

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0617/NCCTG N0628/CALGB 30609/ECOG R0617

A RANDOMIZED PHASE III COMPARISON OF STANDARD- DOSE (60 Gy) VERSUS HIGH-DOSE (74 Gy) CONFORMAL RADIOTHERAPY WITH CONCURRENT AND CONSOLIDATION CARBOPLATIN/PACLITAXEL +/- CETUXIMAB (IND #103444) IN PATIENTS WITH STAGE IIIA/IIIB NON-SMALL CELL LUNG CANCER

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This study is supported by the NCI Cancer Trials Support Unit (CTSUS). [9/22/09]

Institutions not aligned with the RTOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at <http://members.ctsu.org>
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the RTOG. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to RTOG Headquarters unless otherwise directed by the protocol. Do not send study data or case report forms to CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the RTOG. Please send query responses and delinquent data to the RTOG and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and RTOG Headquarters.

(4/8/10) The following Cooperative Group has endorsed this trial via the CTSU Endorsement Plus Option: NCCTG: Co-chair Steven Schild, MD. **NCCTG members will enroll patients to this study via the Cancer Trials Support Unit (CTSUS). Institutions holding dual memberships in NCCTG and RTOG may credit either Group for enrollments, provided the credited PI is a member of the credited Group.**

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RADIATION THERAPY ONCOLOGY GROUP

RTOG 0617/NCCTG N0628/CALGB 30609/ECOG R0617

A Randomized Phase III Comparison of Standard- Dose (60 Gy) Versus High-Dose (74 Gy) Conformal Radiotherapy with Concurrent and Consolidation Carboplatin/Paclitaxel +/- Cetuximab (IND #103444) in Patients with Stage IIIA/IIIB Non-Small Cell Lung Cancer

Schema (6/18/08)

| | | Concurrent Treatment | | Consolidation Treatment | |
|--|---|--|--|---|--------------|
| S T R A T I F Y | RT Technique 1. 3D-CRT 2. IMRT Zubrod 1. 0 2. 1 PET Staging 1. No 2. Yes Histology 1. Squamous 2. Non-Squamous | R A N D O M I Z E | Arm A | → | Arm A |
| | | | Concurrent chemotherapy: Carboplatin & Paclitaxel RT to 60 Gy, 5 x per week for 6 weeks | Consolidation chemotherapy: Carboplatin & Paclitaxel | |
| | | | Arm B | → | Arm B |
| | | | Concurrent chemotherapy: Carboplatin & Paclitaxel RT to 74 Gy, 5 x per week for 7.5 weeks | Consolidation chemotherapy: Carboplatin & Paclitaxel | |
| | | | Arm C | → | Arm C |
| | | | Cetuximab Loading Dose: Week 1, Day 1 then Concurrent chemotherapy, Carboplatin & Paclitaxel, and Cetuximab RT to 60 Gy, 5 x per week for 6 weeks | Consolidation therapy: Cetuximab and Carboplatin & Paclitaxel | |
| | | | Arm D | → | Arm D |
| | | | Cetuximab Loading Dose: Week 1, Day 1 then Concurrent chemotherapy, Carboplatin & Paclitaxel, and Cetuximab: RT to 74 Gy, 5 x per week for 7.5 weeks | Consolidation therapy: Cetuximab and Carboplatin & Paclitaxel | |

See Section 5.0 for credentialing requirements for radiation therapy. **(3/4/10) NOTE:** The site must complete RT pre-planning of the patient prior to registering the patient to determine if 74 Gy can be delivered within protocol specifications.

Patient Population: (See Section 3.0 for Eligibility) **[3/4/10]**

Newly diagnosed unresectable Stage III A or B non-small cell lung cancer (NSCLC); patients who present with N2 or N3 disease and an undetectable NSCLC primary tumor also are eligible; patients with supraclavicular or contralateral hilar adenopathy are ineligible.

Required Sample Size: 500

RTOG Institution # _____

RTOG 0617

ELIGIBILITY CHECKLIST (3/4/10)

Case # _____

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- _____ (Y) 1. Does the patient have histologically or cytologically documented NSCLC within 12 weeks of registration? (patients who present with N2 or N3 disease and an undetectable NSCLC primary tumor also are eligible.)
- _____ (N) 2. Has the tumor been totally resected?
- _____ (Y/NA) Has the patient had a nodal recurrence after surgery for an early-stage NSCLC and have the criteria in Section 3.1.2 been met?
- _____ (Y) 3. Is the patient IIIA/ IIIB with no evidence of distant metastasis (M0)?
- _____ (N) 4. Does the patient have supraclavicular or contralateral hilar disease? (The presence of supraclavicular or contralateral hilar disease would make the patient ineligible).
- _____ (Y) 5. Is the patient's Zubrod Performance Status 0-1?
- _____ (Y) 6. Were all pre-registration labs done within the specified timeframes and are the patient's lab values within the parameters of eligibility in Sections 3.1 and 4.1?
- _____ (Y) 7. Is the FEV1 best value \geq 1.2 liters/second or \geq 50% predicted?
- _____ (Y) 8. Were all the required pre-registration evaluations administered within the specified timeframes in Section 3.1, including CT/MRI of lung and upper abdomen through adrenal glands and MRI/CT of brain with contrast (MRI without contrast only permitted if patient has contrast allergy)?
- _____ (N) 9. Has patient had weight loss greater than or equal to 10% in last 4 weeks?
- _____ (Y/NA) 10. If the patient had exploratory thoracotomy, was it done at least 3 weeks prior to registration?
- _____ (N) 11. Is treatment planned for the patient with maximum dose \geq 66 Gy to the ipsilateral brachial plexus (this treatment plan would make the patient ineligible);
- _____ (N) 12. Has the patient had prior systemic chemotherapy and/or thoracic/neck radiotherapy for any reason for present cancer?
- _____ (N) 13. Has the patient had prior therapy that specifically and directly targets the EGFR pathway?
- _____ (N) 14. Has the patient had a prior severe infusion reaction to a monoclonal antibody?
- _____ (N) 15. Does patient have uncontrolled neuropathy of grade 2 or greater?
- _____ (N) 16. Is there evidence of malignancy within the past 3 years other than those stated in Section 3.2?
- _____ (N) 17. Does the patient have any severe co-morbidities as defined in Section 3.2?
- _____ (Y/NA) 18. If a women of childbearing potential, did the patient have a negative urine or serum pregnancy test within 72 hours prior to the start of treatment?
- _____ (Y/NA) 19. If a woman of childbearing potential or a sexually active man, is the patient willing/able to use medically acceptable forms of contraception?

(Continued on next page)

RTOG Institution # _____

RTOG 0617

ELIGIBILITY CHECKLIST (9/22/09)

Case # _____

(page 2 of 3)

_____(Y/N) 20. Is there evidence of pleural fluid on CXR and CT?

_____(Y) If yes, was a pleuracentesis done that confirmed the fluid to be cytologically negative?

_____(N) 21. If present, is the pleural effusion exudative?

_____(Y) 22. Was the patient evaluated by a Radiation Oncologist and Medical Oncologist and approved prior to the start of treatment?

The following questions will be asked at Study Registration:
IMRT CREDENTIALING IS REQUIRED BEFORE 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; Unknown)
- _____ 11. Gender
- _____ 12. Patient's Country of Residence
- _____ 13. Zip Code (U.S. Residents)
- _____ 14. Method of payment
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Calendar Base Date
- _____ 17. Registration/randomization date: This date will be populated automatically.

(Continued on the next page)

RTOG Institution # _____

RTOG 0617

ELIGIBILITY CHECKLIST (9/22/09)

Case # _____

(page 3 of 3)

- _____ 18. Medical oncologist
- _____ (Y/N) 19. Tissue kept for cancer research?
- _____ (Y/N) 20. Urine kept for cancer research?
- _____ (Y/N) 21. Blood kept for cancer research?
- _____ (Y/N) 22. Tissue kept for medical research?
- _____ (Y/N) 23. Urine kept for medical research?
- _____ (Y/N) 24. Blood kept for medical research?
- _____ (Y/N) 25. Allow contact for future research?
- _____ 26. Specify Radiation Technique (3D-CRT vs. IMRT)
- _____ 27. Specify Zubrod Performance Score (0 vs. 1)
- _____ (Y/N) 28. PET staging?
- _____ 29. Specify histology (squamous vs. non-squamous)
- _____ (Y) 30. I attest that I am willing to treat this patient according to the arm to which he/she is randomized, including the 74 Gy arm.
- _____ (Y/N) 31. Did the patient agree to participate in the Quality of Life component of the study?
- _____ If no, please specify the reason from the following:
1. Patient refused due to illness
 2. Patient refused for other reason: specify _____
 3. Not approved by institutional IRB
 4. Tool not available in patient's language
 5. Other reason: specify _____

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

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Disease Background

Lung cancer remains the leading cause of cancer death in the United States,¹ approximately 75-80% of all cases are non-small cell lung cancer (NSCLC). Of these, 30-40% are considered locally advanced comprising both Stage IIIA and IIIB in the current AJCC staging system. Using cancer incidence data from 2005,¹ we can predict that there will be approximately 162,460 cases of lung cancer this year, therefore between 40,000 and 50,000 patients will be diagnosed with locally-advanced NSCLC.

1.2 Rationale for Proposed Therapeutic Study (6/18/08)

The currently accepted "standard of care" for patients with locally-advanced NSCLC is radiation plus chemotherapy. In recent years, most research has focused on which chemotherapy drugs to use and how to integrate them with radiation therapy. Moreover, little attention has been given to optimizing the radiation therapy component. In particular, the nationally accepted standard radiation prescription dose has remained at the same level (60-63 Gy) for more than 30 years.²

The relative contributions of radiation therapy versus chemotherapy to patient survival are unknown. Curing patients with unresectable NSCLC is not possible without local disease control. One aspect of this study is to show that increased radiation doses will kill more cancer cells, which will result in better local control and survival. This hypothesis will be tested in this phase III trial.

Another aspect that will be explored is the benefit gained through the addition of cetuximab to chemoradiation (CRT). The epidermal growth factor receptor (EGFR) pathway is a validated therapeutic target in NSCLC.³ Agents, such as cetuximab that target the EGFR pathway, have radiation sensitizing properties and are being studied in combination with chemoradiation.⁴⁻⁶ Phase II results from RTOG 0324, a trial which combined cetuximab with conventional (63 Gy) CRT in patients with locally advanced NSCLC, met planned safety and efficacy endpoints.⁷ Although the toxicity was equivalent to that reported for conventional CRT, there was an improvement in median survival to 22.7 months. The results from RTOG 0324 warrant validation in a randomized setting; therefore, we hypothesize that the addition of cetuximab to conventional (60 Gy) CRT or high-dose radiation (74Gy) CRT will lead to improved survival.

This phase III randomized trial is important because local failure following concurrent chemotherapy and radiation therapy for patients treated for stage III NSCLC with conventional radiation doses approximates 85%.⁸ The 60 Gy dose level (2 Gy per fraction) was established by RTOG 7301 and remains the standard radiation therapy dose for this disease.² Local recurrence remains high in recent Phase III trials evaluating concurrent chemotherapy and radiation therapy. The results of these studies are discussed individually below.

There are now prospective data from three groups (see below) showing that 74 Gy is tolerable in the setting of concurrent chemotherapy. On the best arm of RTOG 9410 (using 1.8 Gy per fraction to 60 Gy), the median survival was 17 months.⁹ By escalating radiation dose to 74 Gy, phase II data suggest a median survival of 24 months.¹⁰⁻¹¹ We believe an increase in median survival will translate to an improved overall survival rate on the experimental arm of 74 Gy. As discussed below, there is phase II data demonstrating improved median survival with the addition of cetuximab to conventional CRT (see Section 1.9). We expect that patients on the 74 Gy experimental arms will experience increased acute toxicity. Therefore, we have planned quality of life measures that will assess toxicity on all arms. If the 74 Gy dose level or one of the cetuximab arms proves to be superior to the conventional 60 Gy dose, this will alter practice for patients with NSCLC. The present study is based upon a combination of the data from the studies described above. The addition of biologic therapy with cetuximab to the regimen hopefully will result in even better efficacy. Clearly this study is a logical next step in the attempt to find the optimal regimen for the treatment of advanced NSCLC.

1.3 The Importance of Adding Chemotherapy to Radiation

Conventional RT alone resulted in a median survival of 10 months and 5-year survival of 5%.² In order to improve the outcome of treatment, chemotherapy was added to RT. Multiple phase III trials demonstrated a survival advantage for the addition of chemotherapy to RT for NSCLC. The Cancer and Leukemia Group B (CALGB) reported that induction chemotherapy (cisplatin plus vinblastine) followed by conventional RT (60 Gy/30 fractions) resulted in significantly better survival than conventional RT alone. The median and 5-year survivals were 13.7 months and

17% for the combined therapy versus 9.6 months and 6% for RT alone (p=0.012).¹² Additional phase III trials confirmed that cisplatin (CDDP)-based chemotherapy plus RT produced better survival rates than RT alone.^{8, 13-14} Later phase III trials revealed that concurrent chemotherapy plus RT resulted in significantly better survival than sequential therapy.^{9, 15}

1.3.1 Concurrent Versus Sequential Chemoradiation

To date, three randomized phase III and two randomized phase II trials have been reported comparing concurrent versus sequential chemoradiation in locally advanced NSCLC¹⁵⁻¹⁷ (Table 1). Furuse, et al. from the West Japan Lung Cancer Group compared patients receiving two cycles of MVP (mitomycin, vindesine, and cisplatin) given every 28 days along with split-course radiation therapy (total dose of 56 Gy) with two cycles of MVP followed by continuous course radiation (total dose of 56 Gy). The concurrent arm demonstrated an improved 5-year survival rate (15.8% versus 8.9%, p=0.0001). A subsequent report demonstrated that the difference in survival was attributed to improved intrathoracic tumor control.¹⁸ Local control rates were 50% on the concurrent arm and 35% on the sequential arm (p=0.07). Criticisms of this trial include the split-course radiotherapy used in the concurrent arm and the lower doses of radiotherapy employed.

Table 1: Concomitant (C) versus sequential chemoradiation (SC) therapy

| Trial | Patients, <i>n</i> | Med. Survival, <i>mo</i> | | % Survival, <i>y</i> | | % Esophagitis (Gr. 3-4) | |
|-------------------------|--------------------|--------------------------|------|----------------------|-------|-------------------------|----|
| | | S | C | S | C | S | C |
| Furuse ¹⁵ | 314 | 13.3 | 16.5 | 8 | 16(5) | 4 | 23 |
| RTOG-9410 ¹⁶ | 400 | 14.6 | 17.1 | 12 | 21(4) | 5 | 26 |
| GLOT ¹⁷ | 212 | 13.9 | 15.6 | 24 | 35(2) | 3 | 17 |
| Czech ¹⁹ | 102 | 13.2 | 20.6 | 15 | 42(2) | 4 | 28 |
| BROCAT ²⁰ | 303 | 14.0 | 19.0 | — | — | 0 | 26 |
| LAMP ²¹ | 178 | 13.8 | 17.4 | 31 | 33(2) | 3 | 26 |

In the only phase III trial from North America that compared sequential versus concurrent chemoradiation, the RTOG reported the results of a three-arm phase III trial (RTOG 9410) that included 611 patients.¹⁶ This trial compared hyperfractionated radiation with cisplatin and etoposide, cisplatin plus vinblastine given sequentially with standard radiation therapy, and the same chemotherapy given concurrently with standard radiation. The median survival times were 14.6 months for the sequential arm, 17 months for the cisplatin/vinblastine with daily concurrent radiation arm, and 15.6 months for the cisplatin/etoposide with hyperfractionation arm. Four-year survival rates were higher in the concurrent arms (12%, 17%, and 21% for sequential therapy, concurrent cisplatin/etoposide and hyperfractionated radiation, and cisplatin/vinblastine/radiation arms, respectively). Consistent with the findings of Furuse, et al. the concurrent QD RT arm had superior survival to the sequential therapy arm (p=0.046). Local control rates were 59.2%, 65.6% and 67.4%% for the sequential, concurrent with QD RT, and concurrent with BID RT arms, respectively. Acute grade ≥ 3 toxicities were higher for concurrent therapies and highest for the concurrent/hyperfractionation group: sequential (30%), concurrent/daily (48%), and concurrent/hyperfractionation (62%). However, there was no difference in late toxicity between arms.

