gy and maximum dose of 66Gy to involved areas, over 5.5-6.5 weeks. If the first scheduled radiation day falls on a Thursday, Friday, weekend, or holiday, then RT should be deferred to the next business day (unless the patient is treated over the weekend/holiday) so that the patient receives at least three consecutive early RT fractions before a two-day non-work day interruption.

**6.1.2** Spinal Cord

The dose to any point within the spinal cord should not exceed 48 Gy. Spinal cord dose must be clearly documented. Spinal cord blocks should be inserted into all fields at a dose of 40 -44 Gy to achieve this goal.

**6.1.3** Primary Tumor Bed

Final dose (using shrinking field technique): Minimum 58 Gy to resected regions. Boost to 62-66 Gy for high-risk factors (see Section 3.1.1.1).

**6.1.4** Neck Lymph Nodal Bed

Final dose (using shrinking field technique): Minimum 58 Gy to resected regions. Boost to 62-66 Gy for high-risk factors (Section 3.1.1.1).

**6.1.5** Contralateral and other non-dissected lymph node regions (Levels 2-5 [plus level 1 for oral cavity cancers], and for pharyngeal cancers, the retropharyngeal lymph node region): 50 Gy minimum dose.

**6.1.6** **(8/27/04) ACOSOG Investigators:** ACOSOG Investigators must provide the name of the radiation treatment facility (RTF) at which the patient will receive treatment and the RTF number of that facility at the time the patient is registered (Question 26, page 3 of the Eligibility Checklist). The radiation treatment facility must be monitored by the Radiological Physics Center (RPC) <http://rpc.mdanderson.org/rpc/>. All questions regarding radiation treatment should be directed to the RTOG Principal Investigator/Radiation Oncology Study Chair, Dr. Harari.

**6.2** Treatment Planning

All fields must be designed on a simulator or by using CT-scan based virtual simulation. Immobilization with a mask is strongly recommended. Bite blocks to displace the tongue, palate, or mandible may also be helpful. Three-dimensional planning is not required, although the use of CT-planning (*CT scan with the patient in the treatment position*) for dosimetry is required. Computerized 2-dimensional plans with isodose distributions at a minimum of two levels (at isocenter and at least one other level) are required. Irregular field dose calculations alone without CT-based treatment planning is not permitted.

**6.3** Field Arrangements

**6.3.1** It is expected that most patients will be treated with conventional comprehensive radiotherapy technique, including opposed lateral fields to encompass the primary tumor bed and upper cervical lymph nodes, matched on to an anterior low neck/supraclavicular field. The decision on the "site" of the match is left to the individual investigator, with the recommendation that the match point not be within 2 cm of gross tumor. Electron boosting to the posterior neck will commonly be used to supplement nodal dose following off-cord reduction of the primary photon beams. Intensity modulated radiation therapy (IMRT) is not permitted for treatment in this study.

**6.3.2** For relatively superiorly located tumors, it is acceptable to utilize a "high" match at a level 1-2 cm below the hyoid bone, in order to minimize irradiation of the central larynx. With this technique, the glottic larynx may be shielded in the low neck/supraclavicular field. When using the "high-match" technique in the setting of adenopathy, it should be remembered that there may be underdosing of relatively posteriorly located lymph nodes. Treatment of the low neck/supraclavicular field AP-PA or conedowns of the low-neck field may be necessary to comply with Section 6.1.4.

**6.4** Dosimetry

**6.4.1** Opposed Lateral Fields: For opposed lateral fields the prescription dose should reflect the isodose line selected from CT planning to appropriately encompass the treatment volume.

**6.4.2** Low/Neck Field: For the low/neck supraclavicular field, the prescription dose can be prescribed to a depth of 3 cm or to an isodose line selected to cover the lower neck nodes. With a "high match," this may result in a relative underdose of the posterior cervical nodal chain and field and/or prescription adjustments may be necessary (See Sections 6.1.3 and 6.1.4).

- 6.4.3** Conedowns: Conedowns to areas of prior gross disease may be performed using opposed laterals with “shrinking field” technique, or may be performed with other techniques for lateralized lesions (tonsil), such as a wedge pair or ipsilateral mixed photon-electron beam technique. More complex “conformal” plans are also acceptable. Guidelines for conedowns are as follows:
- 6.4.3.1** For any plan other than shrinking field opposed laterals, CT-planned dosimetry is required.
  - 6.4.3.2** The conedown plan must encompass the preoperative gross tumor volume within the prescription isodose curve.
  - 6.4.3.3** The maximum acceptable “hot spot” on the plan is 10%, with a strong recommendation to keep the maximum “hot spot” below 5%.
  - 6.4.3.4** The maximum spinal cord dose (Section 6.1.2) should be < 48 Gy.

**6.5** Radiation Therapy Interruptions

- 6.5.1** Radiotherapy interruptions or delays only will be permitted for Grade IV mucositis. Radiation can be interrupted for 3-5 days (systemic chemotherapy also should be held) until the reaction subsides to Grade III and radiation (and chemotherapy) is resumed; however, every effort should be made to keep this treatment break as short as possible. The maximum radiation treatment break should be 7 days. Total dose, number of fractions, and elapsed days should be carefully reported.

**6.6** Protocol Compliance Criteria

- 6.6.1** RT Quality Assurance Reviews  
 The Radiation Oncology Chair, Paul M. Harari, MD, will perform an RT Quality Assurance Review after complete data for the first 60 cases enrolled has been received at RTOG Headquarters. Dr. Harari will perform the next review after complete data for the next 60 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. These reviews will be on going and performed at the RTOG semi-annual meetings as well as at RTOG Headquarters.

Score	Target Volume	Spinal Cord Dose	XRT Elapsed Time
Per Protocol	≤ 5%	< 48 Gy	47-56 days
Variation Acceptable	> 5-10%	49-50 Gy	57-63 days
Deviation Unacceptable	> 10%	> 50 Gy	> 64 days

**6.7** Radiation Toxicity

- 6.7.1** Reversible radiation mucositis is expected to develop in the majority of patients. This will commonly manifest as Grades I to III in severity. In those rare cases of Grade IV mucositis, radiation can be interrupted (see Section 6.5.1). Other common radiation toxicities include fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, hypogeusia, dysgeusia, dysphagia, and skin erythema and desquamation within the treatment fields. If a feeding tube is placed for nutritional supplementation, this should be recorded. Less common long-term radiation toxicities include hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis. Much less common radiation toxicities include mandibular osteoradionecrosis (<5% incidence with attention to the dental recommendations provided in Appendix IV), and cervical myelopathy (<1% with restriction of spinal cord dose to ≤ 45 Gy).

**6.8** Radiation Toxicity Reporting **RTOG AE TELEPHONE LINE: 215- 717-2762**

- 6.8.1** All acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) v3.0. A copy of the CTCAE can be downloaded from the CTEP homepage (<http://ctep.cancer.gov/reporting/ctc.html>).
- 6.8.2** Documentation  
 Radiation therapy is combined with chemotherapy administration in this protocol; therefore, ALL serious adverse events are reported using AdEERS as stated in section 7.7 of this protocol.
- 6.8.3** Summary of AE Reporting Involving Radiation Treatment With Chemotherapy Administration
- Report Grade 4/Grade 5 AEs;
  - Telephone report within 24 hours of discovery;

- Document using the appropriate report — MedWatch or AdEERS within 10 days (a dictated summary and CRF's may also be indicated);
- Institutional reporting as required;
- For **DEATH WITHIN 30 DAYS OF COMPLETION OF TREATMENT:**
  - Telephone report to RTOG within 24 hours of discovery;
  - Follow guidelines outlined in section 7.7 of this protocol for AE reporting.

## **7.0 DRUG THERAPY**

During week 1 (seven weeks after surgery), C225 will be administered alone, without radiation therapy. If there are wound complications after surgery, e.g., a major active fistula or wound dehiscence, and C225 will be delayed, contact the Medical Oncology Study Chair, Dr. Kies.

After the loading dose of C225, systemic therapy is to commence within 24 hours from the start of radiotherapy and be administered on Monday, Tuesday, or Wednesday (and on the same day each week). For patients starting radiotherapy on Wednesday, the systemic treatment should also start on Wednesday. To accommodate for holidays, the drug treatment may be advanced or delayed by one day and then return to the original schedule for subsequent weeks.

### **7.1 Treatment Plan**

#### **7.1.1 Both Arms: Cetuximab Loading Dose (Week 1, Day 1)**

Patients will receive a loading dose of cetuximab (C225), 400 mg/m<sup>2</sup>, intravenously (IV) over 120 minutes on Day 1. No chemotherapy or radiation therapy will be given this day or week. Loading dose of C225 should precede start of radiation by >4 and <10 days. Note that C225 should commence by postoperative day 42 in an effort to commence radiation by postoperative day 49.

**All patients will be premedicated with diphenhydramine hydrochloride 50 mg (or similar agent) either by IV 30-60 minutes prior to the first dose of cetuximab or orally 60-120 minutes prior to the first dose of cetuximab in an effort to prevent an allergic/hypersensitivity or cytokine release reaction.** Premedication is recommended prior to subsequent doses, but at the Investigator's discretion, the dose of diphenhydramine may be reduced.

The medical staff must closely observe patients for signs of anaphylaxis or any other potential adverse events. Vital signs (blood pressure, heart rate, respiratory rate, and temperature) should be checked and recorded prior to the administration of cetuximab, midway through the infusion, at the completion of the infusion, and 60 minutes post the infusion in an area with resuscitation equipment and other agents (epinephrine, prednisone equivalents, etc.) available. A nurse must be present in the immediate treatment area throughout the infusion and observation period. A physician must be in close proximity to the patient treatment area. In the event that a patient experiences an allergic/hypersensitivity or cytokine release reaction, see Section 7.5.5.1 for proper management. **Patients should be instructed to report any delayed reactions to the investigator immediately.**

#### **7.1.2 Arm 1, Radiation Plus Weekly C225 Plus Cisplatin:**

**Weeks 2-7:** C225 at 250 mg/m<sup>2</sup> plus cisplatin 30 mg/m<sup>2</sup> in combination with radiation therapy

- C225 is to be administered prior to cisplatin and radiation therapy over 60 minutes.
- Dexamethasone 20 mg IV, and dolasetron 100 mg IV (or equivalent antiemetic) are to be administered 30 minutes prior to delivery of cisplatin only.
- Patients must be adequately hydrated prior to receiving cisplatin. It is highly recommended that all patients receive 1 liter of sodium chloride 0.9% over 2 hours prior to treatment. Attention should be given to K<sup>+</sup> and Mg<sup>++</sup> levels with replacement as needed.
- Cisplatin should be infused over 1 hour. Additional hydration may be given at physician discretion. Patients should be sent home with adequate anti-emetic medication.

