RADIATION THERAPY ONCOLOGY GROUP

RTOG 0234

INDEX (3/27/06)

Institution # _____

Institution #

RTOG 0234 ELIGIBILITY (11/17/05) CHECKLIST

_____ 7. Tissue/blood kept for cancer research?

_____ 8. Tissue/blood kept for medical research?

_____ 9. Allow contact for future research

_____ 20. Medical Oncologist

_____ 21. Specify Zubrod Perfor mance Status (0 vs. 1)

_____ 22. Specify Risk Category (Pos

1.0 INTRODUCTION

1.1 Background (3/16/05)

There are approximately 43,000 cases of head and neck squamous cell carcinoma diagnosed annually in the United States. Approximately two

c a t n i c ^{3} n e^{2} r

AJCC 1998 staging criteria); and radiation therapy fractionation (concomitant boost versus once-daily versus twice daily). Radiation therapy was administered from 6-7 weeks as once daily, twice daily, or concomitant boost. The planned radiation therapy regimen was chosen by

Caucasian. The most seriou4008dverse reactions Cassociated with cetuximab in combination with

Incidence of Selected Adverse Events (

Incidence of Adverse Events (

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.

1.10 Intensity-Modulated Radiotherapy (IMRT) [11/17/05]

The use of intensity-modulated radiotherapy (IMRT) is permitted (as part of Amendment 6 of the study) and will be recorded as a stratification variable. An increasing number of participating centers routinely implement this precision radiation technique to spare normal tissue. It is

- Serum pregnancy test, if applicable, within one week prior to study entry; urine dipstick test

5.0 REGISTRATION PROCEDURES (11/17/05, 2/2/06)

5.1 Pre-Registration Requirements for IMRT Treatment Approach

It is mandatory that the treating physician determine if IMRT will be used prior to the site

5.2.3 For the initial shipment of Cetuximab: **(11/17/05, 2/2/06)**
The Study Agent Shipment Form for this study is available on the RTOG web site, www.rtog.org, next to the protocol. **U.S. and Canadian institutions** must email the shipment form for this study to RTOG_BMS@phila.acr.org as soj-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 **only** if unable to email; **please write legibly**). Allow adequate processing time (7-10 days) before calling to randomize your first patient. Required regulatory documents (see Sections 5.1.1) must be received and approved by BMS and RTOG notified of this approval before drug can be shipped. **See Appendix V for the procedure for resupply requests.**

5.3 *Registration*

5.3.1 Online Registration **(11/17/05)**

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5.4 *Pre-Registration Requirements for ACOSOG Investigators* **(8/27/04)**

5.4.1 **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.

Two e-mails are generated and sent to the registering site and to ACOSOG: the Confirmation of Eligibility and the patient-specific calendar. The

6.1.6 (8/27/04) *ACOSOG Investigators*: ACOSOG Investigators must provide the name of the

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 isadose 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 to any volume larger than 0.03 cc (approximately equivalent to a 3x3x3 mm cube).

6.5 Localization, Simulation, and Immobilization for IMRT

6.5.1 *Immobilization*

Head and neck immobilization device(s) must

Unaccept-able		to give 95%	prescribed dose	prescribed dose		

event that a patient experiences an allergic/hypersensitivity or cytokill49eleasl49eaction, see Section 7.5.5.1 for proper management. **Patients should be instructed to49eport any delayed49eactions to4the investigator immediately.**

7.1.2 *Arm 1, Radiation Plus Weekly C225 Plus Cisplatin:*
Weeks 2-7: C225 at 250 mg/m

Quantities must be ordered in multiples of 24 (keeping in mind that each single-use 50-mL vial contains 100 mg of cetuximab at a concentration of 2 mg/mL and that you will need 7-9 vials for an initial dose, and 4-6 vials for weekly maintenance doses, dependent on patient's BSA). A suggested initial shipment is 24 vials. Allow 5 business days for shipment of drug from receipt of the C225 (Cetuximab) Clinical Supply Shipment Request form. The Drug Supply Shipment Form can be downloaded from the RTOG web site in WORD format.

All product will be shipped via Federal Express in a temperature-controlled container.

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 prot

7.5.5 **Cetuximab Special Instructions** **[11/27/05]** If cetuximab is omitted for more than four consecutive infusions for toxicity, d

[3/16/05] developing dermatologic toxicities while

Kies for review. Subsequent cases will be prepared and sent to Dr. Kies for review, in

All supporting source documentation, if applicab

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

in January and July and will appear on the instituti

11.2.1.4

12.2 Summary of Dosimetry Data Submission for IMRT (Submit to ITC; see Section 12.2.1) (2/2/06)

Item	Due

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).

13.4 Randomization Scheme (11/17/05)

Patients will be randomized to two treatment regimens in order to avoid any patient selection bias. The treatment allocation scheme described by Zelen[45] will be used because it balances patient factors other than institution. Patients will be stratified by Zubrod, risk category (positive margins vs. high risk [i.e. ≥ 2 positive nodes or extracapsular extension]), and use of IMRT (no vs. yes).

37non-administrative censoring (i.e., death without loca

19. Baselga J. New therapeutic agents targeti

37. Harari PM, Mehta MP, Ritter MA, Petereit DG. Clinical promise tempered by reality in the delivery of

APPENDIX IA

RTOG 0234

SAMPLE CONSEDT FOR RESEARCH STUDY

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

Approximately 230 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY? (11/17/05)

If you agree to take part in this study, after your surgery, you will be .2324 Twd 9

HOW LONG WILL I BE IN THE STUDY? (2/15/11)

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, then once a year for your lifetime.

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.

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

Less Likely
Á Inflammation under fingernails and/or toenails, which can lasttaiT000m -1.us ear i6i2 Tc
Á Weakness
Weakness
Á Headache Á
Á Á l6 0815.02 Tj/LT2 a/T-1.7 2.41r89025 0.0 0 nd a[ )-tTfTmFP ppnSFenÃFen
Á ð@ -ia IO ø &g
ƒ L253 9 Tj 27 W et Likely e a k n e s s

Cetuximab also may cause allergic reactions such as hives, itching, and/or skin rash. Some patients have had allergic reactions wit

after surgery, and/or bleeding
- Hair loss
- Weakness
    - Loss of appetite
    - Change in taste
    - Inflammation of eye
    -

and Insurance Coverage – a Resource Guide" helpful in this regard. You may ask your doctor for a copy, or it is available on the worlo .42 web at http://www.nci.nih.gov/ClinicalTrials/insurance

APPENDIX IB

RTOG 0234

SAMPLE CONSENT FORM

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 resu6ts 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 products in 12 0

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

Yes **No**

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;

APPENDIX III

AJCC STAGING SYSTEM
HEAD & NECK, 6th Edition

STAGING

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

both of which are available through local dental supply.

APPENDIX V11/17/05, 2/2/06)TT2 1 Tf-25.18.167..02003 Tw( )Tj0.8981 Tf-6.6047.1

APPENDIX VI (3/27/06) (7/17/07) (6/11/09)

Specimen Plug Kit and Instructions*

The Specimen Plug Kit contains a dermal needle and a shipping tube. **Institutions should NOT dispose of the Plug Kit but should ship it back to the RTOG Biospecimen Resource with their specimen(s).** Sites can call