A third trial comparing concurrent versus sequential chemoradiation reported in 2001 also explored the use of consolidation chemotherapy.¹⁷ In this phase III trial from France, 212 patients were assigned to receive two cycles of cisplatin plus vinorelbine followed by 66 Gy radiation versus cisplatin/etoposide and concurrent radiation to 66 Gy followed by two cycles of consolidation chemotherapy with cisplatin and vinorelbine. Local control rates were improved with the concurrent regimen (40% vs. 24%), and median and two-year survival times were numerically superior (but not statistically superior) for the concurrent arm (13.8 vs. 15 months and 23% vs. 35%, p=0.5). However, the incidence of grade 3 esophagitis was significantly higher in the concurrent arm (28% vs. 6%), and the toxic death rate was high on both arms (9.5% on the concurrent arm and 5.6% on the sequential arm, p=not significant).

These three phase III trials consistently demonstrated longer survival for the concurrent arms, and this difference was significant in two of the three trials. Based on these results, concurrent chemoradiation has become the standard of care since 2001. It is important to note that toxicity is significantly greater with concurrent chemotherapy.

1.3.2 Rationale for Carboplatin and Paclitaxel

The cisplatin-based regimens used in the previously cited randomized trials are less commonly employed in primary chemoradiation therapy regimens today. Based on phase II studies, the most common chemotherapy agents utilized in current regimens include carboplatin and paclitaxel.²²⁻²⁴ This regimen was perceived to be more effective and less toxic than the older regimens. Unfortunately, in the only phase III study to date evaluating carboplatin and paclitaxel with radiation, the median survival time was only 11.4 months.²³ In addition, the toxicity profile appears no safer as the reported grade 3/4 esophagitis and pneumonitis rates are 26-46% and 17-22%, respectively, when carboplatin/paclitaxel therapy is used concurrently with RT. Nevertheless, phase II studies from the RTOG (0117), CALGB (Arm 1 of 30105), and North Carolina University groups are showing encouraging median survival times of approximately 24 months using these agents concurrently with 74 Gy.²⁵⁻²⁷ Since weekly administration of carboplatin and paclitaxel was given concurrently with thoracic irradiation in above studies, we chose to administer these agents in the same fashion for this Phase III trial.

1.3.3 Concurrent Chemoradiation Followed by Consolidation Chemotherapy

Four studies have evaluated the role of consolidation chemotherapy following the completion of chemoradiation in patients with stage III NSCLC.^{17,21,28-30} In the previously discussed phase III trial, the use of consolidation cisplatin/vinorelbine following the initial treatment of cisplatin/etoposide and concurrent radiation resulted in a numerically higher, but not statistically significantly higher survival time when compared to a sequential regimen.¹⁷ The LAMP trial, a randomized phase II study evaluating three different schedules of chemoradiation in this patient population, reported encouraging results for the use of consolidation therapy.²¹ Patients received either two cycles of carboplatin AUC 6 plus paclitaxel at 200 mg/m² followed by 63 Gy radiation (n=92) versus two cycles of the same chemotherapy followed by concurrent weekly carboplatin AUC 2 with paclitaxel 45 mg/m² with the same radiation (n=74) versus the same concurrent chemoradiation followed by two cycles of consolidation carboplatin and paclitaxel (n=92). The median survival times were 13, 12.8, and 16.1 months for the sequential arm, the induction followed by concurrent arm, and the concurrent followed by consolidation arm, respectively.

The Southwest Oncology Group (SWOG) trial 9019 utilized two cycles of consolidation cisplatin/etoposide following the use of concurrent cisplatin/etoposide and radiation.²⁹ The regimen was well tolerated, and the median survival time was approximately 15 months. These results appeared promising compared to historical controls. SWOG also conducted a subsequent trial utilizing the same strategy of consolidation therapy but substituted docetaxel as consolidation therapy in place of cisplatin/etoposide.³⁰ This trial was the first to evaluate the hypothesis that taxane sequencing utilizing a p53 independent agent may lead to improved outcomes. In this multi-institutional single-arm phase II study, 83 patients with unresectable stage IIIB NSCLC were treated with concurrent chemoradiation with cisplatin, etoposide, and thoracic radiotherapy followed by three cycles of docetaxel (75-100 mg/m² given every three weeks). Treatment was generally well tolerated, although two patients died from probable radiation-induced pneumonitis. The median progression-free survival was 16 months, median survival was 26 months, and three-year survival rate was 37%. Based on the promising data from SWOG trial 9504, the Hoosier Oncology Group recently conducted a randomized phase III trial comparing cisplatin/etoposide and concurrent radiation therapy with or without three cycles of consolidation docetaxel. The results of this trial are pending.

There are two basic approaches to giving chemotherapy with radiation. One utilizes full-strength (systemic) chemotherapy, whereas the second approach uses lower dose chemotherapy as a radiation sensitizer. A typical regimen using the first approach would be full-strength cisplatin/etoposide; the second common regimen is carboplatin/paclitaxel in reduced doses. Some oncologists feel that if the latter regimen is used, additional full-dose chemotherapy needs to be given. A recent CALGB trial (39801) to test this assertion is still maturing, but preliminary indications are that the additional chemotherapy could be of benefit.²⁴[19] Finally, some investigators maintain that additional systemic chemotherapy

should be given even if the concomitant component is full strength. There are advocates of all these approaches, but none of them have been tested head-to-head.³¹

1.4 Radiation Therapy for Stage III NSCLC

1.4.1 Radiation Dose and Fields

A curative strategy for locally advanced NSCLC needs to include adequate control of the thoracic disease. Local control with conventional radiotherapy is inadequate; using post-therapy bronchoscopic biopsies, Le Chevalier, et al. found pathological local regional failure rates of approximately 80%.³² Clinically detected local failure rates are lower, but still problematic.

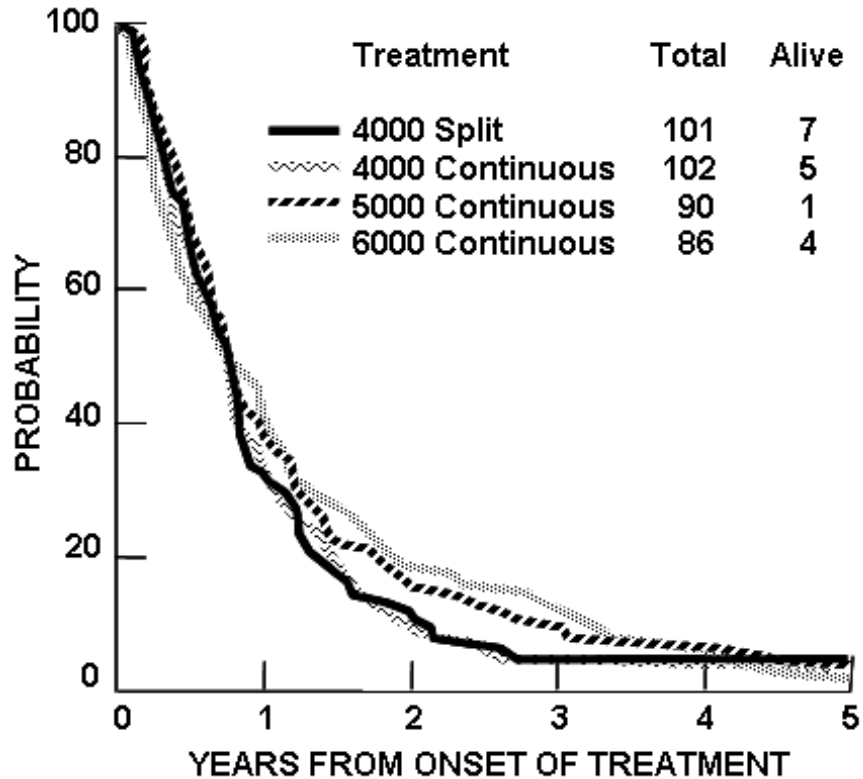


Figure 1: Redrawn survival curves from RTOG 73-01. 60 Gy became the standard dose for advanced NSCLC after this trial was published.

A significant radiation therapy trial begun more than 30 years ago (RTOG 73-01) established 60 Gy as the optimal standard radiation dose for locally advanced NSCLC (see Figure 1).³³ Based on this trial, doses from 55-66 Gy are still used in most studies. It is important to realize that the dose of 60 Gy was established as optimal before the advent of modern imaging. The first computed tomography scanner in the U.S. was installed in 1973 at the Mayo Clinic. Before the widespread use of computed tomography (CT), radiation planning was two-dimensional (2-D) based on plain x-ray. Most of the published phase III studies to date for lung cancer have used 2-D treatment planning. There have been many advances since RTOG 73-01 established 60 Gy as the standard of care. These include CT-based treatment planning, conformal radiation therapy, positron emission tomography (PET), and knowledge of tumor motion during radiation delivery. One major shift in treatment strategy was the irradiation of gross disease without prophylactic/elective nodal irradiation. There were several reasons for this philosophy. The dose of radiation commonly employed (60 Gy/30 fractions) was not enough to sterilize bulky epithelial tumors. Simply increasing the dose delivered to the large volumes of the chest included when irradiating lymph nodes prophylactically was believed to cause unacceptable toxicity. Additionally, irradiating clinically uninvolved nodal areas prophylactically did not appear rational when the gross tumor was infrequently controlled.

RTOG 9311 escalated dose in daily fractions to 70.9 Gy, 77.4 Gy, 83.8 Gy, and 90.3 Gy without concurrent chemotherapy.³⁴ The 90.3 Gy arm was too toxic. Doses of 77.4 and 83.8 Gy

appeared safe in patients with V_{20} values <25% and 25-36%, respectively. University of Michigan investigators performed a dose escalation trial that included 106 patients with stages I-III NSCLC treated with 63-103 Gy in 2.1 Gy fractions using three-dimensional (3-D) conformal radiation therapy.³⁵ Targets included only the primary tumor and any lymph nodes ≥ 1 cm. Eighty-one percent of patients received no chemotherapy. The median survival was 19 months. Multivariate analysis revealed weight loss ($p=0.011$) and radiation dose ($p=0.0006$) were significant predictors for overall survival. The five-year overall survival was 4%, 22%, and 28% for patients receiving 63-69, 74-84, and 92-103 Gy, respectively. Radiation dose was the only significant predictor when multiple variables were included ($p=0.015$). They concluded that higher dose radiation is associated with improved outcomes in patients treated within the range of 63-103 Gy.

Radiographic local control rates with concurrent chemotherapy and radiation therapy appear superior to those of radiation therapy alone or sequential chemotherapy followed by radiation therapy. As referenced previously, the 5 year local control rate on the concurrent QD arm of RTOG 9410 was 65.4%. In RTOG 9801, patients received 69.6 Gy in 1.2 Gy BID fractions and concurrent chemotherapy and were randomized to receive amifostine or not.³⁶ The 4 year local control rates on this trial were 51 % on the control arm and 49% on the amifostine arm (unpublished RTOG data). Therefore, even with concurrent chemotherapy and radiation therapy, local failure remains a significant problem.

1.4.2 Prospective Phase I/II Data Supporting 74 Gy Dose

Three groups have separately performed radiation dose escalation trials for this population and reported results supporting the safety of 74 Gy: the RTOG, the NCCTG, and the University of North Carolina. RTOG 0117 is a phase I/II radiation dose escalation protocol in the setting of concurrent chemotherapy.²⁵ Phase I accrued 17 patients, was completed in January 2004, and was reported at ASCO 2005. The phase II portion of the trial is ongoing. The phase I study began at a dose level of 75.25 Gy in 2.15 Gy daily fractions prescribed to the isocenter. Weekly chemotherapy consisted of carboplatin (AUC = 2) and paclitaxel (50 mg/m²). Three of the eight patients treated to 75.25 Gy developed dose-limiting pulmonary toxicity (one grade 5, two grade 3). The patient who experienced the grade 5 event initially developed radiation pneumonitis and was treated with oral prednisone. A few days later the patient developed evidence of an overwhelming fungal pneumonia which resulted in respiratory failure and death. Since this event may have been precipitated by the RP and need for oral prednisone, it was scored as a related event. Upon reviewing the patient's radiation treatment plan, the normal lung dose was within the tolerance of the study ($V_{20} < 35\%$). The other two patients with grade 3 RP recovered from the events. Nevertheless, because of toxicity concerns, the dose was de-escalated to 74 Gy in 2 Gy daily fractions. An additional nine patients were accrued, of whom one developed a grade 3 esophagitis. Thus, the maximum tolerated radiation dose (MTD), in the setting of concurrent chemotherapy, was determined to be 74 Gy. An additional 20 patients have accrued to the phase II portion. The median survival rate of patients treated with 74 Gy ($n = 24$) is 21.6 months (median follow-up for all patients: 8.9 months; median follow-up for live patients: Though the initial dose level of 75.25 Gy in 2.15 Gy daily fractions resulted in significant toxicity, the latter dose of 74 Gy has not. The reasons for the toxicity difference within this narrow window are unexplained. Other groups have confirmed the relative safety of the 74 Gy dose level.

The NCCTG reported phase I results of a radiation dose escalation study with concurrent chemotherapy at ASTRO 2005 (NCCTG 0028).³⁷ The study accrued 13 patients, who received concurrent weekly carboplatin (AUC = 2) and paclitaxel (50 mg/m²) and 3-D radiotherapy with no elective nodal radiation. Dose escalation began at a level of 70 Gy and was escalated in 4 Gy increments to determine the MTD. No dose-limiting toxicities (DLTs) were reported for the three patients who received 70 Gy. One DLT occurred in the six patients treated to 74 Gy. Two DLTs occurred in the four patients treated to 78 Gy. There were a total of 3 DLTs observed, Grade 3 pneumonitis ($n=2$) and 1 Grade 4 pneumonitis. Similar to the findings of RTOG 0117, the MTD of N0028 was determined to be 74 Gy. With a median follow-up of 28 months, the median survival time was 37 months.³⁸

University of North Carolina investigators reported a phase I/II study that escalated radiation dose to 74 Gy from a starting dose of 60 Gy.³⁹ Limited elective nodal radiation was administered, and all patients received induction chemotherapy before concurrent

chemoradiation therapy. Chemotherapy consisted of induction carboplatin (AUC = 6) and paclitaxel (225 mg/m²) for two cycles followed by concurrent chemoradiation. During radiation therapy, weekly carboplatin (AUC =2) and paclitaxel (45 mg/m²) were given. Three-dimensional conformal radiation therapy (3DCRT) was delivered in 2 Gy fractions to totals of 60 Gy, 66 Gy, 70 Gy, and 74 Gy. With a median follow-up of 43 months, the median survival was 24 months. The overall survival rate was 50% at two years and 38% at three years. Based on this study, 74 Gy was judged to be safe in the setting of concurrent chemotherapy.

North Carolina investigators continued to escalate radiation dose in subsequent trials. Socinski, et al. reported results of a phase I study that escalated total radiation dose to 78 Gy, 82 Gy, 86 Gy, and 90 Gy, sequentially.⁴⁰ Patients on this study received induction chemotherapy (carboplatin AUC = 5, irinotecan 100 mg/m², and paclitaxel 175 mg/m² on days 1 and 22. Concurrent weekly chemotherapy consisted of carboplatin (AUC = 2) and paclitaxel (45 mg/m²) beginning with radiation therapy on day 43. These dose levels were achieved without significant DLT. Grade 3 esophagitis occurred in 16%. Three patients developed late esophageal strictures, two developed bronchial stenosis, and two had fatal hemoptysis. The estimated median survival was 24 months.

North Carolina investigators have reported the results of four sequential prospective phase I/II studies to assess the safety and feasibility of high-dose (74-90 Gy) 3DCRT in the setting of concurrent chemotherapy.²⁷ One hundred twelve patients have been accrued, with a median follow-up of 4.9 years for surviving patients. The median survival was 24 months (range 18-31 months). The one-, three-, and five-year overall survival rates were 69% (60-77%), 36% (27-45%), and 24% (16-33%), respectively. The relatively longer follow-up duration of this population provides information about late complication risks. Late complications (defined as grade 3 or greater occurring > 90 days after radiation therapy) occurred in 22% (25/112). Patients with complications appear to have longer survival than the overall group (p=0.007). Late complications included bronchial stenosis (n=3), fatal hemoptysis (n=2), tracheoesophageal fistula (n=1), esophageal stricture (n=7), myocardial infarction (n=5), pericardial disease (n=4), and bone fracture (n=6).