#### **7.1.3 Arm 2, Radiation Plus Weekly C225 Plus Docetaxel:**

**Weeks 2-7:** C225 at 250 mg/m<sup>2</sup> plus docetaxel 15mg/m<sup>2</sup> in combination with radiation therapy

- C225 is to be administered prior to docetaxel and radiation therapy over 60 minutes.
- Docetaxel will be administered in a 30-minute IV infusion at least 30 minutes following the C225. Premedication with decadron 10 mg IV may be administered at the discretion of the treating physician.

**CAUTION:** Allergic/hypersensitivity or cytokine release reactions may occur during or following cetuximab administration. **Most allergic/hypersensitivity or cytokine release reactions occur with the first infusion of cetuximab, but some patients' first allergic/hypersensitivity or cytokine release reactions have been reported following subsequent doses (a severe reaction occurred in one patient following the 8th dose). The allergic/hypersensitivity or cytokine release reaction may occur during the infusion or be delayed until any time after the infusion.**

7.1.4 (8/27/04) *ACOSOG Investigators*: All questions regarding drug therapy should be directed to the RTOG Medical Oncology Study Chair, Dr. Kies.

## **7.2 Cetuximab (C225) [IND #5804]**

### 7.2.1 Formulation

Cetuximab is an anti-EGFR receptor humanized chimeric monoclonal antibody. Cetuximab is expressed in SP2/0 myeloma cell line, grown in large scale cell culture bioreactors, and purified to a high level purity using several purification steps including protein A chromatography, ion exchange chromatography, low pH treatment, and nanofiltration. Cetuximab is not known to be a vesicant. To obtain a copy of the C225 Investigator Brochure, please contact Bristol-Myers Squibb (BMS) via Allison Hunt at (609) 897-3637 or allison.hunt@bms.com or Randy Gardner-McQuade at (609) 897-3922 or randy.gardner-mcquade@bms.com.

### 7.2.2 Supply

BMS will supply cetuximab free of charge to patients on study. The product is formulated to 2 mg protein/mL with phosphate buffered saline, pH 7.2 ± 0.2 and aseptically filled into sterile glass vials, 100 mg per 50 cc vial, and stored as a liquid at 2 to 8° C. Each vial contains the following active and inactive ingredients per 1.0 mL: 2 mg of cetuximab, 145 nmol/L sodium chloride, and 10 mmol/L sodium phosphate.

### 7.2.3 Safety Precautions

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

### 7.2.4 Preparation and Administration

Cetuximab will be prepared by ImClone under appropriate manufacturing conditions as an injectable solution, in single-use, ready-to-use 50-mL vials containing 2 mg/mL of product. Cetuximab requires no dilution. Cetuximab should not be mixed with or diluted with other drugs or solutions for infusion such as 5%-glucose.

The dose and volume of the study drug to be infused are dependent upon the patient's actual BSA. **The infusion rate must never exceed 10 mg/minute (5 mL/minute).** The dose may subsequently be reduced for individual patients, depending on a patient's toxicity. The infusion rate should not exceed 300 mL/hour. If the patient experiences a Grade I and Grade II hypersensitivity reaction, the infusion rate can be decreased but should not exceed four hours. Observe the patient for one hour after the infusion; the concern with infusions greater than four hours is sterility, not stability. For the duration that patients are on cetuximab therapy, adverse event monitoring should be done continuously. Patients will be evaluated for adverse events at each visit and are to be instructed to call their physician to report any adverse events between visits.

Cetuximab may be administered via an infusion pump or syringe pump with in-line filtration. Cetuximab requires in-line filtration during administration. The 0.22 µm in-line filters in both the recommended Baxter Healthcare and Abbott Laboratories infusion sets have identical in-line filters composed of polyethersulfone. Calculate and draw the appropriate volume of cetuximab into a sterile syringe based on either the 400 mg/m<sup>2</sup> initial dose or 250 mg/m<sup>2</sup> weekly dose, and administer via one of the options detailed below:

#### 1) In-line Filtration by Infusion Pump

Take an appropriate sterile syringe (min 50 mL), attach a suitable needle, and draw up the required volume of cetuximab solution from a vial. Add the cetuximab into a sterile evacuated container or bag. (Glass administration containers are not recommended.) Repeat this procedure until the calculated volume has been added to the container. Next, affix the infusion line with an in-line filter (the cetuximab solution must be filtered with a suitable in-line filter of 0.2µm nominal pore size), and prime it with cetuximab

before starting the infusion. Use an infusion pump for administration. Set and control the rate as noted above.

2) In-line Filtration by Syringe Pump

Take an appropriate sterile syringe (min 50 mL), attach a suitable needle, and draw up the required volume of cetuximab solution from a vial. Remove the needle, and put the syringe into the syringe pump. Take a suitable in-line filter of 0.2µm nominal pore size, and connect it to the infusion line (Note: one filter per dose should be sufficient, but further filters can be used if a filter becomes blocked). Connect the infusion line to the syringe, set and control the rate as described above, and start the infusion after priming the line with cetuximab. Repeat this procedure until the calculated volume has been infused.

Studies have been conducted to demonstrate the compatibility of cetuximab drug product with various infusion systems. Some examples of materials, IV containers, infusion sets, and filters tested and recommended for use with cetuximab are listed below. For further examples of approved materials, please see the Investigator Brochure.

Recommended IV Containers

- IntraVia™ IV Bag with PVC Ports, Model No. 2J8002 (Baxter Healthcare Corporation)
- EVA™ IV Bag, Model No. 2B8152 (Baxter Healthcare Corporation)
- LifeCare™ IV Bag, Model No. 7951-12 (Abbott Laboratories)

Recommended Infusion Sets

- Vented Continu-Flo Solution Set™, Model No. 2C6541s (Baxter Healthcare Corporation) to be used with an in-line filter set, Model No. 2679 (Abbott Laboratories)
- Vented Paclitaxel Set™ with 0.22-µm downstream high-pressure in-line filter, Model No. 2C7553 (Baxter Healthcare Corporation)

Recommended Filters

- Vented Continu-Flo Solution Set™, Model No. 2C6541s (Baxter Healthcare Corporation) to be used with an in-line filter set, Model No. 2679 (Abbott Laboratories)
- Intrapur Plus (B. Braun AG) reference number 409 9800
- Poly-lined filtered Extension set (Alaris Medical Systems) reference number C20350

Normal saline should be used to clear the infusion set of residual cetuximab. The delivered drug product is > 95% for all recommended infusion sets when flushed with 50 mL of normal saline. Use a separate line for cetuximab infusion.

**7.2.5** Storage Requirements/Stability

Cetuximab must be stored under refrigeration at +2°C to +8°C (+36°F to +46°F). **DO NOT FREEZE CETUXIMAB.** Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. Once cetuximab is removed from the vial, the recommended maximum time at room temperature is 8 hours.

- **7.2.6** Adverse Events Hematologic: Leukopenia
- Gastrointestinal: Nausea, vomiting, diarrhea, anorexia, mucous membrane disorder, stomatitis, reduced kidney or liver function
- Dermatologic: Rash, acne, dry skin, pruritus
- Circulatory: Deep vein thrombosis
- Neurological: Confusion, disorientation, seizure, coma; rarely, encephalitis
- Allergy: Allergic reaction, anaphylactoid reaction
- Other: Asthenia, fatigue/malaise, fever, dyspnea, headache, chills, nail disorder, myalgia, arthralgia

**7.2.7** Drug Ordering and Accountability (8/27/04)

For the initial shipment of Cetuximab, **U.S. and Canadian institutions** must email the shipment form for this study (available at:

<http://www.rtog.org/members/protocols/0234/0234shipmentform.doc>) to

[RTOG\\_BMS@phila.acr.org](mailto:RTOG_BMS@phila.acr.org) as soon as the individual responsible for the study agent has been identified and prior to registration of the institution's first case. (Fax 215-574-0300 if unable to

email). Allow adequate processing time (7-10 days) before calling to randomize your first patient. See Appendix V for the procedure for resupply requests.

Initial shipments will consist of 13 boxes (52 vials, each containing 100 mg of cetuximab), which will be sufficient for 8-9 weeks of treatment for 1 patient or 4 weeks of treatment for 2 patients (depending on patients' BSA). Allow 5 business days for shipment of drug from the date of registration of the patient.

All product will be shipped via Federal Express in a temperature-controlled container. Shipments will be made from BMS on Monday through Thursday for delivery to sites on Tuesday through Friday. There will be no weekend or holiday delivery of drugs. Each drug box (4 vials) will contain a large label on the side of the box with the RTOG protocol number. It is possible that sites may have more than one cetuximab clinical study ongoing at the same time. It is imperative that only product designated for RTOG 0234 be utilized for this study.

Inside each shipping container will be a disposable electronic unit (TagAlert™) to ensure the product has remained at the appropriate temperature during shipping. This unit will be attached to an information card. The LCD display will show OK (indicating no alarm has been triggered) or a black bar and the number(s) 1-4 (indicating an alarm/alerts have been triggered). Should an alarm be triggered, follow the instructions on the attached information card. Display results should be recorded on the packing list. For questions regarding drug requisitioning or shipment, contact BMS at 866-339-4267 or 203-677-7017.

#### Important Reorder Instructions

Reorders should be emailed directly to BMS (See Appendix IV) for shipment within 5 days. When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose (~7-9 for initial dose, ~4-6 for weekly maintenance doses, dependent on patient's BSA) and that shipments may take 5 business days from BMS receipt of request. Sites may request more than 52 vials for resupply shipments only if there is adequate storage space. Quantities must be in multiples of 52.

#### Receipt Of Drug Shipment

Study drug shipments will include a TagAlert™ unit and attached information card (see above for description) and a clinical supply packing list (CSPL). The pharmacist/study personnel responsible for the clinical study product will need to indicate the condition of the shipment, record the TagAlert™ results, and sign the CSPL in the designated areas. The pharmacist/study personnel will keep a photocopy for the site's records, and return the original to BMS, using the enclosed, pre-addressed envelope. The TagAlert™ unit can be discarded after the reading is recorded on the CSPL.

#### **7.2.8** Handling and Dispensing of Investigational Product

Investigational product should be stored in a secure area according to local regulations. It is the responsibility of the Investigator to ensure that investigational product is only dispensed to study patients. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

#### **7.2.9** Drug Destruction and Return

Opened vials must be disposed of at the site as chemotherapy or biohazardous waste, provided documented procedures for destruction are in place. Otherwise, opened vials must be returned to the BMS for disposal. At the completion of the study, all unused drugs will be destroyed at the site according to the institution's policy for drug destruction. It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed, including dates and quantities. If approved procedures for destruction are not in place and/or for questions regarding cetuximab destruction, please contact BMS at 866-339-4267 or 203-677-7017.

### **7.3** Cisplatin (Cis-Diamminedichloroplatinum, DDP)

**7.3.1** Formulation: Each vial contains 10 mg of cisplatin, 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.

**7.3.2** Storage and Preparation: The dry, unopened vials should be stored at refrigeration temperature (+4°C to +8°C). Reconstitution results in a solution stable for not more than one

hour at room temperature when exposed to normal room illumination, and not more than 8 hours at room temperature when protected from light.

