INDEX (6/1/06)

RTOG Institution # _____

RTOG Institution # _____

RTOG 0522 **ELIGIBILITY CHECKLIST (6/1/06)**

Case # _____

RTOG Institution # _____

1.0 INTRODUCTION

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

The treatment of locally advanced (stage III-IV) HNSCC has been the subject of intensive investigation during the last two decades. Up to ten years ago, surgical resection, often followed by adjuvant radiotherapy, was the preferred therapy in most cases despite the resulting cosmetic and functional impairment affecting quality of life (QOL).

Attempting to improve therapy outcome, several radiobiologically sound, altered-fractionation regimens were designed and subjected to phase III testing. Collectively, clinical trials revealed that hyperfractionation and various accelerated fractionation regimens improved local-regional

[1] RTOG 90-03 was a RTOG and some trials, also surviv

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[2] There was no difference in the incidence of persistent grade 3 or grade 4 late toxicity among the arms at one year or longer follow up. Since hyperfractionation is much

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1.4 Clinical Studies of Cetuximab in Squamous Cell Carcinoma of the Head and Neck Cancer and Colorectal Cancer Efficacy (8/25/08)

1.4.1 *Squamous Cell Carcinoma of the Head and Neck*

The efficacy and safety of cetuximab in combination with radiation therapy was studied in a randomized, multicenter, controlled trial of 424 patients with locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) of the oropharynx, hypopharynx or larynx versus radiation therapy alone. In addition, cetuximab alone was studied in a single-arm, multi-center clinical trial in 103 patients with recurrent or metastatic SCCHN with documented progression within 30 days after 2-6 cycles of platinum-based chemotherapy.

1.4.2 *Colorectal Cancer*

The efficacy and safety of cetuximab plus best supportive care (BSC) were evaluated in a multicenter, open-label, randomized, clinical trial of 572 patients with EGFR-expressing, previously treated, recurrent, metastatic colorectal cancer versus BSC alone. The efficacy and safety of cetuximab alone or in combination with irinotecan were studied in a randomized, controlled trial (329 patients) and in combination with irinotecan in an open-label, single-arm trial (138 patients). Cetuximab was further evaluated as a single agent in a third clinical trial (57 patients). All trials studied patients with EGFR-expressing metastatic colorectal cancer, whose disease had progressed after receiving an irinotecan-containing regimen.

1.4.3 *Squamous Cell Carcinoma of the Head and Neck: Randomized, Controlled Trial*

The efficacy and safety of cetuximab were studied in combination with radiation therapy in a randomized, controlled trial of 424 patients with locally or regionally advanced squamous cell carcinoma of the head and neck versus radiation alone. 424 patients with Stage III/IV SCCHN of the oropharynx, hypopharynx, or larynx withc 0 Td2311 atients) and in 70ombinat

was 59 years, 63% were male, 98% were Caucasian, and 88% had baseline Karnofsky Performance Status 80. Approximately two-thirds had previously failed oxaliplatin treatment.

The efficacy of Erbitux® plus irinotecan or Erbitux® monotherapy, based on durable objective responses, was evaluated in all randomized patients and in two pre-specified subpopulations: irinotecan refractory patients, and irinotecan and oxaliplatin failures. In patients receiving Erbitux® plus irinotecan, the objective respons

Infusion reactions: Infusion reactions, which included pyrexia, chills, rigors, dyspnea, bronchospasm, angioedema, urticaria, hypertension, and hypotension occurred in 15–21% of patients across studies. Grades 3 and 4 infusion reactions occurred in 2–5% of patients; infusion reactions were fatal in 1 patient.

Infections: The incidence of infection was variable across studies, ranging from 13–35%. Sepsis occurred in 1–4% of patients.

Renal

Incidence of Selected Adverse Events Occurring in

stream molecules, i.e., mitogen-activated protein kinase (MAPK), protein kinase AKT, signal

six weeks and four months post-treatment.[31] In the proposed study, an eight to nine week interval was chosen, since dissection is techni

(FACT). If the EQ-5D is highly correlated with the FACT, depending on the specific questions of interest, it might prove to be an effective short form for collecting both QOL and utility data. Thus, the current study will employ the FACT-H&N, the EQ-5D, and the Performance Status Scale for Head and Neck Cancer (PSS-HN).