The CALGB recently reported preliminary results of a 2-arm phase II trial (CALGB 30105) treating Stage III patients with chemoradiotherapy with both arms using 74 Gy.²⁶ Patients received either induction carboplatin (AUC 6) and paclitaxel (225 mg/m²) followed by concurrent weekly carboplatin (AUC 2) and paclitaxel (45 mg/m²) during radiation versus induction carboplatin (AUC 5) and gemcitabine (1000 mg/m²) followed by concurrent gemcitabine twice weekly (35 mg/m²) during radiation. The trial enrolled 69 patients and was reported with a median follow up of 16.4 months. Median survival times were 24.2 months for the carboplatin/paclitaxel arm and 17 months for the carboplatin/gemcitabine arm. The median progression-free survival was 15.2 months. The gemcitabine arm was closed early due to 13% grade 5 pulmonary events.

The median survival of 24 months using 74 Gy appears favorable to the best arms of the phase II and III studies listed in Table 2.

Table 2: Background Phase I/II Trials supporting 74 Gy given with concurrent carboplatin and paclitaxel chemotherapy

| Phase III Trials (60-63 Gy) | Median survival in months | Phase I/II Trials (74 Gy) | Median survival in months |
|------------------------------|---------------------------|---------------------------|---------------------------|
| Furuse ¹⁵ | 16.5 | RTOG 0117[20] | 21.6 |
| RTOG 9410 ¹⁶ | 17.1 | NCCTG N0028 [33] | 37 |
| GLOT ¹⁷ | 15.6 | North Carolina[35] | 24 |
| Czech ¹⁹ | 20.6 | CALGB [21] | |
| BROCAT ²⁰ | 19.0 | - T/C/74 Gy | 24.2 |
| LAMP ²¹ | 17.4 | - Gem/C/74 Gy | 17 |
| NCCTG 94 24 52 ⁴¹ | 15.0 | | |

1.4.3 Radiation Therapy Technique: Volume, Portals, and Beam Arrangements

The optimal radiation field design for the treatment of advanced NSCLC is not known. There is general agreement that the radiation fields must cover the gross tumor volume (GTV) and allow for breathing if gating or other synchronization techniques are not used. Most investigators agree that the clinical target volume (CTV) extends beyond the GTV because of microscopic disease spread, but there is disagreement as to the likely magnitude of that spread. Also unknown is whether or not the so-called “uninvolved” mediastinal nodes should be treated. “Radiographically uninvolved” means that the lymph nodes are < 1 cm in short diameter. This does not mean that they do not harbor cancer, just that the rate of false-positive radiographic diagnoses increases sharply when lymph nodes are <1 cm.

The size and location of the primary tumor, areas of lymphatic drainage in the hilar and mediastinum, histologic type, and the equipment available determine the volume to be treated and the configuration of the radiation portals. Historically, treatment portals have been designed with a 2 cm margin around any gross tumor seen on posteroanterior radiographs and approximately a 1 cm margin around electively treated regional lymph node areas. When traditional portals are designed to cover potential lymphatic drainage, the following guidelines have been suggested:

Traditional Radiation Therapy Volumes:

- If the primary tumor is in an upper lobe, the ipsilateral supraclavicular region should be included in the treatment portal. The inferior margin of the portal should be 5-6 cm below the carina.
- If the primary tumor is located in a middle or lower lobe and no mediastinal lymphadenopathy is present, there is no need to treat the supraclavicular areas.
- If there is a gross upper mediastinal tumor demonstrated on the CT scan or established by mediastinoscopy, inclusion of the ipsilateral supraclavicular area within the treated volume is desired.
- The ipsilateral hilum is typically included and the contralateral hilum is never included in the irradiated volumes.
- Reduced volumes are irradiated to deliver higher doses to the primary tumor or grossly involved lymph nodes.

1.4.4 Three-Dimensional Conformal Radiation Therapy

With the advent of 3DCRT, traditional portals, target volumes, and beam arrangements have been questioned. Because of high local failure rates reported for NSCLC, one goal of 3DCRT is to increase the dose delivered to the gross tumor and/or minimize the dose to normal tissues. 3DCRT has several significant advantages: tumor and normal tissue delineation, image segmentation and display, accurate dose calculation, and the ability to manipulate beam

geometry and weighting through the forward planning process. The importance of improved target delineation cannot be overemphasized. Once patients are immobilized and CT scanned in the treatment position, the radiation oncologist can delineate the tumor and adjacent tissues in three dimensions, choose beam angles to maximize tumor coverage, and/or minimize normal tissues treated, alter beam weighting, and couch angles for non-coplanar beams. Modern treatment planning systems enable the fusion of complementary imaging modalities, such as PET or single-photon emission computed tomography (SPECT) to better delineate tumor to improve planning. Purdy, et al. have provided an excellent overview of 3DCRT for purposes of reference.⁴²

The International Commission on Radiation Units Report No. 50 guidelines for defining targets has been applied to the treatment of lung cancer.⁴³ The GTV is the primary tumor and any grossly involved lymph nodes. The CTV is the anatomically defined area thought to harbor micrometastasis (hilar or mediastinal lymph nodes or a margin around the grossly visible disease). The planning target volume (PTV) accounts for physiologic organ motion during treatment and the inaccuracies of daily setup in fractionated therapy. When 3-D planning is implemented with the goals of conformal high-dose delivery to the GTV and minimal dose to surrounding normal organs (especially lungs), unique portals and beam arrangements and beam weights result.

It is important not to exceed the maximum doses tolerated by normal critical structures such as lung, spinal cord, and heart. However, partial-volume normal tissue tolerances are not well understood. Special care should be exercised to restrict the radiation dose to these structures whenever possible. 3DCRT plan evaluation is more complex than 2-D isodose curve evaluation. Dose-volume histograms (DVHs) for all normal organs in the chest are evaluated for dose and volume of irradiation. DVH analysis is developing, and preliminary results indicate that we can predict the development of complications such as pneumonitis, leading to improved and more objective treatment planning.⁴⁴⁻⁴⁸ Two commonly employed predictors of radiation pneumonitis are mean lung dose (MLD) and the volume of normal lung exceeding 20 Gy (V_{20}). In general, MLD values of < 20 Gy and V_{20} values of < 37% produce acceptable rates of radiation pneumonitis.

1.4.5 Elective Nodal Irradiation

Before 3DCRT, standard radiation therapy practice in the United States was to deliver 40 to 50 Gy to the electively irradiated regional nodal areas (ipsilateral, contralateral, hilar, mediastinal, and, occasionally, supraclavicular areas) with additional 20 Gy delivered to the primary tumor through reduced fields. This was based on pathologic information regarding the high incidence of hilar and mediastinal node metastases in patients with NSCLC. Perez, et al.⁴⁹ in an analysis of protocol compliance in 316 patients in the RTOG 73-01 trial, reported that in patients with radiographically negative lymph nodes, survival was higher in the group with no protocol variations, who had adequate coverage of the hilar/mediastinal lymph nodes. However, the difference was not statistically significant ($p=0.35$).

As described previously, elective nodal irradiation has not been generally used in dose-escalating studies incorporating modern technology. Two major factors have changed since RTOG 73-01 established standard irradiation doses and volumes: the use of chemotherapy and the advent of 3DCRT based on modern imaging techniques.

For patients with stage I lung cancers, involved field-only radiation therapy is routine and reported elective nodal failure rates are low. Bradley, et al. reported on the results for 56 patients with stage I lung cancers.⁵⁰ The three-year cause-specific survival and local-regional control rates were 63% and 51%, respectively. Only 2 of 33 (6%) patients treated with local radiation fields alone suffered an elective nodal failure.

Elective nodal failure rates for stage III patients also occurred in <10% who received radiotherapy with elective nodal irradiation. Rosenzweig, et al. published results for a series of 171 patients with stages I-III NSCLC treated definitively with 3DCRT to involved field volumes, without elective nodal irradiation.⁵¹ Only 6.4% of patients suffered elective nodal failures, including 1% ipsilateral supraclavicular, 3% contralateral supraclavicular, 4% ipsilateral inferior mediastinal, and 1% contralateral inferior mediastinal failure rates. The RTOG reported results for RTOG 9311, a prospective radiation dose escalation study, for patients with stages I-III

NSCLC.³⁴ This was the first cooperative group study to omit elective nodal regions from the radiation fields. Isolated elective nodal failures occurred in < 8% of patients. Likewise, Senan, et al. reported similar low failure rates in untreated elective nodal areas in stage III patients.⁵²

Yuan, et al. recently reported the results of a randomized trial from China.⁵³ Two-hundred patients with inoperable stage III NSCLC were randomized to involved-field (IFRT) versus elective nodal radiation therapy (ENI) to doses of 68-74 Gy for IFRT or 60-64 Gy for ENI. Two cycles of cisplatin-based chemotherapy were delivered before and after radiation therapy. Radiation pneumonitis occurred more frequently in the ENI group, presumably due to the larger treatment volumes employed (39% vs. 17%, $p=0.044$). The local failure rates were also higher for the ENI group (49% vs. 41%). Only 7% of patients in the IFRT group developed elective nodal failures in untreated lymph nodes. The overall survival at 1, 2, and 3 years was 59.7%, 25.6%, and 19.2% for ENI group vs. 67.2%, 38.7, and 27.3% for IFRT ($P = 0.048$).

The explanation for these lower-than-expected elective nodal failure rates is two-fold. Incidental doses to the ipsilateral hilum, paratracheal, and subcarinal nodes approach 40-50 Gy when these regions are not intentionally irradiated.⁴⁷ Secondly, lung cancer patients suffer from multiple causes of competing mortality, including their cancer and underlying comorbid illness. Patients may die of local failure, distant failure, or intercurrent illness without detection of elective nodal failures.

The staging of regional lymph nodes has been greatly enhanced with the help of PET. The addition of PET to clinical mediastinal staging with CT has improved the sensitivity and specificity to the range of 90% in comparison to CT alone. More accurate clinical staging with PET allows the radiation oncologist to include involved hilar and mediastinal nodes that were not appreciated on the CT scan to reduce the probability of elective nodal failures. As the number of facilities with dedicated FDG-PET scanners, especially combined PET/CT units, increases, this technology will enhance accuracy in planning target volumes.⁵⁴

1.4.6

Normal Tissue Complication Probabilities of Intrathoracic Organs

Less controversial are normal tissue complication probabilities (NTCPs) for several intrathoracic organs. Most investigators agree that the V_{20} and MLD are the best metrics for determining risk of radiation pneumonitis.

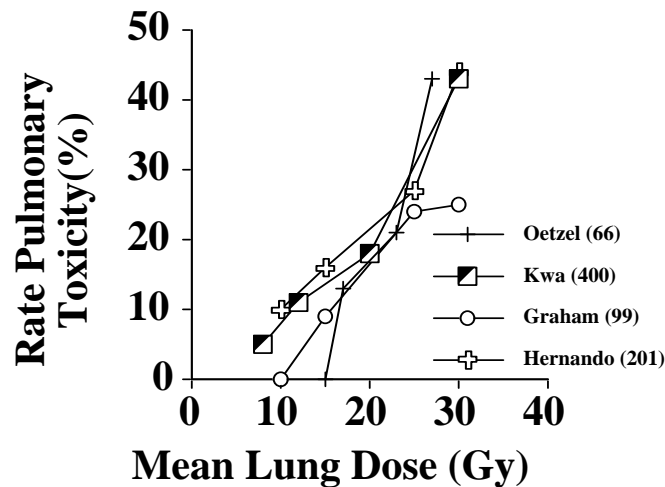


Figure 2: Pulmonary toxicity versus mean lung dose.⁵⁵

That is, if the V_{20} is kept $\leq 37\%$ or the MLD ≤ 20 Gy, the incidence of serious radiation pneumonitis appears to be low. Graham, et al. reported that the risk of grade 2+ pneumonitis was 0% when the V_{20} was $<22\%$, 7% when the V_{20} was 22-31%, 13% when the V_{20} was 32-40%, and 36% when V_{20} was $>40\%$ in an RT-alone cohort.⁴⁸ RTOG 9311 adopted a cut-off point of 37% to identify patients at high risk for radiation pneumonitis.³⁴ Some authors have suggested that values (i.e., V_{10} or V_{13}) may be important when using multiple fields.⁵⁶⁻⁵⁷ Therefore, we will track V_{10} and V_{13} values along with V_{20} and MLD.

Esophageal injury can be reduced by limiting the volume of esophagus in the radiation field or the mean esophageal dose.⁵⁸

Table 3: Esophageal injury after high-dose radiation therapy for NSCLC

| Author (# patients) | Incidence grade ≥ 3 | | Predictive factors |
|----------------------------|--------------------------|------|--|
| | Acute | Late | |
| Singh ⁵⁹ | 5% | 6% | Max/mean dose, for chemo/radiation therapy |
| Rosenman ¹¹ | 8% | 6% | Length 40-60 Gy |
| Maguire ⁶⁰ | 11% | 3% | Chemotherapy, L ₅₀ , V ₅₀ , circumference >80% |
| Komaki ⁶¹ | 37% | 16% | BID, concurrent chemotherapy |
| Werner-Wasik ⁶² | 13% | | NOT length, chemotherapy |

Spinal cord doses with 3-D planning have now become problematic. In the past, it was always felt sufficient to keep cord doses less than, say, 45 Gy, but 2-D planning did not include the contribution from scatter from radiation beams that are “off cord.” Thus, a distinction needs to be made between “direct” (in-field) dose delivered at high doses/fraction (typically 2 Gy+/fraction) and “scatter” dose delivered at low dose/fraction (typically 0.2 Gy/fraction). At any rate, after the conversion from uncorrected to corrected (for tissue inhomogeneity) dose calculations, doses of 50 Gy or below to the spinal cord appear safe.

The likelihood of brachial plexus injury certainly increases with increasing dose. Most investigators prefer to keep the brachial plexus under 66 Gy; therefore, patients with Pancoast tumors or supraclavicular node involvement will be excluded from this study.

“Acceptable” radiation doses to the heart have not been well studied in the setting of the treatment of NSCLC. Typically one does want to limit the dose to all or most of the heart to 40 Gy. We employ the dose limits of Emami, et al. for the heart (60 Gy to <1/3, 45 Gy to <2/3, and 40 Gy to <100% of the heart).⁶³

1.4.7 Radiation Dose Calculations

Unfortunately, most clinical trials in NSCLC that use radiation therapy have used “uncorrected” dose calculations that replace all body tissue by a water equivalent. For much of the body, this is a reasonable approximation, but not for the lungs, which are highly air containing. Based on the methodology proposed by Frank, et al. no modifications to the doses are required.⁶⁴ Using the authors methodology prescriptions are written such that 95% of the PTV gets 100% of the prescribed dose and the minimum PTV dose is 95% of the prescription dose or as close as possible. The authors also demonstrated that using this methodology there were little to no effects on doses to critical normal tissues. For this trial, prescribing 60 Gy to the PTV using heterogeneity corrections provides a similar dose as was given in RTOG 9410, which prescribed 63 Gy to the isocenter using homogeneous dose calculations.

1.5 Epidermal Growth Factor Receptor (6/18/08)

The epidermal growth factor receptor (EGFR) is a commonly expressed transmembrane glycoprotein of the tyrosine kinase growth factor receptor family. EGFR is expressed in many normal human tissues, and activation of this proto-oncogene results in overexpression in many types of human tumors. As a transmembrane glycoprotein, the extracellular domain of the EGFR is a ligand-binding site for transforming growth factor alpha (TGF α) and epidermal growth factor (EGF). Upon ligand binding, the intracellular domain of EGFR is activated, thereby triggering cellular mechanisms that regulate cell growth.⁶⁵

In vitro analysis using cells that express high numbers of EGFR and produce a ligand for these receptors has shown evidence that the EGFR may be activated through an autocrine pathway, thereby leading to the proliferation of cells in culture.⁶⁶ In order to inhibit proliferation of EGFR-rich cells, antagonists to EGFR have been produced that block the ligand-binding site; in this capacity, monoclonal antibodies to EGFR have been shown to inhibit the proliferation of cells that

produce both TGF α and EGF.⁶⁷ An antagonist directed against the ligand-binding site of EGFR offers an interesting approach to the therapy of cancers involving unregulated EGFR-dependent pathways. Among those cancers that overexpress EGFR are some of the most prevalent, including: esophageal 92%, head and neck 90%, colorectal 72%, prostate 65%, bladder 65%, ovarian 60%, cervical 60%, pancreatic 89%, renal cell 50%, and lung 50%.⁶⁸⁻⁷⁰ Prognosis for many of these malignancies is poor if not diagnosed at an early stage, and therapy for advanced disease is limited.