**7.3.3** Administration: Intravenous.

**7.3.4** Pharmacology: The mechanism of action of cisplatin has not been clearly elucidated. However, 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 cisplatin binds to DNA and produces inter-strand cross-links. Also cisplatin is not phase-sensitive and its cytotoxicity is similar in all phases of the cell cycle.

**7.3.5** Side Effects and Toxicities: The major effects in humans have been renal toxicity manifested by BUN and serum creatinine elevation, tinnitus and audiologic impairment in the high frequency range (4000 to 8000 Hz), nausea and vomiting, hyperuricemia, mild to moderate anemia, peripheral neuropathy, and electrolyte abnormalities.

**7.3.6** Supplier: Commercially available. For further information, please see the package insert.

#### **7.4 Docetaxel (Taxotere®) Therapy**

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

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

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

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

##### **7.4.2.1** Preparation and Administration Precautions

- 1) Docetaxel is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing docetaxel solutions. The use of gloves is recommended. Please refer to Handling and Disposal in Section 7.4.2.3.
- 2) If docetaxel concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water. If docetaxel concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.
- 3) Taxotere® for Injection Concentrate requires two dilutions prior to administration. Please follow the preparation instructions provided below. Note: Both the Taxotere® for Injection Concentrate and the diluent vials contain an overfill.

##### **7.4.2.2** Preparation of the Initial Diluted Solution

- 1) Gather the appropriate number of vials of Taxotere® for Injection Concentrate and diluent (13% ethanol in water for Injection). If the vials were refrigerated, allow them to stand at room temperature for approximately 5 minutes.
- 2) Aseptically withdraw the contents of the appropriate diluent vial into a syringe and transfer it to the appropriate vial of Taxotere® for Injection Concentrate. If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/mL will result.
- 3) Mix the initial diluted solution by repeated inversions for at least 45 seconds to assure full mixture of the concentrate and diluent. Do not shake.

- 4) The initial diluted docetaxel solution (10 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

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

**7.4.2.3** Preparation of the Final Dilution for Infusion

- 1) Aseptically withdraw the required amount of initial diluted docetaxel solution (10 mg docetaxel/mL) with a calibrated syringe and inject into an infusion bag or bottle of either 0.9% sodium chloride solution or 5% dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL.

- 2) Thoroughly mix the infusion by manual rotation.

- 3) As with all parenteral products, docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel for Injection initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.

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

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

**7.4.3** Administration: Intravenous.

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

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

**7.4.6** Supplier: Commercially available. For further information, please see the package insert.

**7.5** Dose Modifications

**7.5.1** Cetuximab/Docetaxel/Cisplatin Dose Levels

	<b>Starting Dose</b>	<b>Dose Level –1</b>	<b>Dose Level –2</b>
Cetuximab (C225)	400 mg/m <sup>2</sup> (week 1) 250 mg/m <sup>2</sup> (weekly)	200 mg/m <sup>2</sup> (weekly)	150 mg/m <sup>2</sup> (weekly)
Docetaxel	15 mg/m <sup>2</sup> (weekly)	12 mg/m <sup>2</sup> (weekly)	–
Cisplatin	30 mg/m <sup>2</sup> (weekly)	20 mg/m <sup>2</sup> (weekly)	–

7.5.2 *Cetuximab/Docetaxel/Cisplatin Dose Modification for Hematologic Toxicity*

NCI CTCAE Toxicity Grade (CTCAE v. 3.0)	Cetuximab Dose <sup>a,b</sup> at Start of subsequent Cycles of Therapy	Docetaxel Dose <sup>c,d</sup> at Start of Subsequent cycles of Therapy	Cisplatin Dose <sup>e,f</sup> at Start of Subsequent Cycles of Therapy
<b>Neutropenia</b>			
<b>1</b> (1500-1999/mm <sup>3</sup> )	Maintain dose level	Maintain dose level	Maintain dose level
<b>2</b> (1000-1499/mm <sup>3</sup> )	Maintain dose level	Maintain dose level	Maintain dose level
<b>3</b> (500-999/mm <sup>3</sup> )	Decrease by 1 dose level with occurrence	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and continue when reaches Grade 2	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and continue when reaches Grade 2
<b>4</b> (<500/mm <sup>3</sup> )	Decrease by 1 dose level with occurrence	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and continue when reaches Grade 2	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and continue when reaches Grade 2
<b>Neutropenic Fever<sup>g</sup></b>	Decrease by 1 dose level	Decrease by 1 dose level	Decrease by 1 dose level
<b>Thrombocytopenia</b>			
<b>1</b> (>75,000/mm <sup>3</sup> )	Maintain dose level	Maintain dose level	Maintain dose level
<b>2</b> (50,000- 74,999/mm <sup>3</sup> )	Maintain dose level	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and continue when reaches Grade 1	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and continue when reaches Grade 1
<b>3</b> (25,000- 49,999/mm <sup>3</sup> )	Decrease by 1 dose level with occurrence	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and continue when reaches Grade 1	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and continue when reaches Grade 1
<b>4</b> (<25,000/mm <sup>3</sup> )	Decrease by 1 dose	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and continue when reaches Grade 1	Hold dose for the week; if continues > 7 days, decrease by 1 dose level and continue when reaches Grade 1
<b>Other Hematologic toxicities:</b> Dose mods for leucopenia are based on NCI CTCAE and are the same as recommended above.			

<sup>a</sup>Dose levels are relative to the starting dose in the previous cycle. Dose reductions of Cetuximab below the –2 dose level will not be allowed.

<sup>b</sup>Provided that all the retreatment criteria are met (see section 7.5.5.1)

<sup>c</sup>Dose levels are relative to the starting dose in the previous cycle. Dose reductions of docetaxel below the –1 dose level will not be allowed.

<sup>d</sup>Docetaxel will be delivered only if there is no indication for holding the radiation and if all other hematologic and non-hematologic toxicity criteria are met. If these parameters are not met, continue radiation therapy and omit docetaxel that week.

<sup>e</sup>Dose levels are relative to the starting dose in the previous cycle. Dose reductions of cisplatin below the –1 dose level will not be allowed.

<sup>f</sup>Cisplatin will only be delivered if there is no indication for holding the radiation and if all other hematologic and non-hematologic toxicity criteria are met. If these parameters are not met, continue radiation therapy and omit cisplatin that week.

<sup>g</sup>One reading of oral temperature >38.5°C, or three readings of oral temperature >38°C in a 24-hour period.

7.5.3 Dose Modifications for Non-Hematologic Toxicity (8/27/04)

NCI CTCAE Toxicity Grade (CTCAE v. 3.0)	Cetuximab Dose <sup>b,c,h</sup>	Docetaxel Dose <sup>d</sup>	Cisplatin Dose <sup>e</sup>
<b>Renal-serum Creatine*</b>			
≤ Grade 1	Maintain dose levels	Maintain dose levels	Maintain dose levels
≥ Grade 2	Maintain dose levels	Maintain dose levels	Decrease by 1 dose level
≥ Grade 3	Hold drug until ≤ grade 2	Hold drug until ≤ grade 2	Hold drug until ≤ grade 1, then decrease by one level
<b>Renal-Calculated Creatinine Clearance*</b>			
≥ 50 mL/min	Maintain dose levels	Maintain dose levels	Maintain dose level
< 50 mL/min	Maintain dose levels	Maintain dose levels	Decrease by 1 dose level
<b>Fatigue (Asthenia)</b>	Maintain dose levels	Decrease by 1 dose level	Decrease by 1 dose level
≥ Grade 3			
<b>Nausea/Vomiting</b>	Maintain dose levels	Maintain dose level	Maintain dose level
≤ Grade 2 with maximal medical management			
≥ Grade 3 with maximal medical management		Hold drug until ≤ grade 2	Hold drug until ≤ grade 2
<b>Other non-hematologic Toxicities<sup>f</sup></b>			
Grade 4 <sup>g</sup>	Discontinue from treatment and follow until resolution of toxicity	Hold drug until ≤ grade 1	Hold drug until ≤ grade 1
Grade 3-4 (out of RT field)	Maintain dose levels	Decrease by 1 dose level and resume therapy when reversed to Grade 1	Decrease by 1 dose level and resume therapy when reversed to Grade 1
Grades 2-4 (out of RT field that dose not reverse to Grade 1 at time of treatment)	Maintain dose levels	Delay all therapy for one week; decrease docetaxel by 1 dose level when reversed to Grade 1	Delay all therapy for one week; decrease cisplatin by 1 dose level when reversed to Grade 1

<sup>a</sup>For CTCAE Grade < 2 non-hematologic toxicity not described above, maintain dose level of drug.

<sup>b</sup>Provided that all the retreatment criteria are met as detailed at the beginning of section 7.5.5.1: acne-like rash is ≤ Grade 2, all Grade 3/4 nonhematologic toxicities have resolved to < CTC Grade 2 (except fatigue [asthenia], anorexia, alopecia, and diarrhea).

<sup>c</sup>Dose levels are relative to the previous dose. Dose reductions of C225 below the –2 dose level will not be allowed.

<sup>d</sup>Dose levels are relative to the previous dose. Dose reductions of docetaxel below the –1 dose level will not be allowed.

<sup>e</sup>Dose levels are relative to the previous dose. Dose reductions of cisplatin below the –1 dose level will not be allowed.

<sup>f</sup>Cetuximab: With the exception of allergic/hypersensitivity (see Section 1.5.4), or acne-like rash (rash/desquamation) (see Section 7.5.1.2)

<sup>g</sup>Docetaxel hypersensitivity reactions- no dose reductions will be made unless Grade 4. If Grade 4, discontinue treatment with docetaxel.

<sup>h</sup>In any case of C225 treatment delay, there will be no reloading infusion, and all subsequent treatments will be at the assigned dose level.

\*Choose one or the other study to assess renal function and base treatment decision.