1.8.2 *The Performance Status Scale for Head and Neck Cancer (PSS-HN)*

- Magnesium < 0.9 mg/dl or > 3 mg/dl;
- Potassium < 3 mmol/L or > 6 mmol/L;
- Sodium < 130 mmol/L or > 155 mmol/L

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

3.2.10 Prior allergic reaction to the study drug(s) involved in this protocol;

3.2.11 Prior therapy that specifically and directly targets the EGFR pathway;

3.2.12 Prior severe infusion reaction to a monoclonal antibody.

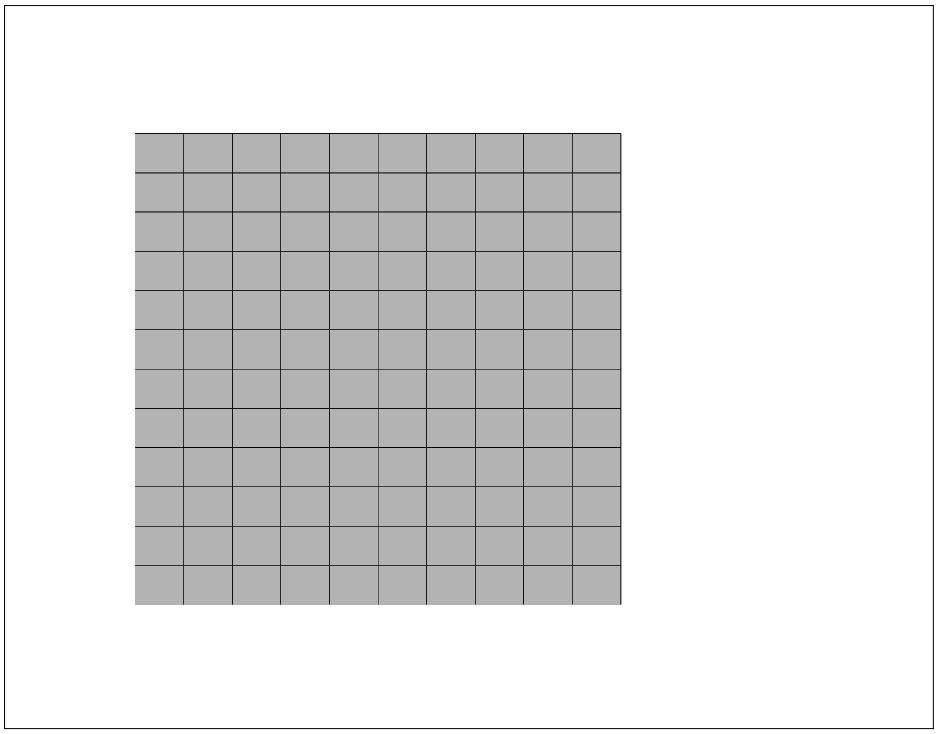
4.0 ADDITIONAL PRETREATMENT EVALUATIONS/MANAGEMENT

4.1 Additional Mandatory Pre-treatment Evaluations/Interventions

5.2.1.2 Next, the institution must successfully complete an IMRT "dry-run" or benchmark case with the ITC. This will require that the institution set up an FTP account for digital data submission by contacting the ITC (itc@castor.wustl.edu).

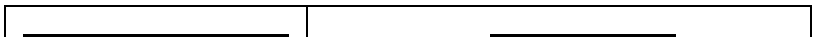
5.2.1.3 Finally, an IMRT phantom study with the Radiological Physics Center (RPC) at MD Anderson Cancer Center must be successfully completed (if the institution has not previously met this credentialing requirement on another RTOG IMRT study). Instructions for requesting and irradiating the phantom are availabn

compensated for by delivering additional BID treatments with a minimum interfraction



common radiation adverse events

7.0 DRU4(1928(THERAPY)]TJET84 726.6 116.22 1.08 refBT/TT0 1 Tf-0.0024



are recommended prior to subsequent doses, but at the Investigator's discretion, the dose of diphenhydramine or dexamethasone may be reduced.

(6/1/06) The medical staff must closely observe

7.3 Cetuximab (C225) [IND exempt]
7.3.1

7.3.8 *Handling and Dispensing of Investigational Product*

7.4.5.2 Treatment of Isolated Drug Fever

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

- **Makeup**: Rash can be covered with makeup; this should not make it worse (use a dermatologist-approved cover-up, e.g., Dermablend, or any other type of foundation). Remove makeup with a skin-friendly liquid cleanser, e.g., Neutrogena, Dove, or Ivory Skin Cleansing Liqui-Gel.
- **Moisturizers**: Use emollients to prevent and alleviate the skin dryness, e.g., Neutrogena Norwegian Formula Hand Cream or Vaseline Intensive Care Advanced Healing Lotion.
- **Sunlight**: It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.
- **Over-the-counter medications**: Over-the-counter acne vulgaris medications (e.g., benzoyl peroxide) are not advised. This rash is not like acne vulgaris and these treatments could make it worse.