1.5.1 EGFR Inhibition and the Cell Cycle

The effects of EGFR blockade on cell cycle progression have been investigated in several human cell types, including DiFi colon adenocarcinoma cells, non-transformed breast epithelial MCF10A cells, A431 squamous epithelial carcinoma cells, and DU145 prostatic cancer cells. These studies suggest that blocking EGFR with monoclonal antibodies such as cetuximab leads to cell cycle arrest in G1 which is accompanied by a decrease in cyclin dependent kinase (CDK) 2 activity, and an increase in the expression of CDK inhibitor p27^{KIP1}.⁷¹⁻⁷² In addition to inducing G1-phase arrest, EGFR blockade also was shown to lead to cell death via apoptosis in DiFi colon adenocarcinoma cells.⁷³

1.5.2 Cetuximab

Cetuximab, a chimerized antibody of the IgG₁ subclass, was originally derived from a mouse myeloma cell line. The chimerization process resulted in an antibody with a relative affinity five-fold greater than the murine monoclonal antibody.⁷⁴⁻⁷⁶ Cetuximab blocks binding of EGF and TGF α to EGFR and inhibits ligand-induced activation of this tyrosine kinase receptor. Cetuximab also stimulates EGFR internalization, effectively removing the receptor from the cell surface for interaction with ligand.⁶⁷ Cetuximab was genetically engineered by cloning the heavy and light chains of M225 and adapting them for expression together with the constant regions of the human kappa light chain and human gamma 1 heavy chain.

Cetuximab binds specifically to the epidermal growth factor receptor (EGFR, HER1, c-ErbB-1) on both normal and tumor cells, and competitively inhibits the binding of EGF and other ligands, such as TGF α .⁷⁷ Binding of cetuximab to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor production.

In vitro assays and *in vivo* animal studies have shown that cetuximab inhibits the growth and survival of tumor cells that overexpress the EGFR. No antitumor effects of cetuximab were observed in human tumor xenografts lacking EGFR expression. In an *in vitro* study, both cetuximab and M225 inhibited A431 cell growth to a similar extent, i.e., 30% of the control. In addition, *in vivo* studies involving A431 tumor xenografts in nude mice suggested enhanced antitumor activity of cetuximab compared with M225. The enhanced antitumor activity was (postulated to be associated with the increased capacity of cetuximab to compete with ligand compared to M225.⁷⁴

1.5.2.1 In Vitro Cetuximab Tissue Binding Studies

A series of immunohistochemical (IHC) studies performed to characterize the binding of cetuximab to human and animal tissues demonstrated that cetuximab reacted positively and specifically with epithelium of human placenta.⁶⁸ Specific staining also was observed in normal epithelia of skin, digestive tract, urogenital system, and tonsillar crypts, and in squamous cell carcinomas and large cell carcinoma of the lung. Specific staining was absent in carcinomas originating from other organs, in melanomas, and in lymphoid tumors. In an interspecies study, human placental control tissues showed positive staining for cetuximab; however, no staining was observed in hepatic tissues of adult Cynomolgus and Rhesus monkeys, baboons, rodents, or canines. Specific details of these studies are available in the Investigator Brochure.⁶⁸

1.5.2.2 Human Pharmacokinetics

Cetuximab, administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy, exhibits nonlinear pharmacokinetics. The pharmacokinetics of cetuximab were similar in patients with squamous cell carcinoma of the head and neck (SCCHN) and those with colorectal cancer.⁷⁷ The area under the concentration time curve (AUC) increased in a greater than dose proportional manner as the dose increased from 20 to 400 mg/m². Cetuximab clearance (CL) decreased from 0.08 to 0.02 L/h/m² as the dose increased from 20 to 200 mg/m², and at doses > 200 mg/m², it appeared to plateau. The

volume of distribution (Vd) for cetuximab appeared to be independent of dose and approximated the vascular space of 2-3 L/m².

Following a 2-hour infusion of 400 mg/m² of cetuximab, the maximum mean serum concentration (C_{max}) was 199 µg/mL (range: 70-380 µg/mL) and the mean elimination half-life was 97 hours (range 41-213 hours). A 1-hour infusion of 250 mg/m² produced a mean C_{max} of 168 µg/mL (range 120-170 µg/mL). Following the recommended dose regimen (400 mg/m² initial dose/250 mg/m² weekly dose), cetuximab concentrations reached steady-state levels by the third weekly infusion with mean peak and trough concentrations across studies ranging from 168 to 235 and 41 to 85 µg/mL, respectively. The mean half-life was 112 hours (range 75-188 hours).

1.5.2.3 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. Potential immunogenic responses to cetuximab were assessed using either a double antigen radiometric assay or an enzyme-linked immunosorbant assay. Due to limitations in assay performance and sampling timing, the incidence of antibody development in patients receiving cetuximab has not been adequately determined. The incidence of antibodies to cetuximab was measured by collecting and analyzing serum pre-study, prior to selected infusions, and during treatment follow up. Patients were considered evaluable if they had a negative pre-treatment sample and a post-treatment sample. Non-neutralizing anti-cetuximab antibodies were detected in 5% (49 of 1001) of evaluable patients.⁷⁷ In patients positive for anti-cetuximab antibody, the median time to onset was 44 days (range 8-281 days). Although the number of sero-positive patients is limited, there does not appear to be any relationship between the appearance of antibodies to cetuximab and the safety or antitumor activity of the molecule.

The observed incidence of anti-cetuximab antibody responses may be influenced by the low sensitivity of available assays, inadequate to reliably detect lower antibody titers. Other factors which might influence the incidence of anti-cetuximab antibody response include sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to cetuximab with the incidence of antibodies to other products may be misleading.

1.6 Clinical Studies of Cetuximab in Squamous Cell Carcinoma of the Head and Neck and Colorectal Cancer Efficacy (6/18/08)

1.6.1 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.

1.6.1.1 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. Four hundred twenty-four patients with Stage III/IV SCCHN of the oropharynx, hypopharynx, or larynx with no prior therapy were randomized (1:1) to receive cetuximab plus radiation therapy (211 patients) or radiation therapy alone (213 patients). Stratification factors were Karnofsky Performance Status (60-80 versus 90-100); nodal stage (N0 versus N+); tumor stage (T1-3 versus T4 using 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. Starting 1 week before radiation, cetuximab was administered as a 400-mg/m² initial dose, followed by 250 mg/m² weekly for the duration of radiation therapy (6-7 weeks). Cetuximab was administered 1 hour prior to radiation therapy, beginning week 2.

Of the 424 randomized patients, 80% were male and 83% were Caucasian. The median age was 57 years (range 34-83). There were 258 patients enrolled in U.S. sites (61%) and 166 patients (39%) in non-U.S. sites. Ninety percent of patients had baseline Karnofsky Performance Status ≥ 80; 60% had oropharyngeal, 25% laryngeal, and 15%

hypopharyngeal primary tumors; 28% had AJCC T4 tumor stage. The patient characteristics were similar across the study arms. Fifty-six percent of the patients received radiation therapy with concomitant boost, 26% received once-daily regimen, and 18% twice-daily regimen.

The main outcome measure of this trial was duration of locoregional control. Overall survival was also assessed. Results are presented below:

Clinical Efficacy in LocoRegionally Advanced SCCHN

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

a CI = confidence interval

1.6.1.2 Single-Arm Trial

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 of a platinum-based chemotherapy regimen. Patients received a 20-mg test dose of cetuximab on Day 1, followed by a 400-mg/m² initial dose, and 250 mg/m² weekly until disease progression or unacceptable toxicity. The median age was 57 years (range 23-77); 82% were male; 100% Caucasian; and 62% had a Karnofsky performance status of ≥ 80. The objective response rate on the monotherapy phase was 13% (95% confidence interval (7%-21%). Median duration of response was 5.8 months (range 1.2-5.8 months).

1.7 Safety of Cetuximab in Clinical Studies (6/18/08)

1.7.1 Anticipated Adverse Events

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data below reflect exposure to cetuximab in 1373 patients with colorectal cancer or SCCHN in randomized phase 3 (Studies 1 and 3) or phase 2 (Studies 2 and 4) trials treated at the recommended dose and schedule for a median of 7 to 14 weeks.

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: Renal failure occurred in 1% of patients with colorectal cancer.

1.7.1.1 Squamous Cell Cancer of the Head and Neck

The data in the table below contains selected adverse events in 420 patients receiving radiation therapy either alone or with cetuximab for locally or regionally advanced SCCHN in Study 1. Cetuximab was administered at the recommended dose and schedule (400 mg/m² initial dose, followed by 250 mg/m² weekly). Patients received a median of 8 infusions (range 1–11).

**Incidence of Selected Adverse Events (≥10%) in Patients with
Locoregionally Advanced SCCHN**

| Body System Preferred Term | Cetuximab plus Radiation (n=208) | | Radiation Therapy Alone (n=212) | |
|--------------------------------|-------------------------------------|----------------|------------------------------------|----------------|
| | Grades 1 – 4 | Grades 3 and 4 | Grades 1 – 4 | Grades 3 and 4 |
| | % of Patients | | | |
| Body as a Whole | | | | |
| Asthenia | 56 | 4 | 49 | 5 |
| Fever ¹ | 29 | 1 | 13 | 1 |
| Headache | 19 | <1 | 8 | <1 |
| Infusion Reaction ² | 15 | 3 | 2 | 0 |
| Infection | 13 | 1 | 9 | 1 |
| Chills ¹ | 16 | 0 | 5 | 0 |
| Digestive | | | | |
| Nausea | 49 | 2 | 37 | 2 |
| Emesis | 29 | 2 | 23 | 4 |
| Diarrhea | 19 | 2 | 13 | 1 |
| Dyspepsia | 14 | 0 | 9 | 1 |
| Metabolic/Nutritional | | | | |
| Weight Loss | 84 | 11 | 72 | 7 |
| Dehydration | 25 | 6 | 19 | 8 |
| Respiratory | | | | |
| Pharyngitis | 26 | 3 | 19 | 4 |
| Skin/Appendages | | | | |
| Acneform Rash ³ | 87 | 17 | 10 | 1 |
| Radiation Dermatitis | 86 | 23 | 90 | 18 |
| Application Site Reaction | 18 | 0 | 12 | 1 |
| Pruritus | 16 | 0 | 4 | 0 |

¹ Includes cases also reported as infusion reaction.

² Infusion reaction is defined as any event described at any time during the clinical study as “allergic reaction” or “anaphylactoid reaction”, or any event occurring on the first day of dosing described as “allergic reaction”, “anaphylactoid reaction”, “fever”, “chills”, “chills and fever”, or “dyspnea”.

³ Acneform rash is defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis”.

The incidence and severity of mucositis, stomatitis, and xerostomia were similar in both arms of the study.

1.7.1.2 Late Radiation Toxicity

The overall incidence of late radiation toxicities (any grade) was higher in cetuximab in combination with radiation therapy compared with radiation therapy alone. The following sites were affected: salivary glands (65% versus 56%), larynx (52% versus 36%), subcutaneous tissue (49% versus 45%), mucous membrane (48% versus 39%), esophagus (44% versus 35%), skin (42% versus 33%), brain (11% versus 9%), lung (11% versus 8%), spinal cord (4% versus 3%), and bone (4% versus 5%). The incidence of Grade 3 or 4 late radiation toxicities were generally similar between the radiation therapy alone and the cetuximab plus radiation treatment groups.

1.7.1.3 Colorectal Cancer

The following table contains selected adverse events in 562 patients receiving best supportive care (BSC) alone or with cetuximab monotherapy for metastatic colorectal cancer.⁷⁷ Cetuximab was administered at the recommended dose and schedule (400 mg/m² initial dose, followed by 250 mg/m² weekly).

| Incidence of Selected Adverse Events Occurring in $\geq 10\%$ of Patients with Advanced Colorectal Carcinoma¹ Treated with Cetuximab Monotherapy | | | | |
|---|---------------------------------------|---------------------------|------------------------------|---------------------------|
| Body System Preferred Term | cetuximab plus BSC (n=288) | | BSC alone (n=274) | |
| | Any Grades² | Grades 3 and 4 | Any Grades | Grades 3 and 4 |
| | % of Patients | | | |
| Dermatology | | | | |
| Rash/Desquamation | 89 | 12 | 16 | <1 |
| Dry Skin | 49 | 0 | 11 | 0 |
| Pruritus | 40 | 2 | 8 | 0 |
| Other-Dermatology | 27 | 1 | 6 | 1 |
| Nail Changes | 21 | 0 | 4 | 0 |
| Body as a Whole | | | | |
| Fatigue | 89 | 33 | 76 | 26 |
| Fever | 30 | 1 | 18 | <1 |
| Infusion Reactions ³ | 20 | 5 | | |
| Rigors, Chills | 13 | <1 | 4 | 0 |
| Pain | | | | |
| Abdominal Pain | 59 | 14 | 52 | 16 |
| Pain-Other | 51 | 16 | 34 | 7 |
| Headache | 33 | 4 | 11 | 0 |
| Bone Pain | 15 | 3 | 7 | 2 |
| Pulmonary | | | | |
| Dyspnea | 48 | 16 | 43 | 12 |
| Cough | 29 | 2 | 19 | 1 |
| Gastrointestinal | | | | |
| Constipation | 46 | 4 | 38 | 5 |
| Diarrhea | 39 | 2 | 20 | 2 |
| Vomiting | 37 | 6 | 29 | 6 |
| Stomatitis | 25 | 1 | 10 | <1 |
| Other-Gastrointestinal | 23 | 10 | 18 | 8 |
| Mouth Dryness | 11 | 0 | 4 | 0 |
| Infection | | | | |
| Infection without neutropenia | 35 | 13 | 17 | 6 |
| Neurology | | | | |
| Insomnia | 30 | 1 | 15 | 1 |
| Confusion | 15 | 6 | 9 | 2 |
| Anxiety | 14 | 2 | 8 | 1 |
| Depression | 13 | 1 | 6 | <1 |

¹ Adverse reactions occurring more frequently in cetuximab treated patients compared with controls.

² Adverse events were graded using the NCI CTC, V 2.0.

- ³ Infusion reaction is defined as any event (chills, rigors, dyspnea, tachycardia, bronchospasm, chest tightness, swelling, urticaria, hypotension, flushing, rash, hypertension, nausea, angioedema, pain, pruritus, sweating, tremors, shaking, cough, visual disturbances, or other) recorded by the investigator as infusion related.

BSC = best supportive care

The most frequently reported adverse events in 354 patients treated with cetuximab plus irinotecan in clinical trials were acneform rash (88%), asthenia/malaise (73%), diarrhea (72%), and nausea (55%). The most common Grade 3/4 adverse events included diarrhea (22%), leukopenia (17%), asthenia/malaise (16%), and acneform rash (14%).

Additional safety information in patients with colorectal cancer is available in the Investigators Brochure.⁶⁸

1.7.2 Infusion Reactions

Serious infusion reactions, requiring medical intervention and immediate, permanent discontinuation of cetuximab included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, and/or cardiac arrest.⁷⁷ Severe (NCI CTC Grade 3 and 4) infusion reactions occurred in 2–5% of 1373 patients in clinical trials, with fatal outcome in 1 patient.

Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines.

Monitor patients for 1 hour following cetuximab infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (e.g., epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Monitor longer to confirm resolution of the event in patients requiring treatment for infusion reactions.

Immediately and permanently discontinue cetuximab in patients with serious infusion reactions.

1.7.3 Pulmonary Toxicity

Interstitial lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (<0.5%) patients receiving cetuximab in clinical trials.⁷⁷ Interrupt cetuximab for acute onset or worsening of pulmonary symptoms. Permanently discontinue cetuximab for confirmed ILD.