7.5.4 CTCAE v. 3.0 Allergic Reaction/Hypersensitivity Management

CTCAE Grade	Treatment Guidelines	
<b><u>Grade 1</u></b>	<b>Cetuximab<sup>a</sup></b> Slow the infusion rate for cetuximab and consider administering prophylactic antihistamine medications for subsequent doses. For mild or moderate hypersensitivity reactions manifesting only as delayed drug fever, maintain the cetuximab dose and infusion rate. Acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) may be administered prior to subsequent cetuximab infusions, if not otherwise contraindicated in subjects.	<b>Docetaxel</b> Consider decreasing the rate of infusion until recovery from symptoms. Stay at bedside and monitor patient, then complete docetaxel infusion at the initial planned rate.
<b><u>Grade 2</u></b>	Slow the infusion rate for cetuximab and consider administering prophylactic antihistamine medications for subsequent doses. For mild or moderate hypersensitivity reactions manifesting only as delayed drug fever, maintain the cetuximab dose and infusion rate. Acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) may be administered prior to subsequent cetuximab infusions, if not otherwise contraindicated in subjects.	-Interrupt docetaxel infusion and give diphenhydramine 50 mg IV with or without dexamethasone 10mg IV. -Monitor patient until resolution of symptoms. -Resume docetaxel infusion after recovery of symptoms. -Depending on the physician's assessment of the patient, docetaxel infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate. (e.g., infuse at a 4-hr rate for 3 minutes, then at a 2-hr rate for 3 minutes, then at a 1-hr rate for 3 minutes, then finally, resume at the initial planned rate.) -Depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the <b>next cycle</b> of treatment, and the rate of infusion should be decreased initially and then increased back to initial planned rate, (e.g., infuse at a 4-hr rate for 3 minutes, then at a 2-hr rate for 3 minutes, then at a 1-hr rate for 3 minutes, and finally, administer at the initial planned rate.)
<b><u>Grade 3</u></b>	Severe hypersensitivity reactions, characterized by airway obstruction (bronchospasm, stridor and hoarseness), urticaria, and/or hypotension, require immediate interruption of cetuximab infusion and permanent discontinuation from further treatment with cetuximab. Appropriate medical therapy including epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.	Immediately discontinue docetaxel infusion. Give diphenhydramine 50mg IV with or without dexamethasone 10mg IV and/or epinephrine as needed. Monitor patient until resolution of symptoms. Follow the same treatment guidelines outlined for Grade 2 symptoms.

<b>Grade 4</b>	Severe hypersensitivity reactions, characterized by airway obstruction (bronchospasm, stridor and hoarseness), urticaria, and/or hypotension, require immediate interruption of cetuximab infusion and permanent discontinuation from further treatment with cetuximab. Appropriate medical therapy including epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.	<b>NO FURTHER STUDY DRUG THERAPY</b>
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<sup>a</sup> **Study Therapy Retreatment Following Hypersensitivity Reactions:** Once a C225 infusion rate has been decreased due to an allergic/hypersensitivity reaction, it will remain decreased for all subsequent infusions. If the subject has a second allergic/hypersensitivity reaction with the slower infusion rate, the infusion should be stopped, and the subject should receive no further C225 treatment. If a subject experiences a Grade 3 or 4 allergic/hypersensitivity reaction at any time, the subject should receive no further C225 treatment. If there is any question as to whether an observed reaction is an allergic/hypersensitivity reaction of Grades 1-4, the Study Chair or designee should be contacted immediately to discuss and grade the reaction.

### 7.5.5 **Cetuximab Special Instructions**

If C225 is omitted for more than four consecutive infusions for toxicity due to C225, or for an intercurrent illness (e.g., infection) requiring interruption of therapy, the subject should be discontinued from further C225 therapy. If toxicities prevent the administration of C225, the subject may continue to receive radiation therapy.

#### 7.5.5.1 Treatment of Cetuximab Infusion Reactions

Cytokine release syndromes/acute infusion reactions are different from allergic/hypersensitivity reactions, although some of the manifestations are common to both adverse events. Cytokine release syndrome/acute infusion reactions may occur with an agent that causes cytokine release, e.g., with a monoclonal antibody such as cetuximab. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms are similar to those of allergic reaction/hypersensitivity: arthralgia, bronchospasm, cough, dizziness, dyspnea, fatigue, fever, headache, hypertension, hypotension, myalgia, nausea, pruritus/itching, rash/desquamation, rigors/chills, sweating, tachycardia, tumor pain, urticaria, and vomiting.

In each case of an infusion reaction, the Investigator must use his/her clinical judgment to classify the reaction. In general, the reaction should be classified as cytokine release if the patient has never had prior exposure to a murine monoclonal antibody or other murine products, or as a hypersensitivity reaction if the patient has had prior exposure to a murine monoclonal antibody or other murine products. Adverse events should be attributed accordingly.

In each case of an infusion reaction, the Investigator should institute treatment measures according to the best available medical practice. In the event of isolated fever, the investigator must use clinical judgment to determine if the fever is related to the study drug or to an infectious etiology. If an infectious etiology is suspected, appropriate therapy should be introduced, and the event coded as **CTCAE v3.0 Infection**. Based on previous experience with cetuximab reactions, the treatment guidelines above may be applicable.

#### 7.5.5.2 Retreatment Criteria for C225

C225 may only be administered if all of the following criteria are met regardless of cycle, providing no criteria for discontinuation are met (see Section 11.2):

- Acne-like rash is ≤ Grade 2 (see Section 7.5.1.3)
- All Grade 3 - 4 hematologic toxicities have resolved to ≤ CTC Grade 2
- All Grade 3 - 4 non-hematologic toxicities have resolved to < CTC Grade 2, (except fatigue (asthenia), anorexia and alopecia)

#### 7.5.5.3 Acne-Like Rash (rash/desquamation)

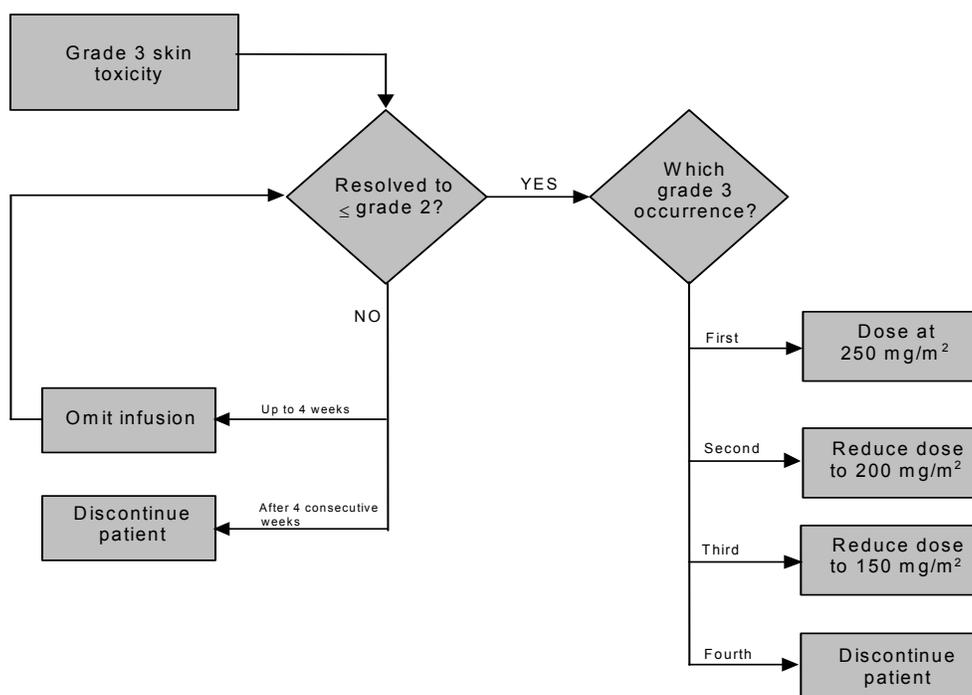
If a subject experiences Grade 3 acne-like rash (acne/acneiform rash), cetuximab may be interrupted. If the rash improves and is no longer severe, treatment may be resumed

without any change in dose level. The recurrence of Grade 3 acne-like rash may require further interruption of therapy, with dose reductions at re-treatment after improvement (initially to 200 mg/m<sup>2</sup> and subsequently to 150 mg/m<sup>2</sup>) or eventual discontinuation of therapy. A rash that occurs within the radiation field should be coded separately as “Rash: dermatitis associated with radiation.”

Acneiform rash has been treated with supportive care as for acne vulgaris including the use of anti-staphylococcal antibiotics as appropriate. A number of therapeutic interventions have been attempted in managing the rash, including oral and topical antibiotics (consider Cleocin T gel), topical steroids, and rarely, oral steroids. The value of these measures is unknown since definitive clinical trials have not been performed.

Because there is no definitive data regarding the value of antibiotic treatment for the acne-like rash, the choice to use specific antibiotics or creams is left to the discretion of the treating physician.

### Management of C225 Skin Toxicity



## 7.5.6 Docetaxel Special Instructions

### 7.5.6.1 Liver Function

Liver function tests should be evaluated at a minimum of every 4 weeks. Patients who develop abnormal liver function tests for any reason while on the study will have the following dose reductions:

### **Dose Modifications for Abnormal Liver Function (Docetaxel [Taxotere®])**

	AST or ALT:			
<b>ALK PHOS:</b>	<b>≤ ULN</b>	<b>&gt;1X but ≤1.5X ULN</b>	<b>&gt;1.5X but ≤5X ULN</b>	<b>&gt;5X ULN</b>
<b>≤ ULN</b>	Full Dose	Full Dose	Full Dose	Hold*
<b>&gt;1X but ≤ 2.5X</b>	Full Dose	Full Dose	Reduce Dose	Hold*
<b>&gt;2.5X but ≤ 5X</b>	Full Dose	Reduce Dose	Hold*	Hold*
<b>&gt;5X ULN</b>	Hold*	Hold*	Hold*	Hold*

\* Hold until recovered, maximum 21 days, then re-treat at a reduced dose. "Recovered" is defined as meeting the study baseline eligibility criteria.

#### **7.5.6.2** Bilirubin

Docetaxel should not be administered to patients with serum total bilirubin > 1.5 X ULIN. If serum total bilirubin is >1.5 X ULIN on treatment day, hold docetaxel until serum total bilirubin is ≤ 1.5 X ULIN (maximum 21 days), then re-treat at a reduced dose.

#### **7.5.6.3** Stomatitis

If stomatitis is present on day 1 of any cycle, treatment should be withheld until stomatitis has resolved. If stomatitis is ≤ Grade 1 on day 8 or day 15 of any cycle, treat at current dose. The Taxotere dose should be reduced for Grade 2 stomatitis without treatment delay. If Grade 3/4 stomatitis occurs at any time, the dose of docetaxel should be held until resolution and reduced for subsequent treatment.

#### **7.5.6.4** Peripheral Neuropathy

If neuropathy is present on day 1 of any cycle, treatment should be withheld until neuropathy has resolved. If neuropathy is ≤ Grade 1 on day 8 or day 15 of any cycle, treat at current dose. The docetaxel dose should be reduced for Grade 2 neuropathies without treatment delay. Treatment should be discontinued or modified for Grade 3/4 neuropathies at Investigator discretion.

### **7.6** Duration of Treatment

#### **7.6.1** Discontinuation from Protocol Treatment

Study therapy MUST be immediately discontinued for the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Termination of the study by the sponsor.
- Any clinical adverse event, laboratory abnormality or intercurrent illness, which, in the opinion of the investigator, indicates that continued treatment with all study therapy is not in the best interest of the subject.
- Pregnancy.
- Subject non-compliance with the protocol.
- Imprisonment or the compulsory detention for treatment of either a psychiatric or physical (e.g., infectious disease)
- Progressive disease.
- Any clinical event requiring discontinuation from therapy as detailed in Section 7.5.