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

7.5 Modality Review

The Medical Oncology Co-Chairs, Rita Axelrod, MD and Eric Sherman, MD, will perform a Drug Therapy Assurance Review of all patients who receive or are to receive chemotherapy in this

8.3 Surgical Quality Assurance Reviews

EQ-5D	X

12.0 DATA COLLECTION

12.1 Summary of Data Submission to RTOG (8/25/08)

Data should be submitted to:

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

Patients will be identified by initials only (first middl

12.3 Summary of Data Submission to ACRIN (8/25/08)

Note: Data submission is for sites participating in the PET component of this study. Sites must contact the PET Core Laboratory at petcorelab@phila.acr.org **prior** to submitting data for their **first** case (see Section 5(12for details). Instituti)Tj0.0004 Tc -0.0028 Tw 13.659 0 Td(ons should expect an e-mail response fr)Tj-0.00

from the addition of cetuximab differs by HPV status. A Cox regression model will be used with the following covariates: 1) assigned treatment; 2) HPV status; and 3) assigned treatment by HPV status interaction. The covariate for interaction will provide an estimate as to whether the treatment effect is similar for the HPV+ and the HPV- patients.

	1.50	1.75	2.00	2.25

[redacted]

RTOG 0522

treatment. The EQ 5D will be used to generate health utilities, which will then be used in deriving quality adjusted survivals. The utility scores lie between 0 “Worst health state” and 1 “Best health state”. It will provide two utility scores, one of which is from five-item index score and other from visual analogue scale (VAS), and both will be used in generating separate

patients on the 0522 experimental arm available for analysis. Treatment delivered per protocol prescription will be used to evaluate patient tolerability for the experimental arm (Arm 2). Tolerability will be measured by the percentage of patients who receive the following:

- Á Two chemotherapy cycles;
- Á The initial dose of cetuximab;
- Á At least five of the weekly cetuximab doses;
- Á Radiation therapy scored by the study chair as per protocol or with minor deviation.

The tolerability rate for the control arm without cetuximab (Arm 1) is approximately 82% based on two prior RTOG studies. For the 0522 experimental arm, 75% will be considered the minimum acceptable rate of tolerability. If the observed tolerability rate falls between 50% and 65%, then possible modifications to the regimen will be explored to improve the tolerability rate. If the observed rate is less than 50%, the tolerability rate will be considered unacceptably low, and a recommendation will be made to the RTOG DMC to discontinue the study. Assuming a ed will be conminimum accty rated Td(theen 50% and)c 0.05 -08Tw-17.132 -tion DMC to diy. Ata Twe

0532.

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your

- Fever
- Dry skin
- Localized acne-like skin reactions, rash, itching
- Low calcium in the blood
-

- ACRIN
- Qualified representatives of ImClone, makers of cetuximab
- Qualified representatives of Bristol-Myers Squibb, marketer and distributor of cetuximab

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing

Please circle your answer.

I choose to take part in the Quality of Life Study. I agree to fill out the 2 Quality of Life Questionnaires and answer some questions about my speech and my eating abilities.

APPENDIX II

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.

The neck dissection specimens must be divided and oriented into discrete anatomic levels in the operating room by the supervising surgeon and submitted for pathologic reviContinued( )Tjs08448 T 7282619 0 T[(ew8(6d(8(6dsepapere c(

APPENDIX V

Cervical Lymph Node Dissection: Documentation and Processing of the Specimen

Operative report

Buffy coat:

please *For* *oat,*

APPENDIX VIII (6/1/06)

RTOG 0522

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, a Word version of the initial 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 complete this form electronically and email the form to 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.

NOTE: The initial shipment form must be processed pfore t he institution is approved to receive drug. In addition, required regulatory documents (see Sections 5.4.1 and 5.4.2) must be received (pfore drug can be shipped.)]TJ0.1109

(see next page) for use only

____ if the RTOG web site is unavailable. Fax the form(s) to 215-574-0300. Forms must be legible.

DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) associated with this study must be submitted to the RTOG-0522 web page located on the CTSU registered member Web site.

APPENDIX IX (Continued) [12/9/10]

4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via AdEERS within 30 days of AML/MDS diagnosis.

DRUG PROCUREMENT (Section 7.0)

1. Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in section 7 of the protocol.

2. You may navigate to the drug forms on the CTSU Members' Web Site by select