1.7.4 Dermatologic Toxicity

Dermatologic toxicities, including acneform rash, skin drying and fissuring, paronychia inflammation, and infectious sequelae (for example, *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, cheilitis) occurred in patients receiving cetuximab therapy. Acneform rash occurred in 76–88% of 1373 patients receiving cetuximab in clinical trials.⁷⁷ Severe acneform rash occurred in 1–17 % of patients.

Acneform rash usually developed within the first two weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event continued beyond 28 days. Monitor patients receiving cetuximab for dermatologic toxicities and infectious sequelae. Instruct patients to limit sun exposure during cetuximab.

1.7.5 Cetuximab Use in Combination with Radiation and Cisplatin

The safety of cetuximab in combination with radiation therapy and cisplatin has not been established. Death and serious cardiotoxicity were observed in a single-arm trial with cetuximab, radiation therapy, and cisplatin (100 mg/m²) in patients with locally advanced SCCHN.⁷⁷ Two of 21 patients died, one as a result of pneumonia and one of an unknown cause. Four patients discontinued treatment due to adverse events. Two of these discontinuations were due to cardiac events.

1.7.6 Hypomagnesemia and Electrolyte Abnormalities

In patients evaluated during clinical trials, hypomagnesemia occurred in 55% of patients (199/365) receiving cetuximab and was severe (NCI-CTC Grade 3 and 4) in 6–17%.⁷⁷ The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to months after initiation of cetuximab. Periodically monitor patients for hypomagnesemia, hypocalcemia, and hypokalemia, during and for at least 8 weeks following the completion of cetuximab. Replete electrolytes as necessary.

1.7.7 Cardiopulmonary Arrest

Cardiopulmonary arrest and/or sudden death occurred in 4 (2%) of 208 patients treated with radiation therapy and cetuximab as compared to none of 212 patients treated with radiation

therapy alone in a randomized, controlled trial in patients with SCCHN. Three patients with prior history of coronary artery disease died at home, with myocardial infarction as the presumed cause of death. One of these patients had arrhythmia and one had congestive heart failure. Death occurred 27, 32, and 43 days after the last dose of cetuximab. One patient with no prior history of coronary artery disease died one day after the last dose of cetuximab. Carefully consider use of cetuximab in combination with radiation therapy in head and neck cancer patients with a history of coronary artery disease, congestive heart failure, or arrhythmias in light of these risks. Closely monitor serum electrolytes, including serum magnesium, potassium, and calcium, during and after cetuximab.

1.8 Rationale for the Addition of Cetuximab to Concurrent Chemoradiation (6/18/08)

Several agents designed to block the effects of the EGFR have undergone clinical testing in patients with NSCLC. At the 2001 ASCO meeting, the results of a phase II trial utilizing the oral EGFR tyrosine kinase inhibitor OSI-774 were reported.⁷⁸ In that trial of patients with recurrent NSCLC, 19% of patients had received > 3 prior chemotherapy regimens. Overall, 1.8% of patients achieved a CR, 10.5% PR, and 26.3% SD with OSI-774. Importantly, the duration of PR's lasted 17-36 weeks. Subsequently, the results of a phase I study with OSI-774 in combination with docetaxel were reported at the 2002 ASCO annual meeting.⁷⁹ This study included patients with NSCLC and, as of the time of the report, minor response and stable disease had been observed in NSCLC patients.

Also, at the 2002 ASCO annual meeting, several studies of another EGFR tyrosine kinase inhibitor, ZD 1839, were reported.⁸⁰⁻⁸² Two of the trials, designated IDEAL 1 (n=210) and IDEAL 2 (n=216), evaluated the activity of oral, single agent ZD 1839 in patients with NSCLC.⁸² Patients on the IDEAL 1 trial had failed one or two prior regimens, at least one containing a platinum compound while patients on IDEAL 2 had failed two or more previous regimens containing platinum and docetaxel. Response rates for the IDEAL 1 trial were 18.4% with a dose of 250 mg/day and 19% with a dose of 500 mg/day. In terms of second and third line treatment, response rates were similar at 17.9% and 19.8%, respectively. Toxicity was milder with the 250 mg/day dose, primarily rash, diarrhea, pruritus, and dry skin. The conclusion from the IDEAL 1 trial was that ZD 1839 demonstrated clinically significant antitumor activity and a favorable safety profile. Response rates obtained with the IDEAL 2 trial were 11.8% (250 mg/day) and 8.8% (500 mg/day). The duration of tumor response ranged from 3 to 7+ months, and median survival was 6.1 months for the 250 mg/day group and 6.0 months for the 500 mg/day group. As with IDEAL 1, toxicity was mild in IDEAL 2, consisting mostly of diarrhea and skin rash. The results of IDEAL 2 indicated that ZD 1839 also had clinically significant antitumor activity in heavily pretreated patients with NSCLC. Additional evidence for the efficacy of single agent ZD 1839 in NSCLC came from a compassionate use study, in which potential benefit (partial response + minor response + stable disease) was observed in 26.6% of the patients enrolled.⁸¹

The question of whether overexpression of EGFR correlates with response to EGFR inhibiting therapies also has been examined. An exploratory analysis using tumor biopsies taken prior to treatment from patients enrolled in two phase II studies of gefitinib in advanced NSCLC did not reveal any evidence of a correlation between the levels of membrane EGFR expression as measured and tumor response.⁸³

Clearly the precedent has been set for the use of anti-EGFR therapy in NSCLC with the oral tyrosine kinase inhibitor compounds OSI-74 and ZD 1839, and it is a logical step to evaluate the activity of cetuximab in this disease. Baselga, et al. have reported on three phase I cetuximab studies in which a total of eight patients with NSCLC were given cetuximab, two as single agent therapy and six in combination with cisplatin.⁸⁴ Although results were not reported by disease state, patients in all three studies experienced disease stabilization and cetuximab-associated toxicity was minimal.

At the 2003 ASCO annual meeting, the results of several phase II studies were reported regarding the combination of cetuximab with chemotherapy.⁸⁵ In a phase I/II study in untreated metastatic NSCLC combining cetuximab with paclitaxel and carboplatin (cetuximab loading dose of 400 mg/m² then weekly 250 mg/m² maintenance; paclitaxel 225 mg/m² q 3 weeks; carboplatin AUC 6), 31 patients were accrued. The overall response rate (ORR) was 29% (9 patients), time to progression was 5.4 months, and the median survival was 15.7 months. The most common

toxicity was rash, with 9.7% (3 patients) having a grade 3/4 acne-like rash. The most common grade 3 toxicity was fatigue at 19.4% (6 patients).

A phase I/II study in untreated metastatic NSCLC combining cetuximab with gemcitabine and carboplatin accrued 35 patients and reported an ORR of 28.6% (10 patients); time to progression was 5.5 months, and median survival was 10.3 months.⁸⁶ The most common toxicity was rash at 80% (28 patients), with 20% (7 patients) experiencing a grade 3 acne-like rash. These studies demonstrated the feasibility of combining cetuximab with systemic chemotherapy in NSCLC. Both regimens had acceptable safety profiles, and encouraging clinical activity.

At ASCO 2005 a randomized phase II study comparing concurrent and sequential approaches in untreated metastatic NSCLC combining cetuximab with paclitaxel and carboplatin accrued a total of 225 patients, 106 in the concurrent arm and 119 in the sequential arm. The reported ORR (37% vs. 25%) and disease stabilization rates (75% vs. 69%) though not statistically significant favored the concurrent arm over the sequential arm. While the progression free survival (PFS) was identical between the two arms at 4 months there was a nonstatistically significant trend in MS favoring the concurrent arm (10 vs. 9 months).⁸⁷ The most common toxicity was a grade 3 acne-like rash at 12% and 10% for the concurrent and sequential arms respectively.⁸⁷

A randomized phase III trial, BMS-99, comparing the doublet of a taxane and carboplatin to that of the triplet of a taxane, carboplatin, and cetuximab in patients with chemo-naïve stage IIIB with malignant pleural effusion or stage IV NSCLC was presented at the 12th World Lung Conference in 2007.⁸⁸ This study accrued a total of 676 patients, 338 per arm, and was powered for PFS, not for survival. The primary endpoint was PFS and favored the experimental arm (4.4 months) over the standard arm (4.24 months) although this was not statistically significant. However, the difference in response rate was statistically significant favoring the experimental arm (25.7% vs. 17.2%). The addition of cetuximab to cytotoxic chemotherapy proved to be well tolerated. Survival data is not yet available.

In the Spring of 2008 the preliminary results of the FLEX trial were reported demonstrating a statistically significant survival benefit with the addition of cetuximab to chemotherapy versus chemotherapy alone (press release). The FLEX trial is a randomized phase III study that compared vinorelbine and cisplatin to the experimental arm of vinorelbine, cisplatin, and cetuximab in patients with untreated metastatic NSCLC. Approximately 1100 patients were accrued to this study. This is the first randomized trial to demonstrate a survival benefit in the metastatic setting from the addition of cetuximab to cytotoxic chemotherapy. A unique aspect of this trial was that all patients had to demonstrate immunohistochemistry evidence of EGFR expression in order to be eligible for enrollment on to the study. The results are to be presented at ASCO 2008.

The preliminary results of RTOG 0324, a phase II trial that evaluated the addition of cetuximab to chemoradiation (CRT) in patients with locally advanced NSCLC, were presented ASCO 2007. A total of 87 patients were evaluable for toxicity and RTOG 0324 demonstrated that cetuximab could safely be added to concurrent chemoradiation.⁷ The toxicity seen with the RTOG 0324 regimen is comparable to that seen with standard CRT with a 63% grade > 3 non-hematologic adverse event rate (see Table 1). The grade > 3 esophagitis and pneumonitis rates were 8% and 9% versus 28% and 16% for LAMP/ACR 427.²¹ Additionally, there have been phase I trials of chemotherapy, RT, and gefitinib (Iressa™) that have not had undue toxicities (Gefitinib is a small molecule inhibitor of EGFR, the same target affected by cetuximab).⁸⁹

In an unselected patient population, with a historical median survival of 16 months, the median survival for patients enrolled on RTOG 0324 was 22.7 months with a 2-year survival of 49%. This median survival is the best survival data that has been seen in this patient population with the exception of the SWOG 9504, with a median survival of 25 months and 2-year survival of 54%. The median survival achieved on this study also compares very favorably with the RTOG historical median survival and the precursor study to RTOG 0324, the locally advanced multimodality protocol (ACR 427), which with the same chemotherapy and radiation regimen as RTOG 0324 achieved a median survival of 16.3 months and a 2-year overall survival of 31%.²¹ Based on the promising data from RTOG 0324, further evaluation of the combination of cetuximab with chemoradiation is warranted.

Comparison of Grade >3 Non-Hematologic Events Between Two RTOG Studies

| Grade 3-5 non-hematologic toxicities | ACR 427 | | RTOG 0324 | |
|--|-----------|-----|-----------|-----|
| | No.of pts | (%) | No.of pts | (%) |
| Cardiac | 7 | 8 | 4 | 4 |
| Gastrointestinal | 32 | 35 | 14 | 15 |
| Pulmonary/upper respiratory | 15 | 16 | 17 | 18 |
| Neurology | 10 | 11 | 8 | 8.6 |
| Total Adverse Event Rate (All Events) | 60% | | 63% | |

1.8.1 CALGB Phase II Study with Cetuximab

The CALGB recently completed a phase II randomized study, CALGB 30407, comparing concurrent pemetrexed and carboplatin with and without cetuximab with higher doses of radiation therapy (70 Gy). Though the toxicity data are preliminary, the results have been submitted for ASCO 2008 and are available to support the addition of cetuximab to concurrent chemotherapy and 74 Gy arm of the proposed trial. CALGB's study enrolled 106 patients (54 in arm A and 52 in arm B) from September 2005 to December 2007. The preliminary toxicity data (percentage of \geq grade 3 adverse events) by arms (arm A/arm B) are as follows: neutropenia 36/37; febrile neutropenia 5/7, thrombocytopenia 30/34, nausea/vomiting 10/12, esophagitis 35/22, skin rash 3/23 and fatigue 22/18.90 One patient died of fatal hemoptysis. Thus, the addition of cetuximab to 70 Gy thoracic irradiation with concurrent chemotherapy (pemetrexed and carboplatin) does not appear to increase toxicity compared to the same regimen without cetuximab.

1.9 Health-Related Quality of Life (HRQOL)

The main toxicities from concurrent chemoradiation for lung cancer are esophagitis and pneumonitis. Both of these toxicities have been shown to be both volume and dose dependent. For example, McGuire, et al. found that the rate of severe esophagitis was related to the volume of esophagus receiving >50 Gy (V50).⁶⁰ Similarly, the volume of lung receiving >20 Gy (V20) or the median lung dose (MLD) are the best indices for determining the risk of radiation pneumonitis. [43] While increasing the radiation dose on the experimental arm of this randomized trial will hopefully improve local control and/or survival, it may also increase the treatment related toxicity, thereby decreasing HRQOL and limiting the ultimate benefit.

Why is it important to collect prospective HRQOL data? Why not simply collect the NCI-CTC toxicity information? More and more, studies are demonstrating a "disconnect" between physician and patient reported outcome (PROs). This was evident from RTOG 98-01, a phase III trial of amifostine, a radioprotector, in patients with stage III NSCLC receiving concurrent chemotherapy and hyperfractionated radiation. Movsas et. al. reported that amifostine did not significantly reduce severe esophagitis (\geq grade 3) as per the NCI-CTC criteria.³⁶ However, based on the prospective HRQOL instrument (EORTC-QLQ), there was a significant difference in the pain subscale by treatment arm (p=.015), favoring amifostine. Moreover, compared to controls, patients on the amifostine arm had less weight loss (p=.05) and reported significantly less difficulty swallowing during treatment per the patients swallowing diaries (p=.04), using an area under the curve (AUC) analysis. Importantly, patient related difficulty swallowing was significantly related to changes in the HRQOL dysphagia score (p=.03). Overall, RTOG 9801 demonstrated that the patient's evaluation of difficulty swallowing and pain provides critical information that is distinct from physician-related assessments. This "disconnect" illustrates the critical role of patient reported outcomes (PRO) in this setting. RTOG 9801 also demonstrated that the patient's swallowing diary was useful and a sensitive PRO.

There is another important reason to collect PRO data on this randomized trial. In a recent analysis based on data from 1450 patients treated on 9 prospective RTOG non-operative NSCLC studies activated during the 1990s, Movsas, et. al. reported that sociodemographic factors, even

more than treatment variables, were significant predictors of grade ≥ 3 pneumonitis and esophagitis.⁹¹ For example, on multivariate analysis, significant predictors for severe pneumonitis included having a married/live-in relationship ($p=0.0074$) or the presence of family/friends with cancer ($p=0.028$). One could hypothesize that, rather than being more prevalent, severe pneumonitis is more readily reported/diagnosed in those patients that have a stronger “voice” (for example, married/live-in, having family/friends). Similarly, White patients had higher rates of severe esophagitis. Incorporating patient reported outcomes (e.g. HRQOL) will prospectively capture this information directly from the patient perspective and thereby help avoid under-reporting of symptoms or toxicities.

In addition to collecting prospective HRQOL data, this study will incorporate a method to measure utilities for calculation of Quality-Adjusted Life Years (QALY). Utilities are the numerical judgments of the desirability of a set of outcomes and range from a value of 0 (representing death) to 1 (representing perfect health). Utilities can be measured by a variety of techniques, including the EQ-5D, which will be utilized in this study. QALYs are then calculated by multiplying the utility for a specific time period by the time period to arrive at the quality-adjusted survival. The ability to analyze quality adjusted survival will be critical in this study, particularly if, as predicted, the more intensive arm yields a better treatment outcome at the expense of increased toxicity and inferior quality of life.

The primary QOL hypothesis for this randomized trial is that patients on the more intensive chemoradiation arm (the higher radiation dose arm) will have clinically meaningfully lower QOL as measured by the lung cancer (LCS) subscale of the FACT-Trials Outcome Index (FACT-TOI) instrument. The primary time point for the analysis will be three months post completion of the concurrent chemoradiation. Moreover, beyond this subacute effect, it is expected that, due to the increased chronic effects of the more intensive dose arm, the lower QOL (as measured by LCS) will be maintained at longer follow-up time points as well (e.g., 1 and 2 years).