The reason(s) for discontinuation from protocol treatment should be documented in the patient's medical record and Case Report Form (CRF). All patients should be followed as specified in Sections 11.1 and 12.1.

#### **7.6.2** Treatment Compliance

Trained medical personnel will administer study therapy. Treatment compliance will be monitored by drug accountability, as well as recording treatment administration in the patient's medical record and Case Report Forms.

#### **7.6.3** Modality Review

Institutional participation in chemotherapy studies must be in accordance with the medical oncology quality control guidelines stated in the RTOG Procedures Manual. All cases will undergo modality review by the modality study chair.

The Medical Oncology Co-Chair, Merrill S. Kies, MD, will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The scoring mechanism is: **per protocol; variation, acceptable; deviation unacceptable; not evaluable for chemotherapy review, or, incomplete chemotherapy.** The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. When complete data has been received at RTOG Headquarters for ten cases, these cases will be prepared and sent to Dr. Kies for review. Subsequent cases will be prepared and sent to Dr. Kies for review, in increments of 20-25 cases, after complete data for those cases is received at RTOG Headquarters. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

**7.7 Adverse Drug Reaction Reporting RTOG AE TELEPHONE LINE: 215-717-2762**

**7.7.1** This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all treatment related adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov/reporting/ctc.html>). The CTEP home page also can be accessed from the RTOG web page at <http://www.rtog.org/regulatory/regs.html>. All appropriate treatment areas should have access to a copy of the CTCAE v3.0. See the RTOG procedure manual for general Adverse Event Reporting Guidelines.

**7.7.2** Reporting Requirements

All investigators are required to follow the reporting guidelines as determined by the phase of the study and the study sponsor. Sites are responsible for reporting adverse events as specified by their Institutional Review Board.

**7.7.3** This study will utilize the electronic Adverse Event Expedited Reporting System (AdEERS) to report all serious adverse events. Sites can access AdEERS at <http://ctep.cancer.gov/reporting/adeers.html>

**7.7.4** The following table outlines the reporting requirements for this study: **(8/27/04)**

UNEXPECTED EVENTS		EXPECTED EVENTS	
Grades 2 - 3 Attribution Possible, Probable, or Definite	Grades 4 and 5 Regardless of Attribution	Grades 1 - 3	Grades 4* and 5 Regardless of Attribution
Expedited report within 10 working days.  (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to RTOG Headquarters within 24 hours of discovery.  Expedited report to follow within 10 working days. Death—see below	Adverse Event Expedited Reporting NOT required.	Report by phone to RTOG within 24 hours of discovery. Expedited report within 10 working days.  *Grade 4 Myelosuppression events submitted on case report forms.
Note 1	Telephone number available 24 hours daily: (215) 717-2762		
Note 2	Report the events using Common Terminology Criteria for Adverse Events (CTCAE) version 3.0		
Note 3	For <b>Hospitalization</b> only – Any medical event equivalent to CTCAE Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of expected or unexpected and attribution.		
Note 4	A list of agent specific expected adverse events can be found in the protocol document and/or consent form.		
Note 5	<b>Reactions considered <i>definitely</i> not treatment-related should not be reported.</b> However, a report should be submitted if there is reasonable suspicion of drug effect.		

**Known/expected adverse events** are those that have been previously identified as having resulted from administration of the agent or treatment. They may be identified in the literature, the protocol, the consent form, noted in the drug insert, or in the Investigator's Brochure.

**Unknown/unexpected adverse events** are those thought to have resulted from the agent, e.g., temporal relationship but not previously identified as a known effect.

**All deaths on study must be reported using the Adverse Event Expedited Reporting System (AdEERS) regardless of causality. Attribution to treatment or other cause should be provided.**

## **8.0 SURGERY**

**8.1 (8/27/04)** Patients must have undergone gross total surgical resection of high-risk, pathological Stage III/IV squamous cell carcinoma of the head and neck within 7 weeks of randomization (see Section 3.1.1.1).

### **8.2 Surgical Quality Assurance Reviews**

The Surgical Oncology Co-Chair, Jeffrey N. Myers, M.D., will perform a Quality Assurance Review after complete data for the first 50 cases enrolled has been received at RTOG Headquarters. Dr. Myers will perform the next review after complete data for the next 50 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.

## **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.

## **10.0 PATHOLOGY**

**(For patients who have consented to participate in the tissue/blood component of the study; see Appendix IB)**

**10.1 Translational Research** to be conducted with tissue bank samples:

#### **10.1.1 *Rationale***

The RTOG has been collecting pretreatment diagnostic tissue from head and neck cancer protocols over the last eight to ten years. A number of histologic, cell kinetic/proliferation, and molecular markers are under active investigation, with several showing promise for the stratification of patients in future trials. The EGFR represents one of the most promising head and neck biomarkers studied to date with regard to clinical outcome in advanced head and neck cancer. The results of the current studies will expand and refine investigation of EGFR relationship to clinical outcome in head and neck cancer and may lead to identification of promising similar or new biomarkers with the goals of 1) identifying factors predictive of outcome such that patients may be better stratified in future trials, and 2) developing novel treatment strategies which target the molecular abnormalities identified. In this particular trial, we will gain specific information regarding any correlation between various forms of the EGFR (along with several downstream markers such as phosphorylated MAPK, AKT, and Stat-3) and clinical outcome in head and neck cancer patients who receive an EGFR inhibitory agent.

#### **10.1.2 *Specimen Collection***

The following materials will be provided to the RTOG Tissue Bank for translational research:

**10.1.2.1** One H & E stained slide

**10.1.2.2** A paraffin-embedded tissue block of the tumor or a 2 mm diameter core of tissue punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number.

**NOTE:** A kit with the punch, tube, and instructions can be obtained from the Tissue Bank. If both of these tissue types are unavailable, 15 unstained slides may be submitted. Block, core, or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

**10.1.2.3** A Pathology Report documenting that the submitted blocks, core, or slides contain tumor; the report must include the RTOG protocol number and the 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.

- 10.1.2.4** A Specimen Transmittal Form clearly stating that the tissue is being submitted for translational research; the form must include the RTOG protocol number and the patient's case number.
- 10.1.2.5** Specimens for translational research will be retained until the study is terminated.
- 10.1.3 (8/27/04)** Submit materials to:

**LDS Hospital  
Dept. of Pathology  
E.M. Laboratory  
8<sup>th</sup> Ave & C Street  
Salt Lake City, UT 84143  
(801) 408-5626  
FAX (01) 408-5020  
holly.goold@ihc.com**

**10.2 Reimbursement**

RTOG will reimburse submitting institutions \$300 per case for fresh or flash frozen tissue or \$200 per case for a block or core of material. After confirmation from the RTOG Tissue Bank that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are twice a year in January and July and will appear on the institution's summary report with the institution's regular case reimbursement.

**10.3 Confidentiality/Storage**

(See Appendix IB and the RTOG Patient Tissue Consent Frequently Asked Questions, <http://www.rtog.org/tissuebank/tissuefaq.ht> mL for further details.)

- 10.3.1** Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The Tissue Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.
- 10.3.2** Specimens for translational research will be retained until the study is terminated, unless the patient consents 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 (8/27/04)**

<u>Assessment</u>	<u>Pre-Treatment</u>	<u>Weekly During RT</u>	<u>3 months from start of RT</u>	<u>6 months from start of RT</u>	<u>Follow Up<sup>i</sup></u>
History/Physical	X <sup>a</sup>		X	X	X
Performance Status/Weight	X <sup>a</sup>	X	X	X	X
CBC/Diff/PLT	X <sup>a</sup>	X	X	X <sup>g</sup>	X <sup>g</sup>
Serum Chemistry Tests (per 3.1.4)	X <sup>a</sup>	X	X	X <sup>g</sup>	X <sup>g</sup>
Electrolytes, Mg <sup>++</sup> , Creatinine		X <sup>e</sup>			
Pregnancy Test	X <sup>b</sup>				
CT/MRI Tumor	X <sup>c</sup>		X <sup>g</sup>	X	X <sup>g</sup>
CXR or Thoracic CT	X <sup>d</sup>				X <sup>h</sup>
Toxicity Evaluation		X	X	X	X
Dental Evaluation	X				
Nutritional Evaluation (Feeding tube recommended)	X				
Surgical clearance	X				
Medical Oncology Exam	X <sup>a</sup>	X <sup>f</sup>	X <sup>g</sup>	X <sup>g</sup>	X <sup>g</sup>

- a. Within 4 weeks prior to study entry
- b. Within 1 week prior to study entry
- c. Pre-operatively for clinical staging
- d. Within 90 days prior to study entry
- e. Prior to chemotherapy must be drawn a minimum of q 4 weeks
- f. Every three weeks during chemotherapy
- g. Only if clinically indicated
- h. Annually for 5 years
- i. Every 3 months from start of treatment for years 1 & 2; q 6 months for years 3 through 6.

**11.2 Response Criteria/Outcome Definitions**

**11.2.1 Response Criteria**

- 11.2.1.1 No evidence of disease (NED):** All patients must have no measurable tumor following surgery.
- 11.2.1.2 Local-Regional Relapse:** Recurrent cancer in the tumor bed and/or neck not clearly attributable to a second primary neoplasm; biopsy confirmation is necessary.
- 11.2.1.3 Distant Relapse:** Clear evidence of distant metastases (lung, bone, brain, etc.); Biopsy is recommended where possible. A solitary lung mass/nodule is considered a second primary neoplasm unless proven otherwise.
- 11.2.1.4 Second Primary Neoplasm:** A new cancer developing within or outside of the field of original treatment; cancer re-appearing within the treatment field will be reviewed among the members of the Center for Head and Neck Cancer for determination of whether it represents a local recurrence of the index cancer or a new primary. Multiple lung nodules/masses are considered distant metastases from the index cancer unless proven otherwise.
- 11.2.1.5 Disease-free survival (DFS):** Duration for which the patient is without evidence for local-regional or distant relapse, second primary, or death.

**12.0 DATA COLLECTION (8/27/04)**

**Data should be submitted to:**

**RTOG Headquarters  
1818 Market Street, Suite 1600, Philadelphia, PA , 19103**

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 (10/15/04)**

<u>Item</u>	<u>Due</u>
Demographic Form <b>(A5)</b>	Within 2 weeks of study entry
Initial Evaluation Form <b>(I1)</b>	
Pathology Report <b>(P1)</b>	
Slides/Blocks <b>(P2)</b>	
Operative Note <b>(S2)</b>	
Surgical Path Report <b>(S5)</b>	
<u>Preliminary Dosimetry Information:</u>	Within 1 week of start of RT
RT Prescription (Protocol Treatment Form) <b>(T2)</b>	
Films (simulation and portal) <b>(T3)</b>	
Calculations <b>(T4)</b>	
Preoperative CT Scan Report <b>(C3)</b>	
<u>Final Dosimetry Information:</u>	Within 1 week of RT end
Daily Treatment Record <b>(T5)</b>	
Isodose Distribution <b>(T6)</b>	
Boost Films (simulation and portal) <b>(T8)</b>	
Radiotherapy Form <b>(T1)</b>	Within 1 week of RT end

Treatment Form (TF)	At end of treatment
Follow-up Form (F1)	Thirteen weeks (90 days) from start of RT, then every 3 months thereafter for years 1 & 2; q 6 months for years 3 through 6. Also at early termination of treatment, at progression/relapse, and at death (if death occurs within 6 years from the start of treatment).
Adverse Event Form (AE)	At end of treatment, at 13 weeks (90 days), then, if applicable, every 3 months for years 1 & 2, q 6 months for years 3 through 6. If applicable, at early termination of treatment, at progression/relapse, and at death (if death occurs within 6 years from the start of treatment).
Autopsy Report (D3)	As applicable

- 12.2 (8/27/04)** ACOSOG Investigators must submit data (Case Report Forms) directly to RTOG, as specified in Section 12.0; data should not be submitted to ACOSOG. Include the RTOG protocol number and patient case number as well as the ACOSOG study number and patient number. The required forms can be accessed on the RTOG web site at <http://www.rtog.org/members/forms/0234/main.html> (no password required).

RTOG will send queries regarding data and forms due reports to ACOSOG Investigators. Investigators' responses to queries should be submitted directly to RTOG.

**NOTE:** ACOSOG Investigators must submit Serious Adverse Event (SAE) regulatory requirements electronically via AdEERS, with an email copy to ACOSOG Headquarters. (RTOG will receive the SAE report directly from AdEERS).

## **13.0 STATISTICAL CONSIDERATIONS**

### **13.1 Study Endpoints**

- 13.1.1** Disease-free survival (failure: local, regional, or distant disease progression, second primary, or death)
- 13.1.2** Patient tolerance of the treatment regimens
- 13.1.3** Frequency of Grade 5 and acute non-hematologic Grade 4 toxicity
- 13.1.4** Frequency of other acute and late toxicity
- 13.1.5** Overall Survival (Failure: death to any cause)
- 13.1.6** Local-regional control (Failure: local or regional disease progression)
- 13.1.7** Correlation of EGFR (total and phosphorylated), pMAPK, pAKT, Stat-3, Ki-67, COX-2, and cyclin B1 expression with local-regional control, and overall and disease-free survival

### **13.2 Overview and Sample Size**

This trial is designed to determine if either regimen is promising enough to be pursued in a subsequent phase III study. This selection will be primarily based on whether there is improvement in disease-free survival relative to similar patients treated on the chemoradiation arm of the completed intergroup trial RTOG 9501.

Using the method of Dixon and Simon,<sup>43</sup> 104 analyzable patients are required for each arm to detect a  $\geq 33\%$  reduction in the failure rate (for DFS) as compared to RTOG 9501 with 80% statistical power (one-sided 0.05). This equates to an improvement in the two-year DFS rate from 53.9% (observed in RTOG 9501) to 66.1%.

Secondary considerations are patient tolerance and acute toxicity. Tolerability will be defined as having received  $\geq 90\%$  of the protocol radiation dose to the primary,  $\geq 4$  cycles of C225, and  $\geq 4$  cycles of cisplatin or docetaxel. In RTOG 95-01, a chemoradiation program with cisplatin was evaluated in similar patients with high-risk, resectable tumors. Seventy-nine percent received

within 10% of the protocol radiation dose and at least 2 (of 3) doses of cisplatin. With 104 patients for each arm, we have a  $\geq 95\%$  (two-sided) confidence interval around the estimated tolerance rate for each of the two arms with margin of error  $\leq 9.6\%$ .

Each regimen will be monitored for excessive acute toxicity (defined as non-hematologic Grade 4 toxicity within 90 days of the start of radiation therapy or any Grade 5 toxicity) in the first 49 entries. In RTOG 9501, 13% of the evaluable patients experienced the above toxicity, and 2 (2%) treatment-related deaths were reported. For this study, we will assume a baseline rate of 15%, and a rate of acute toxicity  $> 30\%$  will be considered unacceptable.

Adjusting the sample size by 10% to account for patient ineligibility or loss, a total sample size of 230 will be required for the study.

### **13.3 Patient Accrual**

Patient accrual will not only come from RTOG institutions but also from institutions in other cooperative groups; ACOSOG has already agreed to participate in this trial. The patient accrual is projected to be 10 patients per month. At this rate, it will take approximately 29 months to reach the target accrual assuming that there will be little accrual during first six months while institutions are obtaining their IRB approvals. If the average monthly accrual is less than two cases after the initial six months, the study will be re-evaluated with respect to feasibility.

### **13.4 Randomization Scheme**

Patients will be randomized to two treatment regimens in order to avoid any patient selection bias. The treatment allocation scheme described by Zelen<sup>44</sup> will be used because it balances patient factors other than institution. Patients will be stratified by Zubrod and risk category (positive margins vs. high risk [i.e.  $\geq 2$  positive nodes or extracapsular extension]).

### **13.5 Toxicity Monitoring**

As mentioned above, the acute toxicity rate in this patient population is approximately 13%. For planning purposes, we assume a 15% acute toxicity rate. We wish to ensure that this treatment is tolerable and does not significantly increase acute toxicity. A toxicity rate of 30% is set as the highest acceptable rate. Fleming's One-Stage Multiple Testing Procedure<sup>45</sup> is utilized. Each regimen would be monitored as follows: If at least 8 patients (32%) demonstrate unacceptable toxicity among the initial 25 evaluable patients, or at least 12 (24%) among the initial 50 evaluable patients, or at least 23 (22%) among 104 evaluable patients (targeted sample size), the regimen would be considered to have an unacceptable toxicity profile. Analysis of the acute toxicity will be performed when the data are available for the first 25, first 50, and all patients entered. If the boundary for unacceptable toxicity is crossed in the initial 25 or 50 patients for a regimen, the study chairs will review all data pertaining to the events, and a recommendation will be made to the RTOG Research Strategy Committee for their consideration. The results of this review will determine the future course of action; accrual *may be* suspended for that regimen. If the boundary is crossed for the final analysis of the 104 evaluable patients, the associated regimen will be considered to have an unacceptable toxicity profile and would not be further tested in a phase III trial unless the RTOG Head and Neck Committee deems the efficacy results so positive as to warrant such toxicity. This monitoring plan has 0.97 probability of identifying a regimen with at least 30% unacceptable toxicity rate and 0.97 probability of accepting a regimen with no more than 15% unacceptable toxicity rate.

Total Number Entered	Rejected $H_a$ ( $p = 0.30$ ) # with toxicity $<$	Reject $H_0$ ( $p = 0.15$ ) # with toxicity $>$
25	3	8
50	11	12

### **13.6 Analysis and Reporting Plan**

**13.6.1** This study will be monitored by the Clinical Data Update System (CDUS) version 1.1. Abbreviated reporting of cumulative CDUS data will be submitted quarterly by electronic means. Reports are due January 31, April 30, July 31, and October 31.

#### **13.6.2 Interim Reports:**

Interim reports will be prepared every six months until the final analysis. In general, the interim reports include information about:

- patient accrual rate with a projected completion date for the accrual phase;
- institutional accrual;

- distribution of pretreatment characteristics of patients accrued;
- compliance rate of treatment delivery with respect to the protocol prescription;
- frequency and severity of toxicities.

### **13.6.3 Analysis and Reporting of Final Treatment Results:**

The analysis to report the final results of treatment will be undertaken when each patient has been potentially followed for a minimum of 2 years. The usual components of this analysis are:

- tabulation of all patients entered and any excluded from the analysis with reasons for exclusion;
- patient accrual rate;
- institutional accrual;
- distribution of the important baseline prognostic variables;
- compliance rate of treatment delivery with respect to the protocol prescription;
- frequency and severity of toxicities;
- observed results with respect to the endpoints described in Section 13.1.

Overall and disease-free survival will be estimated using the Kaplan-Meier method.<sup>46</sup> Local-regional control will be estimated using the method of cumulative incidence<sup>47</sup>, as this accounts for non-administrative censoring (i.e., death without local-regional failure). All failure time variables will be measured by the time interval from the date of registration to the date of the first failure. The one and two-year rates of local-regional control, disease-free and overall survival will be estimated along with 95% confidence intervals. The study was not designed to compare the efficacy of the two treatment programs against one another but rather each program will be tested against the RTOG 9501 chemoradiation arm. However, should both experimental arms demonstrate an improvement in disease free survival as compared to the RTOG 9501 chemoradiation arm, and the other factors (i.e. toxicity and tolerability) are not dissimilar, the RTOG will use statistical selection theory to choose which arm should be considered for further testing in a follow-up trial.<sup>48</sup> Briefly, its criterion is to select the treatment arm with the highest response regardless of how small or “non-significant” the advantage is over the other treatment arm.

### **13.7 Tumor Marker Evaluation**

In addition to the clinical endpoints, this study will also evaluate several tumor markers (EGFR [total and phosphorylated], pMAPK, pAKT, Stat-3, Ki-67, COX-2, cyclin B1 expression). Each marker will be considered dichotomous (i.e., present/absent or overexpressed/not overexpressed) and correlated with local-regional control and disease-free and overall survival using Cox proportional hazards models,<sup>49</sup> which will be stratified by the RTOG Recursive Partitioning Analysis (RPA) prognostic class.<sup>50</sup>

Because of the moderate number of failures expected, only very large differences in outcome can be detected with adequate statistical power. For this reason, all results will be considered hypothesis generating to be confirmed in a future study.

### **13.8 Inclusion of Women and Minorities**

In conformance with the National Institutes of Health (*NIH*) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have considered the two possible interactions *treatment by race and treatment by gender*. The study was designed to evaluate disease-free survival, the treatment tolerance rate, and acute toxicity under the assumption of the same rates across the genders and across the races. A statistical analysis will be performed to examine the possible difference between the genders and among the races. In RTOG 95-01, 84% of the patients eligible for this trial were male; 16% were female; 74% were white; 26% were non-white. For planning purposes, we assume 85% of patients entered into this protocol will be male, 15% female, 75% white, and 25% non-white. We will use a binomial distribution for the two-year DFS rate (success – alive without disease). For males we have a 95% confidence interval for the two-year DFS rate with margin of error  $\leq 10.4\%$ ; for females  $\leq 24.5\%$ ; for whites  $\leq 11.1\%$ ; for non-whites  $\leq 19.2\%$ . The following table gives the expected number of patients in each race and gender group:

**Gender and Minority Accrual Estimates**

Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	0	8	8
Not Hispanic or Latino	35	187	222
<b>Ethnic Category: Total of all subjects</b>	35	195	<b>230</b>
<b>Racial Category</b>			
American Indian or Alaskan Native	0	0	0
Asian	0	7	7
Black or African American	9	42	51
Native Hawaiian or other Pacific Islander	0	0	0
White	26	146	172
<b>Racial Category: Total of all subjects</b>	35	195	<b>230</b>

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## **APPENDIX IA**

### **RTOG 0234**

#### **SAMPLE CONSENT FOR RESEARCH STUDY**

#### **A PHASE II RANDOMIZED TRIAL OF SURGERY FOLLOWED BY CHEMORADIOTHERAPY PLUS C225 (CETUXIMAB) FOR ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK**

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, "Taking Part in Clinical Trials: What Cancer Patients Need To Know," is available from your doctor.