2.0 OBJECTIVES (6/18/08)

2.1 Primary objective:

- 2.1.1 To compare the overall survival of patients treated with high-dose versus standard-dose conformal radiation therapy in the setting of concurrent chemotherapy;
- 2.1.2 To compare the overall survival of patients treated with cetuximab versus without cetuximab in the setting of concurrent chemotherapy.

2.2 Secondary objectives:

- 2.2.1 To compare progression-free survival (PFS) and local-regional tumor control between high-dose versus standard-dose radiation therapy and between concurrent cetuximab versus no cetuximab;
- 2.2.2 To compare the toxicity of high-dose versus standard-dose conformal radiation therapy in the setting of concurrent chemotherapy with or without cetuximab;
- 2.2.3 To investigate the prognostic and predictive effects of gross tumor volume on overall survival;
- 2.2.4 To assess quality of life (QOL) between high-dose versus standard-dose conformal radiation therapy;
- 2.2.5 To correlate outcomes (survival, toxicity, QOL) with biological parameters;
- 2.2.6 To analyze the predictive value of pre-treatment SUV of PET scan in predicting survival, distant metastasis, and local-regional control in patients with stage III NSCLC treated with concurrent chemoradiotherapy with conventional radiation dose of 60 Gy and escalated dose of 74 Gy;
- 2.2.7 To explore biological markers to predict clinical outcome including survival, distant metastasis, local-regional control, quality of life including toxicity in patients with stage III NSCLC treated with conventional dose (60 Gy) and high dose (74 Gy) radiation therapy in the setting of concurrent chemotherapy with or without cetuximab;
- 2.2.8 To prospectively collect and bank tissue specimen, blood and urine samples for future biomarker analyses in predicting clinical outcome including survival, distant metastasis, local regional control, and quality of life in patients with stage III NSCLC treated with conventional dose (60) Gy and high dose (74 Gy) radiation therapy in the setting of concurrent chemotherapy with or without cetuximab;
- 2.2.9 To investigate associations between EGFR expression and toxicity, response, overall survival, and progression-free survival.

3.0 PATIENT SELECTION

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

3.1 Conditions for Patient Eligibility (10/29/10)

- 3.1.1** Pathologically proven (either histologic or cytologic) diagnosis of Stage IIIA or IIIB non-small cell lung cancer (NSCLC); excluding patients with N3 disease based on supraclavicular or contralateral hilar adenopathy, [according to AJCC Staging, 6th edition; see appendix III] within 12 weeks of registration; patients who present with N2 or N3 disease and an undetectable NSCLC primary tumor also are eligible.
- 3.1.2** Patients must be considered unresectable or inoperable; **Note:** Patients who have had a nodal recurrence after surgery for an early-stage NSCLC are eligible if the following criteria are met:
- Nodal recurrence must be N1 or N2; N3 is not eligible.
 - The initial primary must have been staged as T1-2, N0, M0.
 - The node must be biopsied within 12 weeks of registration.
 - The node must be measurable.
 - The patient must not have received prior chemotherapy or radiation for this lung cancer.
 - Prior curative surgery must have been at least 6 months prior to the nodal recurrence.
 - The exception to a prior invasive malignancy (Section 3.2.7) does not apply to the initial lung primary.
- 3.1.3** Stage III A or B disease, including no distant metastases, based upon the following minimum diagnostic workup are acceptable:
- 3.1.3.1** History/physical examination, including documentation of height, weight, BSA, and vital signs within 8 weeks prior to registration;
- 3.1.3.2** Computed tomographic (CT)/MRI imaging of the lung and upper abdomen through the adrenal glands within 6 weeks prior to registration;
- 3.1.3.3** An MRI of the brain with contrast (or CT with contrast if MRI is medically contraindicated) within 6 weeks prior to registration; **Note:** The use of intravenous contrast is required for the MRI or CT. An MRI without contrast is only permitted if the patient has a contrast allergy.
- 3.1.3.4** Whole-body FDG-PET or PET/CT or if no PET is available, a bone scan is required within 6 weeks prior to registration; **Note:** If a PET is done that shows clear adrenals and lungs, then a CT scan of chest only is permitted.
- 3.1.4** If a pleural effusion is present, the following criteria must be met to exclude malignant involvement (incurable T4 disease):
- 3.1.4.1** When pleural fluid is visible on both the CT scan and on a chest x-ray, a pleuracentesis is required to confirm that the pleural fluid is cytologically negative.
- 3.1.4.2** Exudative pleural effusions are excluded, regardless of cytology;
- 3.1.4.3** Effusions that are minimal (i.e. not visible on chest x-ray) that are too small to safely tap are eligible.
- 3.1.5** Patients must have measurable or evaluable disease.
- 3.1.6** Patients with post-obstructive pneumonia are eligible.
- 3.1.7** Patients must be at least 3 weeks from prior thoracotomy (if performed).
- 3.1.8** Zubrod Performance Status 0-1;
- 3.1.9** Age \geq 18;
- 3.1.10** PFTs including FEV1 within 12 weeks prior to registration; for FEV1, the best value obtained pre- or post bronchodilator must be \geq 1.2 liters/second or \geq 50% predicted.
- 3.1.11** CBC/differential obtained within 2 weeks prior to registration on study, with adequate bone marrow function defined as follows:
- 3.1.11.1** Absolute neutrophil count (ANC) \geq 1,800 cells/mm³;
- 3.1.11.2** Platelets \geq 100,000 cells/mm³;
- 3.1.11.3** Hemoglobin \geq 10.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb \geq 10.0 g/dl is acceptable.)
- 3.1.12** Serum creatinine within normal institutional limits or creatinine clearance \geq 60 ml/min;
- 3.1.13** Bilirubin must be within or below normal institutional limits;
- 3.1.14** AST and ALT $<$ 2.5 x the IULN;
- 3.1.15** Patient must sign study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (8/29/08)

- 3.2.1** N3 supraclavicular disease;

- 3.2.2 Patients for whom treatment is planned with a maximum dose of ≥ 66 Gy to the ipsilateral brachial plexus;
- 3.2.3 Greater than minimal, exudative, or cytologically positive pleural effusions;
- 3.2.4 Pancoast tumors;
- 3.2.5 Involved contralateral hilar nodes (i.e. greater than 1.5 cm on short axis or positive on PET scan);
- 3.2.6 $\geq 10\%$ weight loss within the past month;
- 3.2.7 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years; non-invasive conditions such as carcinoma in situ of the breast, oral cavity, or cervix are all permissible.
- 3.2.8 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable.
- 3.2.9 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
- 3.2.10 Prior therapy that specifically and directly targets the EGFR pathway;
- 3.2.11 Prior severe infusion reaction to a monoclonal antibody;
- 3.2.12 Severe, active co-morbidity, defined as follows:
 - 3.2.12.1 Significant history of uncontrolled cardiac disease; i.e., uncontrolled hypertension, unstable angina, myocardial infarction within the last 6 months, uncontrolled congestive heart failure, and cardiomyopathy with decreased ejection fraction.
 - 3.2.12.2 Transmural myocardial infarction within the last 6 months;
 - 3.2.12.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
 - 3.2.12.4 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before registration;
 - 3.2.12.5 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects;
 - 3.2.12.6 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.
- 3.2.13 Pregnancy 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.
- 3.2.14 Any history of allergic reaction to paclitaxel or other taxanes, or to carboplatin;
- 3.2.15 Uncontrolled neuropathy grade 2 or greater regardless of cause.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

Note: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

- 4.1 **Required Evaluations/Management (6/18/08)**
See Appendix II; note that failure to perform one or more of these tests may result in assessment of a protocol violation.
 - 4.1.1 The patient must be evaluated by a Radiation Oncologist and Medical Oncologist and must be approved to proceed prior to initiation of study treatment.
 - 4.1.2 Women of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to initiation of treatment.
- 4.2 **Highly Recommended Evaluations/Management (9/22/09)**
Note that these evaluations/interventions are highly recommended as part of good clinical care of patients on this trial but are not required.
 - 4.2.1 An EKG within 4 weeks prior to registration;
 - 4.2.2 It is recommended that baseline alk phos and glucose are collected and results documented.
 - 4.2.3 Formal nutritional assessment by a nutritionist;
 - 4.2.4 FDG-PET evaluations are not required for study entry, but are generally recommended for staging purposes.
 - 4.2.5 For endotracheal or endobronchial lesions, bronchoscopy is recommended.

- 4.2.6 Specimens for Translational Research (see Section 10 for details): tissue from pre-treatment biopsy, blood, and urine samples.
- 4.2.7 Patient-Reported Outcomes: Trial Outcome Index of the Functional Assessment of Cancer Therapy-Lung FACT-TOI and EQ-5D and Patient Swallowing Diary.

5.0 REGISTRATION PROCEDURES

5.1 Preregistration Requirements (3/4/10)

NOTE: THE SITE MUST COMPLETE RT PRE-PLANNING OF THE PATIENT PRIOR TO REGISTERING THE PATIENT TO DETERMINE IF 74 GY CAN BE DELIVERED WITHIN PROTOCOL SPECIFICATIONS.

5.1.1 Pre-Registration Requirements for IMRT Treatment Approach (9/22/09)

In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the Radiological Physics Center (RPC) web site. Visit <http://rpc.mdanderson.org/rpc> and select “Credentialing” and “Credentialing Status Inquiry”.

An IMRT phantom study with the RPC must be successfully completed (if the institution has not previously met this IMRT credentialing requirement). Instructions for requesting and irradiating the phantom are available on the RPC web site at <http://rpc.mdanderson.org/rpc/>; select “Credentialing” and “RTOG”. Upon review and successful completion of the phantom irradiation, the RPC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. Subsequently, RTOG Headquarters will notify the institution that the site can enroll patients on the study.

- 5.1.1.2 The institution or investigator must complete a new IMRT Facility Questionnaire, send it to RTOG for review prior to entering any cases, and/or set up a secure FTP account for digital data submission, both of which are available on the Image-Guided Center (ITC) web site at <http://atc.wustl.edu>. Upon review and successful completion of the “Dry-Run” test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients on the study.

5.1.2 Pre-Registration Requirements for 3DCRT Treatment Approach (3/9/09)

Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in 3DCRT Quality Assurance Guidelines may enter patients on to this study.

The new Facility Questionnaire (one per institution, available on the ATC web site at <http://atc.wustl.edu>) is to be sent to RTOG for review prior to entering any cases. Upon review and successful completion of a “Dry-Run” QA test, the ITC will notify both the registering institution and RTOG Headquarters that the institution has successfully completed this requirement. RTOG Headquarters will notify the institution when all requirements have been met and the institution is eligible to enter patients onto this study. Institutions that have previously enrolled patients on 3DCRT trials of this same disease site may enroll patients on this study without further credentialing.

5.2 Regulatory Pre-Registration Requirements (9/22/09)

- 5.2.1 **U.S. and Canadian institutions** must fax copies of the documentation below to the CTSU Regulatory Office (215-569-0206), along with the completed CTSU-IRB/REB Certification Form, http://www.rtog.org/pdf_file2.html?pdf_document=CTSU-IRBCertifForm.pdf, prior to registration of the institution’s first case:

- IRB/REB approval letter;
- IRB/REB approved consent (English and native language versions*)
*Note: Institutions must provide certification of consent translation to RTOG Headquarters.
- IRB/REB assurance number

5.2.2 Pre-Registration Requirements FOR CANADIAN INSTITUTIONS

- 5.2.2.1 Prior to clinical trial commencement, Canadian institutions must complete and fax to the CTSU Regulatory Office (215-569-0206) Health Canada’s Therapeutic Products Directorates’ Clinical Trial Site Information Form, Qualified Investigator Undertaking Form, and Research Ethics Board Attestation Form.

5.2.3 Pre-Registration Requirements FOR NON-CANADIAN INTERNATIONAL INSTITUTIONS

5.2.3.1 **For institutions that do not have an approved LOI for this protocol:**

International sites must receive written approval of submitted LOI forms from RTOG Headquarters prior to submitting documents to their local ethics committee for approval. See http://www.rtog.org/pdf_forms.html?members/forms=Intl_LOI_Form.doc

5.2.3.2 **For institutions that have an approved LOI for this protocol:**

All requirements indicated in your LOI Approval Notification must be fulfilled prior to enrolling patients to this study.

5.2.4 Pre-Registration Requirements for Shipment of Cetuximab and for Canadian Sites, Shipment of Paclitaxel (10/9/08)

5.2.4.1 **U.S. and Canadian Institutions:** All pre-registration requirements must be met before calling to register the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, www.rtog.org (next to the protocol). U.S. and Canadian institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified.

5.2.4.2 **(9/22/09) Non-Canadian International Institutions:** Please refer to your LOI Approval Notification.

Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study. Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document. After receipt of written approval of submitted LOI forms from RTOG Headquarters, Non-Canadian International institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF available on the RTOG web site, www.rtog.org (next to the protocol) and must submit the SASF and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300). This must be done prior to registration of the institution's first case.

5.3 **Registration**

5.3.1 **Online Registration (6/18/08)**

Patients can be registered only after eligibility criteria are met.

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

- The investigator and research staff must have completed Human Subjects Training and been issued a certificate (Training is available via <http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp>).
- A representative from the institution must complete the Password Authorization Form at 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 (<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.

(9/22/09) Institutions can contact RTOG web support for assistance with web registration: websupport@acr-arrs.org.

In the event that the RTOG web registration site is not accessible, participating sites can register a patient by calling RTOG Headquarters, at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask for the site's user name and password. This information is required to assure that mechanisms usually triggered by web registration (e.g., drug shipment, confirmation of registration, and patient-specific calendar) will occur.

6.0 RADIATION THERAPY (3/4/10)

NOTE: THE SITE MUST COMPLETE RT PRE-PLANNING OF THE PATIENT PRIOR TO REGISTERING THE PATIENT TO DETERMINE IF 74 GY CAN BE DELIVERED WITHIN PROTOCOL SPECIFICATIONS.

Questions regarding Radiation Therapy should be directed to Dr. Bradley, Dr. Schild, Dr. Bogart, or Dr. Dobelbower (preferably by e-mail or alternatively by phone).

Protocol treatment must begin within 4 weeks after patient registration to the trial.

6.1 Dose Specifications (3/4/10)

Note: See Section 7.0 for details of concurrent chemotherapy and cetuximab.

- 6.1.1** Patients on **Arm A** will receive treatment 5 days per week, in once daily fractions, 2 Gy per fraction. **The total dose will be 60 Gy in 30 fractions.** There are no field reductions. All fields must be treated daily and the entire PTV must be treated daily. On days when chemotherapy is given concurrently with RT, chemotherapy should be administered prior to RT.
- 6.1.2** Patients on **Arm B** will receive treatment 5 days per week, in once daily fractions, 2 Gy per fraction. **The total dose will be 74 Gy in 37 fractions.** There are no field reductions. All fields must be treated daily and the entire PTV must be treated daily. On days when chemotherapy is given concurrently with RT, chemotherapy should be administered prior to RT.
- 6.1.3** Patients on **Arm C** will receive treatment 5 days per week, in once daily fractions, 2 Gy per fraction. **The total dose will be 60 Gy in 30 fractions.** There are no field reductions. All fields must be treated daily and the entire PTV must be treated daily. On days when chemotherapy is given concurrently with RT, chemotherapy should be administered prior to RT. Patients on Arm C will also receive concurrent cetuximab.
- 6.1.4** Patients on **Arm D** will receive treatment 5 days per week, in once daily fractions, 2 Gy per fraction. **The total dose will be 74 Gy in 37 fractions.** There are no field reductions. All fields must be treated daily and the entire PTV must be treated daily. On days when chemotherapy is given concurrently with RT, chemotherapy should be administered prior to RT. Patients on Arm D will also receive concurrent cetuximab.
- 6.1.5** Normalization of the treatment plan will cover 95% of the PTV with the prescription dose. The minimum PTV dose must not fall below 95% of the prescription dose. All radiation doses will be calculated with inhomogeneity corrections that take into account the density differences within the irradiated volume (i.e., air in the lung and bone). The MTD will be quoted as the PTV minimum target dose. This dose will be for a point that is at least 0.03 cc (approximately 3x3x3 mm) in size. The maximum and minimum point doses (within the PTV) will be reported for points that have a volume of 0.03 cc. The maximum dose must not exceed a value that is 120% of the prescribed dose.
- 6.1.6** Variations of dose prescription: See Section 6.7.
- 6.1.7** Heterogeneous dose calculations: For purposes of this protocol, superposition/convolution dose calculation algorithms demonstrate agreement between planned versus delivered dose. Institutions with treatment planning software utilizing superposition/convolution dose calculation algorithms will need to complete a questionnaire and submit a digital "dry-run" test to the ITC. Institutions using alternative algorithms (i.e. Clarkson or pencil beam) will need to credential their treatment planning system by irradiating the Radiation Physics Center (RPC) lung

phantom. Doses falling within criteria established by the Medical Physics Committee will be deemed acceptable.