You are being asked to take part in this study because you have cancer of the head and neck.

#### **WHY IS THIS STUDY BEING DONE?**

A standard form of treatment for advanced head and neck cancer patients is surgery under general anesthesia followed by radiation therapy. However, some patients still experience recurrence of their cancer despite the surgery and radiation.

In this study, all participants will receive surgery and chemoradiation. All patients on this study will also receive weekly infusions of an agent called C225 (cetuximab). Patients will receive chemotherapy — cisplatin or docetaxel — depending on their treatment group.

C225 was approved in 2004 as a treatment for patients with colorectal cancer, but is an experimental treatment for patients with head and neck cancer. C225 is an agent from a new family of drugs that block certain chemical pathways that lead to tumor cell growth. C225 may delay tumor growth.

This study is being done because we do not know which of the radiation, C225, and chemotherapy combinations being studied may better control your cancer, or have fewer side effects, or prevent recurrence.

In addition, if you agree, laboratory tests will be performed on your tumor following surgery to analyze growth patterns that may help to predict and treat head and neck cancer patients in the future.

## **HOW MANY PEOPLE WILL TAKE PART IN THE STUDY**

Approximately 230 people will take part in this study.

## **WHAT IS INVOLVED IN THE STUDY? (8/27/04)**

If you agree to take part in this study, after your surgery, you will be randomized into one of the two treatment groups described below. Randomization means that you are put into a group by chance. A computer will determine into which treatment group you are placed.

### **Both Groups**

Radiation therapy and drug therapy will begin within 7 weeks of your surgery, when your doctors feel that you have healed adequately from your surgery. In general, most of your treatment will be done as an outpatient at your institution.

Before your first dose of C225, you will be given some medications through your vein to prevent an allergic reaction to C225. Then you will be given the first dose of C225 through your vein for approximately 2 hours. You will not receive chemotherapy or radiation therapy on the day you receive the first dose of C225.

Your blood pressure and overall physical condition will be closely monitored while you receive C225 and for at least one hour afterwards. If you have a severe allergic reaction to the first dose of C225 or any later doses, your doctor will treat you for the reaction, and you will not receive further treatment on this study. You and your doctor can discuss other treatments that you can receive off study.

If you tolerate the first dose of C225 well, the following week you will begin receiving radiation therapy, C225, and chemotherapy. You have an equal chance of being assigned to either of the two treatment groups of the study.

<b><u>Group 1</u></b>	
Radiation therapy	Once a day, five days a week, for six weeks; treatments take about 20 minutes
C225	Once a week before radiation and chemotherapy for 6 weeks; treatment takes about an hour
Cisplatin	Once a week before radiation therapy and after C225 for 6 weeks; treatment takes about an hour

<b>Group 2</b>	
Radiation therapy	Once a day, five days a week, for six weeks; treatment takes about 20 minutes
C225	Once a week before radiation and chemotherapy for 6 weeks; treatment takes about an hour
Docetaxel	Once a week before radiation therapy and after C225 for 6 weeks; treatment takes about 30 minutes

In addition, if you take part in this study, you will have the following tests and procedures:

Prior to Study Entry	<ul style="list-style-type: none"> <li>▪ History and Physical Examination by several doctors</li> <li>▪ Blood tests</li> <li>▪ Pregnancy test for women able to have children</li> <li>▪ CT/MRI of tumor</li> <li>▪ Chest x-ray</li> <li>▪ Evaluation of your teeth</li> <li>▪ Evaluation of your nutrition – Insertion of a feeding tube is strongly encouraged to make sure you get adequate nutrition during treatment because sores inside your mouth and throat will make chewing and swallowing difficult</li> </ul>
Weekly During Radiation Therapy	<ul style="list-style-type: none"> <li>▪ Physical exam</li> <li>▪ Blood Tests</li> </ul>
Every Three Weeks	<ul style="list-style-type: none"> <li>▪ Exam by Medical Oncologist</li> </ul>
Three Months from start of Radiation Therapy	<ul style="list-style-type: none"> <li>▪ Physical exam</li> <li>▪ Blood Tests</li> <li>▪ CT/MRI of tumor (If your doctor advises it)</li> <li>▪ Exam by Medical Oncologist (If your doctor advises it)</li> </ul>
Five Months from start of Radiation Therapy	<ul style="list-style-type: none"> <li>▪ Physical Exam</li> <li>▪ Blood tests (If your doctor advises)</li> <li>▪ CT/MRI of tumor</li> <li>▪ Exam by Medical Oncologist (If your doctor advises it)</li> </ul>
Follow-up Visits: Every three months for 2 years, then every six months for three years	<ul style="list-style-type: none"> <li>▪ Physical exam</li> <li>▪ Blood tests (If your doctor advises)</li> <li>▪ CT/MRI of tumor (If your doctor advises it)</li> <li>▪ Chest X-ray (once a year)</li> <li>▪ Exam by Medical Oncologist (If your doctor advises it)</li> </ul>

## **HOW LONG WILL I BE IN THE STUDY? (8/27/04)**

You will receive treatment for about 2 months. You will be seen in follow-up visits every 3 months for years 1 and 2 and every 6 months for years 3 through 6, for a total of 6 years of follow up.

The doctor may decide to take you off this study if it is in your medical best interest, your condition worsens, or new information becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped due to lack of funding or participation.

You can stop participating at any time. However, if you decide to stop participating in the study, we ask you to talk to the study doctor and your regular doctor first.

## **WHAT ARE THE RISKS OF THE STUDY?**

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs may be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the docetaxel, cisplatin, C225 and radiation therapy are stopped, but in some cases side effects can be serious or long lasting or permanent. You may experience some or all of the side effects listed below.

### **Risks Associated with Radiation Therapy to the Head and Neck**

#### **Very Likely**

- Sores in the mouth and/or throat which can be painful and make it very difficult to chew and or swallow foods
- Mouth dryness or changes in taste and/or smell that may be permanent
- Thick saliva
- Hoarseness
- Tanning or redness of the skin in the head and neck area being treated with radiation
- Ear pain and/or pressure
- Fatigue
- Weight loss
- Permanent hair loss in the area treated with radiation
- Loss of teeth, or cavities in the teeth, if strict dental care is not followed; hypersensitivity of teeth

#### **Less Likely, But Serious**

- Decrease in function of the thyroid gland that may require you to take thyroid replacement medicine to prevent you from feeling tired or sleepy
- Serious damage to the spinal cord, nerves in the neck, jawbone, voice box, skin, or other parts of the head and neck that may require a major operation to correct and, rarely, can even be life threatening
- Temporary pain or scarring around nerves in the shoulder that could cause numbness and/or weakness
- Breathing problems

- Difficulty with swallowing and eating for which you might need a long term or permanent feeding tube; possibility of inhaling food and/or liquids into the lungs – which could also result in pneumonia.
- Serious ear infections and/or hearing loss
- Damage to the spinal cord leading to permanent weakness and/or symptoms like a “stroke”
- Permanent hair loss (of the face/chin/neck)

### **Risks Associated with Cetuximab (C225)**

#### Very Likely

- Weakness
- Headache
- Fever
- Nausea and/or vomiting
- Diarrhea
- Dry skin
- Localized acne-like skin reactions

#### Less Likely

- Inflammation under fingernails and/or toenails, which can last for several months after C225 is stopped
- Mouth sores
- Chills
- Muscle aches
- Joint pain
- Reduced appetite, which could lead to weight loss
- Confusion, not being oriented
- Shortness of breath

#### Less Likely, But Serious

- Reduced white blood cell count which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily; this lowering of blood counts, if severe, can lead to need for treatment with antibiotics, transfusions, or hospitalization.
- Blood clots within a blood vessel in the legs or pelvis
- Seizure
- Coma
- Reduced kidney and/or liver function, which could lead to being hospitalized, or rarely, to death

#### Rare

- Inflammation of the lining of the brain

Cetuximab also may cause allergic reactions such as hives, itching, and/or skin rash. Some patients have had allergic reactions with the first dose of cetuximab, but some patients have had reactions with later doses. The allergic reactions also can be

severe, involving shortness of breath, wheezing, difficulty swallowing, lightheadedness, very low blood pressure, and rarely, heart attack and/or death.

Your condition will be closely monitored during doses of cetuximab and for at least one hour afterwards. If you have a severe reaction, your doctor will treat you for the reaction, and you will not receive further treatment on this study. If you have a delayed severe reaction after receiving cetuximab, you must immediately tell your doctor.

In addition, the combination of cetuximab with chemotherapy and radiation therapy could increase the likelihood and/or severity of the side effects of chemotherapy and radiation therapy.

### **Risks Associated with Cisplatin**

#### **Very Likely**

- Decrease in blood counts, which can lead to a risk of infection, decreased healing after surgery, and/or bleeding
- Anemia
- Loss of appetite and/or taste; metallic taste in your mouth
- Nausea and/or vomiting
- Fatigue
- Generalized loss of strength
- Hearing loss, ringing in the ears
- Loss of muscle or nerve function that may cause weakness or numbness in your hands and feet
- Loss of appetite and weight loss

#### **Less Likely**

- Allergic reactions (sweating, difficulty breathing, rapid heartbeat)
- Muscle cramps or spasm
- Facial swelling
- Loss of taste
- Loss of coordination
- Involuntary movement
- Restlessness

#### **Less Likely, But Serious**

- Decrease in the kidneys' ability to handle the body's waste, which may be permanent
- Decrease in liver function
- Another cancer called acute leukemia

## **Risks Associated with Docetaxel**

### **Very Likely**

- Decrease in blood counts, which can lead to a risk of infection, decreased healing after surgery, and/or bleeding
- Hair loss
- Weakness
- Loss of appetite
- Change in taste
- Inflammation of eye
- Fatigue, unusual sleepiness
- Mouth sores
- Muscle aches and/or joint pains
- Nausea and/or vomiting
- Headache
- Seizures
- Fever
- Allergic reaction that may cause rash, fever, swelling, chills, low back pain
- Bloating
- Diarrhea
- Numbness or tingling in the hands or feet

### **Less Likely, But Serious**

- Allergic reaction, which can cause difficulty breathing, irregular heartbeat, low blood pressure, and can even be life threatening
- Changes in your nails
- Liver damage
- Lung damage

## **Reproductive Risks**

This study may be harmful to a nursing infant or an unborn child. Enough medical information is not available to determine whether the study treatment administered to a pregnant woman causes significant risks to the fetus. If you are a woman able to have children and have not been surgically sterilized (tubal ligation or hysterectomy), you should have a pregnancy test before enrolling in this study. If you are unwilling to use adequate birth control measures while on treatment and for at least three months thereafter to prevent pregnancy, you should not participate in this study. If you should become pregnant while on study, you must tell your doctor immediately.

If you are a man able to father children, the treatment you receive may risk harm to an unborn child unless you use a form of birth control approved by your doctor. If you are unwilling to use adequate birth control measures while on treatment and for at least three months thereafter to prevent pregnancy, you should not participate in this study. If you suspect you have caused anyone to become pregnant, you must tell your doctor immediately.

## **ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with head and neck cancer in the future.

The benefit of C225, chemotherapy, and radiation therapy to patients with head and neck cancer is unknown. This treatment may keep your cancer from growing, and this may provide relief from symptoms and improve your quality of life. This treatment may improve control of your head and neck cancer. However, none of these benefits is guaranteed, and the effects of a combination of C225, chemotherapy, and radiation therapy may be no different or worse than chemotherapy or radiation therapy alone.

### **WHAT OTHER OPTIONS ARE THERE?**

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) once or twice a day radiation therapy; (2) chemotherapy that does not include the study drug (C225 is not available off study); (3) surgery; or (4) no treatment except medications to make you feel better. With the latter choice, your tumor may continue to grow and your disease may spread. These treatments could be given either alone or in combination with each other. There may also be other treatment trials in which you could participate.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments.

Please talk to your regular doctor about these and other options.

### **WHAT ABOUT CONFIDENTIALITY? (8/27/04)**

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI), Bristol-Myers Squibb, and ImClone Systems Incorporated (suppliers of C225), Aventis Pharmaceuticals (manufacturers of Taxotere® [docetaxel]), the American College of Surgeons Oncology Group (ACOSOG), and the Radiation Therapy Oncology Group (RTOG).

## **WHAT ARE THE COSTS?**

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems. You may find a National Cancer Institute Guide: “Clinical Trials and Insurance Coverage – a Resource Guide” helpful in this regard. You may ask your doctor for a copy, or it is available on the world wide web at <http://www.nci.nih.gov/ClinicalTrials/insurance> (and click on printable version).

The study drug, C225, will be provided free of charge by Bristol-Myers Squibb in collaboration with ImClone Systems Incorporated for the participants in this study. Every effort has been made to ensure that adequate supplies of C225, free of charge, will be available for all participants. If, however, this study drug becomes commercially available for head and neck cancer like yours while you are being treated, there is a possibility that you or your insurance company will be charged for future supplies.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for all other costs of treatment, continuing medical care, and/or hospitalization.

You will receive no payment for taking part in this study.

## **WHAT ARE MY RIGHTS AS A PARTICIPANT?**

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A group of experts in cancer of the head and neck from the RTOG Head and Neck Committee, the study chairs, and the RTOG study statistician will be reviewing the data from this research periodically throughout the study.

**WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?**

***(This section must be completed)***

For information about your disease and research-related injury, you may contact:

\_\_\_\_\_  
Name Telephone Number

For information about this study, you may contact:

\_\_\_\_\_  
Name Telephone Number

For information about your rights as a research subject, you may contact:  
*(OPRR suggests that this person not be the investigator or anyone else directly involved with the research)*

\_\_\_\_\_  
Name Telephone Number

**WHERE CAN I GET MORE INFORMATION?**

You may call the NCI's Cancer Information Service at  
**1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615.**

Visit the NCI's Web sites for comprehensive clinical trials information at  
<http://cancertrials.nci.nih.gov> or for accurate cancer information  
including PDQ (Physician Data Query) visit <http://cancernet.nci.nih.gov>.

**SIGNATURE**

**I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.**

**I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).**

\_\_\_\_\_  
Patient's Name

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Person Obtaining  
Consent

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

## APPENDIX IB

### RTOG 0234

#### SAMPLE CONSENT FORM FOR USE OF TISSUE FOR RESEARCH

#### A PHASE II RANDOMIZED TRIAL OF SURGERY FOLLOWED BY CHEMORADIOTHERAPY PLUS C225 FOR ADVANCED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK

##### ABOUT USING TISSUE FOR RESEARCH

You have had surgery to see if you have cancer. Your doctor has removed or will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care. We would like to keep some of the tissue that remains for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Your tissue may be helpful for research whether you do or do not have cancer.

If you are considered to be a surgery candidate after treatment on this study, we would also like to keep some of the tissue that is left over from the surgery.

The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

All possible methods will be used to ensure your privacy and confidentiality. Identifying information will be taken off anything associated with your tissue before it is given to a researcher. Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

##### THINGS TO THINK ABOUT

The choice to let us keep the left over tissue for future research is up to you. **No matter what you decide to do, it will not affect your care or your participation in the main study.**

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you

do not want us to use your tissue and then any tissue that remains will no longer be used for research; or, you may request that your tissue, if any remains, be returned to you or your designee.

In the future, people who do research may need to know more about your health. While \_\_\_\_\_ (doctor/institution) may give researchers reports about your health, your doctor/institution will not give researchers your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research. However, the research done with your tissue may help to develop new products in the future, or your tissue may be used to establish a cell line that could be patented and licensed. If this occurs, you will not be financially compensated.

## **BENEFITS**

The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

## **RISKS**

### Physical Risks

Most patients will heal satisfactorily after having surgery or a needle biopsy to remove tissue. Risks and side effects of a biopsy/surgery can include bleeding, pain, delayed healing, possible infection, and rarely, creation of an abnormal opening or passage.

### Social-Economic Risks

There is a very small chance that information from your health records could be incorrectly released. All possible methods will be used to protect your privacy and ensure confidentiality. Unless you have given your specific permission, your \_\_\_\_\_ (doctor/institution) will not release your personal results or information to third parties such as employers or insurers.

In the case of injury or illness resulting from participating in this research, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

## **MAKING YOUR CHOICE**

If you have any questions about the research involving your tissue/blood or about this form, please talk to your doctor or nurse, or call the institution's research review board at \_\_\_\_\_ (IRB's phone number).

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". **No matter what you decide to do, it will not affect your care or your participation in the main study.**

1. My tissue may be used for the research in the current study.

**Yes                  No**

2. My tissue may be kept for use in research to learn about, prevent, or treat cancer.

**Yes                  No**

3. My tissue may be kept for use in research to learn about, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

**Yes                  No**

4. Someone from \_\_\_\_\_ (doctor's office/institution) may contact me in the future to ask me to take part in more research.

**Yes                  No**

**Participant statement:**

I have read and received a copy of this consent form. I have been given an opportunity to discuss the information with my doctor/nurse, and all of my questions/concerns have been answered to my satisfaction. My answers above and my signature below indicate my voluntary participation in this research.

\_\_\_\_\_

Patient's Name

\_\_\_\_\_

Signature

\_\_\_\_\_

Date

**Witness statement:**

I have explained the information in this consent form to the patient and have answered any questions raised. I have witnessed the patient's signature.

\_\_\_\_\_

Name of Person Obtaining Consent

\_\_\_\_\_

Signature

\_\_\_\_\_

Date

## **APPENDIX II**

### **KARNOFSKY PERFORMANCE SCALE**

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

### **ZUBROD PERFORMANCE SCALE**

0	Fully active, able to carry on all predisease activities without restriction (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work (Karnofsky 70-80).
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 (Karnofsky 50-60).
3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).
5	Death (Karnofsky 0).

## APPENDIX III

### **AJCC STAGING SYSTEM HEAD & NECK, 6<sup>th</sup> Edition**

#### **STAGING-PRIMARY TUMOR (T)**

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

#### **PHARYNX**

##### **Nasopharynx**

- T1 Tumor confined to the nasopharynx
- T2 Tumor extends to soft tissues of oropharynx and or nasal fossa
  - T2a without parapharyngeal extension
  - T2b with parapharyngeal extension
- T3 Tumor invades bony structures and/or paranasal sinuses
- T4 Tumor with intracranial extension and/or involvement of cranial nerves, infratemporal fossa, hypopharynx, orbit, or masticator space.

##### **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
- T4a Tumor invades the larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible.
- T4b Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery.

##### **Hypopharynx**

- T1 Tumor limited to one subsite of hypopharynx and 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.**
- T4a Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus or central compartment soft tissue.
- T4b Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures.

#### **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 minor thyroid cartilage erosion (e.g., inner cortex).
- T4a 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 Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures.

## **APPENDIX III (Continued)**

### **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, or with impaired vocal cord mobility
- T3 Tumor limited to the larynx with vocal cord fixation, and/or invades paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex).
- T4a Tumor invades through 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 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 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 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.**

### **DISTANT METASTASIS (M)**

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

**APPENDIX III (Continued)**

**STAGE GROUPING Excluding Nasopharynx**

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

**STAGE GROUPING Nasopharynx**

Stage 0	T <sub>is</sub> , N0, M0
Stage I	T1, N0, M0
Stage IIA	T2a, N0, M0
Stage IIB	T1-T2a, N1, M0 T2b, N0-1, M0
Stage III	T1-T2b, N2, M0 T3, N0-2, M0
Stage IVA	T4, N0-2, M0
Stage IVB	Any T, N3, M0
Stage IVC	Any T, Any N, M1

## APPENDIX IV

### **MANAGEMENT OF DENTAL PROBLEMS IN IRRADIATED PATIENTS**

#### **Dental Care for Irradiated Patients**

Goals for a dental care program include:

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

#### **Preirradiation 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 which 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 post-irradiation surgery or other traumas. Conservative management should be tried first, though in more aggressive lesions a more radical approach may ultimately be necessary.

**APPENDIX V (8/27/04)**

**C225 (Cetuximab) CLINICAL SUPPLY SHIPMENT REQUEST TO INVESTIGATIONAL SITE**

Cetuximab will be shipped only to institutions that have identified a single individual for receipt of shipment.

For the initial shipment of Cetuximab, U.S. and Canadian institutions must email the shipment form for this study to [RTOG\\_BMS@phila.acr.org](mailto:RTOG_BMS@phila.acr.org) as soon as the individual responsible for the study agent has been identified and prior to registration of the institution's first case. (Fax 215-574-0300 if unable to email). Allow adequate processing time (7-10 days) before calling to randomize your first patient.

For Resupply Requests, email this form to [cetuximab.drug@bms.com](mailto:cetuximab.drug@bms.com). (Fax to 866-227-7229 if unable to email). For questions call 800-743-9224.

**NOTE: THE SHIPMENT FORM FOR THIS STUDY IS AVAILABLE AT**  
<http://www.rtog.org/members/protocols/0234/0234shipmentform.doc>