6.2 Technical Factors

6.2.1 Beam Energy: 6 - 18 MV are to be used.

6.2.2 Beam Shaping: Multi-leaf collimation (MLC) or individually-shaped custom blocks should be used to protect normal tissues outside of the target volume.

6.3 Localization, Simulation, and Immobilization

6.3.1 A volumetric treatment planning CT study will be required to define gross tumor volume (*GTV*), clinical target volume (*CTV*), and planning target volume (*PTV*)(see definitions below). Each patient will be positioned in an immobilization device in the treatment position on a flat table. Contiguous CT slices, having 3 mm thickness through the regions harboring gross tumor and grossly enlarged lymph nodes and 8-10 mm thickness of the remaining regions are to be obtained starting from the level of the cricoid cartilage and extending inferiorly through the entire liver volume. The *GTV*, *CTV*, and *PTV* and normal organs will be outlined on all appropriate CT slices.

6.3.2 A treatment planning FDG PET/CT scan (or FDG-PET alone) with the patient in the treatment position is encouraged for treatment planning. In the case where the PET/CT is obtained in the treatment position, the CT from this study may be used as the planning CT scan.

6.3.3 Intravenous (*i.v.*) contrast during the planning CT is optional provided a diagnostic chest CT was done with contrast to delineate the major blood vessels. If not, *i.v.* contrast should be given during the planning CT. If contrast is used, the densities can be over-ridden or the contrast scan must be registered to a non-contrast scan for planning purposes. Optimal immobilization is critical for this protocol. Immobilization to assure reproducibility of the set up is necessary.

6.3.4 The use of four-dimensional radiation treatment planning is highly encouraged. Acceptable methods of accounting for tumor motion include: design of the *PTV* to cover the excursion of the lung primary cancer and nodes during breathing such as an *ITV* approach, a maximum intensity projection (*MIP*) approach, automatic breath-hold (i.e., Elekta ABC device) or a gating approach (e.g., Varian RPM system)

6.4 Treatment Planning/Target Volumes

6.4.1 Target Volumes: The definitions of volumes will be in accordance with the 1993 ICRU Report #62.³⁷

6.4.1.1 Definition of the *GTV*: The primary tumor and clinically positive lymph nodes seen either on the planning CT (> 1 cm short axis diameter) or pretreatment PET scan (*SUV* > 3) will constitute the *GTV*. This volume(s) may be disjointed. In the event of a collapsed lobe or lung segment, the use of PET to distinguish tumor from fluid/atelectasis is encouraged. The *ITV* includes the envelope that encompasses the tumor motion for a complete respiratory cycle.

6.4.1.2 Definition of the *CTV*: The *CTV* is defined to be the *GTV* plus a 0.5 cm to 1 cm margin as appropriate to account for microscopic tumor extension. If an *ITV* approach is used then the *ITV* plus 0.5 cm to 1 cm is added to the *ITV* to form the *CTV*. Elective treatment of the mediastinum and supraclavicular fossae will not be done.

6.4.1.3 Definition of the *PTV*:
Free-breathing non-*ITV* approach (i.e. standard CT simulation without 4DCT or fusion of inhalation and exhalation scans):

There are two components to the *PTV* expansion. the internal motion (*IM* margin) which should be at least 1 cm in the inferior-superior direction, and 0.5 cm in the axial plane and an additional set-up margin (*SU* margin) of 0.5 cm. Thus, the total *PTV* includes the *CTV* plus a total margin of at least 1.5 cm to the superior-inferior dimensions and at least 1.0 cm in the axial plane.

Breath-hold or gating non-*ITV* approach:

For breath-hold or gating approaches, the *PTV* margin should be at least 1 cm in the inferior-superior direction and 0.5 cm in the axial plane. It is expected that daily imaging will be used for both breath-hold and gating techniques.

ITV approach: (10/29/10)

If the *ITV* approach is used, then the *PTV* margin should account for setup uncertainties and may be individualized but should not be less than 1.0 cm. If daily imaging is used to align the vertebral bodies, then the margins for setup margins may be reduced to 0.5 cm.

For institutions not using 4DCT, the use of fluoroscopy to determine the margin for motion in the inferior superior direction is encouraged.

For institutions with gating technology, the use of respiratory gating is encouraged.

There are 2 components to the PTV expansion. the internal motion (IM margin) which should be at least 1 cm in the inferior-superior direction, and 0.5 cm in the axial plane and an additional set-up margin (SU margin) of 0.5 cm. Thus, the total PTV includes the CTV plus a total margin of at least 1.5 cm to the superior-inferior dimensions and at least 1.0 cm in the axial plane. In cases in which the PTV expansion extends outside of the skin, towards the spinal cord, or into the spinal canal, it can be assumed that tumor motion will not occur in this direction, and the PTV margin in this direction can be limited. PTV margin can be limited to 0.5 cm towards this particular dimension (skin or spinal canal).

6.4.1.4 Normal anatomy to be identified: The normal anatomy to be outlined on each CT image will include the lungs (right and left done separately), heart, skin, esophagus and spinal cord. The heart should be contoured from its base to apex, beginning at the CT slice where the ascending aorta originates. The esophagus should be contoured from the bottom of the cricoid to the gastroesophageal junction. The skin and spinal cord should be contoured on each CT slice.

6.4.2 Treatment Planning

6.4.2.1 3D Conformal Therapy: The PTV is to be treated with any combination of coplanar or noncoplanar 3-dimensional conformal fields shaped to deliver the specified dose while restricting the dose to the normal tissues. Field arrangements will be determined by 3D planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient will be based on an analysis of the volumetric dose including DVH analyses of the PTV and critical normal structures. Each field is to be treated daily.

6.4.2.2 Intensity Modulated Radiation Therapy (IMRT): IMRT is allowed as long as the participating institution is credentialed by the RTOG for intra-thoracic IMRT treatments. The NCI Guidelines for the Use of IMRT can be found on the RTOG home page, <http://www.rtog.org/>. The credentialing process consists of two parts. Part 1 is the irradiation of the RPC phantom. Part 2 is a report from the institution to the RTOG which documents the institution's ability to control respiratory motion to a maximum excursion of 1.0 cm. Acceptable approaches include abdominal compression, breath-hold using the ABC device or other computer controlled spirometry, or gating, or other technologies. Each institution will be asked to document how they intend to limit motion and document the efficacy of their approach.

6.5 Critical Structures

Normal tissue constraints shall be prioritized in the following order for treatment planning: 1=spinal cord, 2=lungs, 3=esophagus, 4=brachial plexus, and 5=heart

6.5.1 Spinal Cord: The spinal cord dose limitation is the highest priority dose constraint and thus must be met irrespective of other constraints. Total "direct" plus "scatter" dose to the spinal cord must not exceed 50.5 Gy.

6.5.2 Lungs: The dose-volume constraint to the lungs is the second highest priority and must be met, except if it conflicts with the cord dose constraints. The volume of *both* lungs that receive more than 20 Gy (the V_{20}) should not exceed 37% of the total. Alternatively, the mean lung dose should optimally be ≤ 20 Gy. (By total lung volume we mean the total lung minus the CTV).

6.5.2.1 If either of these constraints is exceeded, several solutions can be entertained. First, one might increase the weighting of AP / PA treatments by one and reduce the obliques. This can be done as long as the cord dose (above), which takes precedence, is not exceeded.

Second, one can reduce the CTV to the minimum range suggested above.

Third, one can try to reduce the PTV by using respiratory gating techniques.

If after all attempts to decrease the V_{20} to below 37%, the V_{20} value still exceeds this limit, the patient should be treated to the dose on the arm to which they were randomized.

6.5.3 Brachial Plexus: Brachial plexus doses should be kept <66 Gy. In principle, this means that patients with Pancoast tumors, supraclavicular adenopathy, or other lung cancers wherein the GTV is close to or overlies the brachial plexus should not be entered into this trial.

6.5.4 Esophagus: The mean dose to the esophagus is optimally kept below 34 Gy.[47] This is not an absolute requirement, but is strongly recommended unless other, more critical constraints force

the situation. The V60 (% volume of esophagus exceeding 60 Gy) should be calculated for each patient.

- 6.5.5** Heart: The following limits are recommended: 60Gy to <1/3, 45 Gy to <2/3, and 40 Gy to <100% of the heart.

6.6 Documentation Requirements

- 6.6.1** Portal image of each field of 3-D radiotherapy or orthogonal images that localize the isocenter placement of IMRT must be obtained on the first day of therapy but should not be submitted.
- 6.6.2** Weekly verification or orthogonal images are required to be taken, but not submitted. This verification information also can be gathered with cone-beam CT or other CT devices that are present in the treatment room.
- 6.6.3** Isodose plans for 3-D radiotherapy and IMRT and DVHs of GTV, CTVs, and critical normal structures for IMRT.

6.7 Compliance Criteria (3/4/10)

- 6.7.1** Per Protocol: See Section 6.1.5

6.7.2 Variation Acceptable: Deviations of this magnitude are not desirable, but are acceptable for treatment situations in which the target to critical structure geometry is challenging. The prescribed dose can cover as little as 90% of the PTV as still be a Variation Acceptable. The minimum dose within the PTV can fall to 93% of the prescribed dose. The max dose can exceed 102% of the prescribed dose, but it cannot go above 125% of that dose.

6.7.3 Deviation Unacceptable: Dose distributions falling in this region are not acceptable, and plan modifications should be attempted to improve results. A Deviation Unacceptable occurs if any of the Variation Acceptable dose limits stated above are exceeded. Additionally, a Deviation Unacceptable is assigned if more than 1 cm³ of tissue outside the PTV receives \geq 120% of the prescribed dose.

6.8 R.T. Quality Assurance Reviews (6/18/08)

The Radiation Oncology Principal Investigators, Jeffrey Bradley, M.D. Steven Schild, M.D. Jeffrey Bogart, M.D., and/or M. Christian Dobelbower, M.D., Ph.D. will perform an RT Quality Assurance remote review after complete data for the first 20 cases enrolled have been received at the ITC. Dr. Bradley will perform the next remote review after complete data for the next 20 cases enrolled have been received at the ITC. 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 have been received at ITC, whichever occurs first.

6.9 Radiation Therapy Adverse Events (3/9/09)

6.9.1 Reversible or permanent alopecia, bone marrow toxicity, skin pigmentation, and esophagitis are expected side effects of radiation therapy. Radiation induced myocarditis or transverse myelitis rarely occur at doses lower than 50 Gy. Radiographic evidence of radiation change and subsequent fibrosis of the lung will occur within lung volume receiving \geq 20 Gy, usually within the first six months after initiation of treatment. It is essential to spare as much normal lung as possible in order to avoid symptomatic lung injury.

6.9.2 Cetuximab in Combination with Radiation Therapy (6/18/08)

Cetuximab in combination with radiation therapy should be used with caution in patients with a history of coronary artery disease, congestive heart failure, and arrhythmias. Although the etiology of these events is unknown, close monitoring of serum electrolytes, including serum magnesium, potassium, and calcium, during and after cetuximab therapy is recommended.

6.9.3 Esophagitis

Esophageal complaints are common with combined modality therapy. Esophagitis does not constitute a reason to interrupt or delay radiotherapy or chemotherapy provided oral intake is sufficient to maintain hydration. Patients should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Viscous Xylocaine, Carafate, or other medications should be used for symptomatic relief. Occasionally, narcotics may be required.

It is not necessary to biopsy acute esophagitis in the first 2 weeks of combined therapy since it is rarely due to underlying viral or fungal disease. Acute esophagitis may persist for 4-6 weeks. If Grade 4 esophagitis occurs, and a treatment interruption is being considered, every effort should be made to limit it to 3 treatment days or less. Patients requiring hospitalization because of esophagitis may have their treatment interrupted. In this event, please notify Dr. Bradley or Dr. Masters.

Esophagitis should be graded according to the CTCAE v.3.0.

Table 4: Esophagitis Grading System

| Grade | Clinical Scenario |
|-------|--|
| 1 | Asymptomatic pathologic, radiographic, or endoscopic findings only |
| 2 | Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements), IV fluids indicated <24 hrs |
| 3 | Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake), IV fluids, tube feedings, or TPN indicated >24 hrs |
| 4 | Life-threatening consequences |
| 5 | Death |

Treatment should be interrupted for grade 4 or greater dysphagia or odynophagia. Acute esophageal toxicity, which typically can occur within two weeks of the initiation of treatment and manifests as dysphagia, odynophagia, reflux symptoms, etc. should be pharmacologically managed with the following approach and should be initiated at the first signs or symptoms of esophageal toxicity. Recommended treatments are in Table 5.

Table 5: Suggestions for Management of Radiation Esophagitis

| |
|---|
| 1) Ketoconazole 200 mg PO q day OR |
| 2) Fluconazole 100 mg PO q day until the completion of radiation |
| 3) Mixture of: 2% viscous lidocaine: 60 cc Mylanta: 30 cc sucralfate (1 gm/cc): 10 cc Take 15-30 cc PO q3-4 hrs prn. (Contraindications: pts on Dilantin, Cipro, Digoxin) |
| 4) Ranitidine 150 mg PO BID (or other H2 blocker or a proton pump inhibitor such as omeprazole) until the completion of radiation |
| 5) Grade 4 esophagitis: hold RT + chemotherapy until grade 2 or less. We expect a significant portion of patients will experience grade 3 esophagitis. |

6.10 Functional Imaging

FDG-PET functional imaging is not a required component of this protocol, but is strongly encouraged for cancer staging.

6.10.1 Adverse Events

Adverse events from FDG-PET are exceedingly rare. If an adverse event from functional imaging is to occur, it would most likely be related to the intravenous catheter infusion site, consisting of erythema and discomfort from the i.v. An allergic reaction to the FDG is possible as well.

6.11 Radiation Adverse Event Reporting

See Section 7.0 for Adverse Event Reporting.

7.0 DRUG THERAPY

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

7.1 Treatment Plan (3/4/10)

7.1.1 Concurrent Chemotherapy for Arms A & B: The doses of chemotherapy to be given **concurrently with conformal radiotherapy** will be paclitaxel (45 mg/m²/wk) and carboplatin (AUC=2/wk), respectively. Drug therapy can be administered on any day of each week. Patients will receive the paclitaxel and carboplatin on the following days of conformal radiotherapy:

- Arm A (60 Gy): Days 1, 8, 15, 22, 29, and 36;
- Arm B (74 Gy): Days 1, 8, 15, 22, 29, 36 and 43;

Concurrent Cetuximab and Chemotherapy for Arms C & D: The patients randomized to Arms C and D will have cetuximab added to their treatment regimen. For Arms C and D, cetuximab will be administered on day 1, week 1 with chemoradiation to begin on day 8. The doses of chemotherapy to be given **concurrently with conformal radiotherapy** will be paclitaxel (45 mg/m²/wk) and carboplatin (AUC=2/wk), respectively. Patients will receive the paclitaxel and carboplatin on the following days of conformal radiotherapy:

- Arm C (60 Gy): Days 8, 15, 22, 29, 36, 43;
- Arm D (74 Gy): Days 8, 15, 22, 29, 36, 43, and 50.

7.2 Cetuximab Loading Dose for Arms C and D (Week 1, Day 1) [6/18/08]

Patients on Arms C and D will receive a loading dose of cetuximab, 400 mg/m², intravenously (IV) over 120 minutes on Day 1. No chemotherapy or radiation therapy will be given this day or week. **All patients will be premedicated with diphenhydramine hydrochloride 50 mg (or equivalent antihistamine) by IV 30-60 minutes prior to the first dose of cetuximab** Premedication may be administered prior to subsequent doses, but at the Investigator's discretion, the dose of diphenhydramine (or a similar agent) may be reduced.

The initial dose of cetuximab is 400 mg/m² intravenously administered over 120 minutes, followed by weekly infusions at 250 mg/m² IV over 60 minutes. **The infusion rate of cetuximab must never exceed 5 mL/min.** Patients must be continuously observed during the infusion for signs of anaphylaxis.

A 1-hour observation period is recommended after the cetuximab infusion. Longer observation periods may be required in patients who experience infusion reactions.

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 7.5.3.1 for proper management. **Patients should be instructed to report any delayed reactions to the investigator immediately.**

7.3 Concurrent Cetuximab and Chemoradiation for Arms C and D (Weeks 2-8) [3/4/10]

Beginning Day 8, patients will receive weekly treatment with cetuximab 250 mg/m² IV over 60 minutes before administration of chemotherapy and radiation therapy for 6 or 7 weeks (see Section 7.6.4 for details of administration). Patients will receive the cetuximab on the following days of conformal radiotherapy:

- Arm C (60 Gy): Days 8, 15, 22, 29, 36, 43;
- Arm D (74 Gy): Days 8, 15, 22, 29, 36, 43, and 50.

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

Following a 30-60 minute observation period after the delivery of cetuximab, patients will receive paclitaxel 45 mg/m² over 60 minutes and carboplatin AUC=2 over 30 minutes administered weekly for 6 or 7 weeks during concurrent RT. If patients have been pre-medicated with diphenhydramine hydrochloride for cetuximab administration, there is no need to pre-medicate patients again prior to paclitaxel infusion. Drug therapy can be administered on any day of each week.

7.4 Chemotherapy for All Arms (10/29/10)

7.4.1 Carboplatin dose should be calculated using the Calvert formula [(Total carboplatin dose mg) = (target AUC) x (CrCl + 25)].

The Cr Cl should be calculated using the Cockcroft-Gault equation (below) and should not exceed 125 mL/min.:

$$\text{CrCl (ml/min)} = (140 - \text{age}) (\text{Actual weight in kg}) \times 0.85 \text{ (females only)} \\ 72 \times \text{serum Creatinine (mg/dl)}$$

Maximum carboplatin dose (mg)=target AUC(mg x mg/mL) x 150 mL/min. Therefore, the maximum carboplatin dose should not exceed target AUC (mg x min/mL) x 150 mL/min, but it may be less.

A measured CrCl from a 24 hour urine collection may also be used.

Note: For subsequent weekly doses, a >10% change in the serum creatinine, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose

7.4.2 All drugs will be administered intravenously by intravenous drip. The paclitaxel will be given over 1 hour with standard premedication consisting of diphenhydramine 25-50 mg, an H2-blocker, and dexamethasone (oral or intravenous is acceptable according to local custom) at least 30 minutes prior to paclitaxel. The carboplatin will be given after the paclitaxel over 30 minutes with standard antiemetics.

7.4.3 (9/22/09) The chemotherapy should be delivered prior to the radiation therapy on the day of treatment. If the day of chemotherapy falls on a holiday, chemotherapy should be administered on the next full working day following the holiday (i.e., if the day 8 dose falls on Labor Day, the next chemotherapy dose would be given the following Tuesday). Doses that are missed during the weekly schedule concurrent with radiation therapy will not be made up but will be documented. If treatment breaks are required for longer than 15 days, protocol treatment should be discontinued. Follow up and data collection will continue as specified in the protocol. Further treatment off protocol is at the discretion of the treating physician.

7.4.4 Concurrent Treatment Summary Tables (9/22/09)

Arm A

| | Dose | Schedule |
|-------------|---------------------------------|--|
| Paclitaxel | 45mg/m ² | Days 1, 8, 15, 22, 29, and 36 |
| Carboplatin | AUC=2 | Days 1, 8, 15, 22, 29, and 36 |
| Radiation | 60 Gy, 5 X per week for 6 weeks | Days 1-5, 8-12, 15-19, 22-26, 29-33, 36-38 |

Arm B

| | Dose | Schedule |
|-------------|-----------------------------------|--|
| Paclitaxel | 45mg/m ² | Days 1, 8, 15, 22, 29, 36, and 43 |
| Carboplatin | AUC=2 | Days 1, 8, 15, 22, 29, 36, and 43 |
| Radiation | 74 Gy, 5 X per week for 7.5 weeks | Days 1-5, 8-12, 15-19, 22-26, 29-33, 36-38, 43-47, and 50-51 |

Arm C

| | Dose | Schedule |
|-------------|---------------------------------|---|
| Cetuximab | 400 mg/m ² | Day 1 |
| Cetuximab | 250 mg/m ² | Days 8, 15, 22, 29, 36, and 43 |
| Paclitaxel | 45mg/m ² | Days 8, 15, 22, 29, 36, and 43 |
| Carboplatin | AUC=2 | Days 8, 15, 22, 29, 36, and 43 |
| Radiation | 60 Gy, 5 X per week for 6 weeks | Days 8-12, 15-19, 22-26, 29-33, 36-38, 43-47. |

Arm D

| | Dose | Schedule |
|-------------|-------------------------------|--|
| Cetuximab | 400 mg/m ² | Day 1 |
| Cetuximab | 250 mg/m ² | Day 8, 15, 22, 29, 36, 43, and 50 |
| Paclitaxel | 45mg/m ² | Day 8, 15, 22, 29, 36, 43 and 50 |
| Carboplatin | AUC=2 | Day 8, 15, 22, 29, 36, 43 and 50 |
| Radiation | 74 Gy, 5 X week for 7.5 weeks | Day 8-12, 15-19, 22-26, 29-33, 36-38, 43-47, 50-54, 57-59. |

Note: Patient receives Cetuximab on day 57. Patient does not receive paclitaxel and carboplatin on day 57. (First day of week 8)

7.5 Consolidation Treatment (6/18/08)

7.5.1 Consolidation Chemotherapy for Arms A and B:

Two additional cycles of chemotherapy will be administered after the completion of combined chemotherapy and radiation. The doses will be paclitaxel 200 mg/m² and carboplatin AUC=6, respectively.

- Patients in Arm A will receive the paclitaxel and carboplatin on days 64 and 85.
- Patients in Arm B will receive the paclitaxel and carboplatin on days 71 and 92.

To begin consolidation chemotherapy, all previous toxicities including neuropathy must have resolved to CTCAE, v. 3.0 < grade 2.

The paclitaxel will be given over 3 hours with standard premedication consisting of diphenhydramine 25-50 mg, an H2-blocker, and dexamethasone (oral or intravenous is acceptable according to local custom) at least 30 minutes prior to paclitaxel. The carboplatin will be given over 30 minutes with standard anti-emetics after the paclitaxel. If the patient is unable to initiate chemotherapy at the specified time point following radiation therapy, the chemotherapy may be delayed up to an additional 4 weeks. If the chemotherapy cannot be given during this time interval, the patient will be considered off protocol treatment; however, the patient will remain on study and will still be followed.

7.5.2 Consolidation Treatment for Arms C and D:

- Arm C: Following the completion of concurrent cetuximab and chemoradiation, patients will receive cetuximab on days 50, 57, 64, 71, 78, 85, 92, 99, and 106.
- Arm D: Following the completion of concurrent cetuximab and chemoradiation, patients will receive cetuximab on days 57, 64, 71, 78, 85, 92, 99, 106, and 113.

The cetuximab will be given 250 mg/m² IV over 60 minutes.

To begin consolidation chemotherapy, all previous toxicities including neuropathy must have resolved to CTCAE, v. 3.0 < grade 2.

- Patients on Arm C will receive the paclitaxel and carboplatin on days 71 and 92. (Cetuximab will be given 30-60 minutes prior to paclitaxel and carboplatin on these days.)
- Patients on Arm D will receive the paclitaxel and carboplatin on days 78 and 99. (Cetuximab will be given 30-60 minutes prior to paclitaxel and carboplatin on these days.)

7.5.2.1 Cetuximab Administration

Premedication may be administered prior to subsequent doses, but at the Investigator's discretion, the dose of diphenhydramine (or a similar agent) may be reduced. After a 30-60 minute observation period, paclitaxel will be administered at 200 mg/m² over 3 hours and carboplatin at AUC=6 IV over 30 minutes.

- Patients on Arm C will receive the paclitaxel and carboplatin on days 71 and 92, corresponding to the beginning of weeks 4 and 7 of consolidation treatment.
- Patients on Arm D will receive the paclitaxel and carboplatin on days 78 and 99, corresponding to the beginning of weeks 4 and 7 of consolidation treatment.

If patients have been pre-medicated with diphenhydramine hydrochloride for cetuximab administration, there is no need to pre-medicate patients again prior to paclitaxel infusion.

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.**

7.5.2.2 Paclitaxel and Carboplatin Administration

The paclitaxel will be given over 3 hours with standard premedication consisting of diphenhydramine 25-50 mg, an H2-blocker, and dexamethasone (oral or intravenous is acceptable according to local custom) at least 30 minutes prior to paclitaxel. The carboplatin

will be given over 30 minutes with standard anti-emetics after the paclitaxel. If the patient is unable to initiate chemotherapy at the specified time point following radiation therapy, the chemotherapy may be delayed up to an additional 4 weeks. If the chemotherapy cannot be given during this time interval, the patient will be considered off protocol treatment; however, the patient will remain on study and will still be followed.

7.5.3 Consolidation Treatment Summary Tables

Arm A

| Agent | Dose | Schedule |
|-------------|----------------------|----------------|
| Paclitaxel | 200mg/m ² | Days 64 and 85 |
| Carboplatin | AUC=6 | Days 64 and 85 |

Arm B

| Agent | Dose | Schedule |
|-------------|----------------------|----------------|
| Paclitaxel | 200mg/m ² | Days 71 and 92 |
| Carboplatin | AUC=6 | Days 71 and 92 |

Arm C

| Agent | Dose | Schedule |
|-------------|-----------------------|-----------------------------------|
| Cetuximab | 250 mg/m ² | Days 50,57,64,71,78, 85,92,99,106 |
| Paclitaxel | 200mg/m ² | Days 71 and 92 |
| Carboplatin | AUC=6 | Days 71 and 92 |

Arm D

| Agent | Dose | Schedule |
|-------------|-----------------------|---|
| Cetuximab | 250 mg/m ² | Days 57,64,71,78, 85,92,99,106, and 113 |
| Paclitaxel | 200mg/m ² | Days 78 and 99 |
| Carboplatin | AUC=6 | Days 78 and 99 |

7.6 Cetuximab (10/9/08) IND #103444

Refer to package insert and investigator brochure for additional information. The investigator brochure is available on the RTOG web site at <http://www.rtog.org/investbrochure.html>.

7.6.1 Formulation (10/9/08)

Cetuximab is an anti-EGFR human-to-murine 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.

7.6.2 Supply

BMS will supply cetuximab free of charge to patients on study. The product is a sterile, clear, colorless liquid of pH 7.0 to 7.4, which may contain a small amount of easily visible, white, amorphous cetuximab particulates. Each single-use 50-mL vial contains 100 mg of cetuximab at a concentration of 2 mg/mL and is formulated in a preservative-free solution containing 8.48 mg/mL sodium chloride, 1.88 mg/mL sodium phosphate dibasic heptahydrate, 0.42 mg/mL sodium phosphate monobasic monohydrate, and water for injection, USP. Cetuximab for injection will be supplied by BMS in single-use, ready-to-use 50 or 100-mL vials containing 2 mg/mL of product.

7.6.3 Safety Precautions

Appropriate mask, protective clothing, eye protection, gloves, and Class II vertical-laminar-airflow safety cabinets are recommended during preparation and handling. Cetuximab therapy should be used with caution in patients with known hypersensitivity to cetuximab, murine proteins, or any component of this product. 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.

7.6.4 Preparation and Administration

Cetuximab must not be administered as an IV push or bolus.

Cetuximab must be administered with the use of a low protein binding 0.22-micrometer in-line filter.

Cetuximab is supplied as a 50-mL, single-use vial containing 100 mg of cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible white amorphous cetuximab particulates. **DO NOT SHAKE OR DILUTE.**

Cetuximab can be administered via infusion pump or syringe pump.

Infusion Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).
- Fill cetuximab into a sterile evacuated container or bag such as glass containers, polyolefin bags (e.g., Baxter Intravia), ethylene vinyl acetate bags (e.g., Baxter Clintec), DEHP plasticized PVC bags (e.g., Abbott Lifecare), or PVC bags.
- Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.
- Administer through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).
- Affix the infusion line and prime it with cetuximab before starting the infusion.
- Maximum infusion rate should not exceed 5 mL/min.
- Use 0.9% saline solution to flush line at the end of infusion.

Syringe Pump:

- Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike may be used).
- Place the syringe into the syringe driver of a syringe pump and set the rate.
- Administer through a low protein binding 0.22-micrometer in-line filter rated for syringe pump use (placed as proximal to the patient as practical).
- Connect up the infusion line and start the infusion after priming the line with cetuximab.
- Repeat procedure until the calculated volume has been infused.
- Use a new needle and filter for each vial.
- **Maximum infusion rate should not exceed 5 mL/min.**
- Use 0.9% saline solution to flush line at the end of infusion.

Cetuximab should be piggybacked to the patient's infusion line.

Following the cetuximab infusion, a 1-hour observation period is recommended.

7.6.5 Storage Requirements/Stability

Store vials under refrigeration at 2° C to 8° C (36° F to 46° F). **DO NOT FREEZE.** Increased particulate formation may occur at temperatures at or below 0° C. This product contains no preservatives. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2° C to 8° C (36° F to 46° F) or up to 8 hours at controlled room temperature (20° C to 25° C; 68° F to 77° F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2° to 8° C. Discard any unused portion of the vial.

7.6.6 Adverse Events (6/9/10)

**Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Cetuximab (NSC 714692)**

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with **bold** and **italicized** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. *Frequency is provided based on 2282 patients.* Below is the CAEPR for Cetuximab.

| Adverse Events with Possible Relationship to Cetuximab (CTCAE 4.0 Term) [n= 2282] | | | EXPECTED AEs FOR ADEERS REPORTING Agent Specific Adverse Event List (ASAEI) |
|---|----------------------------|--|---|
| Likely (>20%) | Less Likely (<=20%) | Rare but Serious (<3%) | Expected |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| | Anemia | | |
| EAR AND LABYRINTH DISORDERS | | | |
| | External ear inflammation | | |
| | Tinnitus | | |
| EYE DISORDERS | | | |
| | Conjunctivitis | | Conjunctivitis |
| | Dry eye | | Dry eye |
| | Uveitis | | Uveitis |
| | Watering eyes | | Watering eyes |
| GASTROINTESTINAL DISORDERS | | | |
| | Abdominal pain | | Abdominal pain |
| | Cheilitis | | Cheilitis |
| | Constipation | | Constipation |
| Diarrhea | | | Diarrhea |
| | Dry mouth | | Dry mouth |
| | Dyspepsia | | Dyspepsia |
| | Mucositis oral | | Mucositis oral |
| Nausea | | | Nausea |
| | Vomiting | | Vomiting |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| | Chills | | Chills |
| | Edema limbs | | |
| Fatigue | | | Fatigue |
| Fever | | | Fever |
| | Flu like symptoms | | Flu like symptoms |
| | Infusion related reaction | | Infusion related reaction |
| | Non-cardiac chest pain | | |
| IMMUNE SYSTEM DISORDERS | | | |
| | Allergic reaction | | Allergic reaction |
| | | Anaphylaxis | |
| INFECTIONS AND INFESTATIONS | | | |
| | Infection ² | | |
| | | Infections and infestations – Other (aseptic meningitis) | |
| INVESTIGATIONS | | | |
| | Neutrophil count decreased | | |
| | Weight loss | | Weight loss |
| | White blood cell decreased | | White blood cell decreased |
| METABOLISM AND NUTRITION DISORDERS | | | |
| | Anorexia | | Anorexia |
| | Dehydration | | Dehydration |
| | Hypocalcemia | | |
| | Hypomagnesemia | | Hypomagnesemia |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| | Arthralgia | | Arthralgia |
| | Back pain | | Back pain |

| | | | |
|--|----------------------|--|-----------------------------|
| | Myalgia | | Myalgia |
| NERVOUS SYSTEM DISORDERS | | | |
| Headache | | | Headache |
| | Syncope | | |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| | Allergic rhinitis | | Allergic rhinitis |
| | Bronchospasm | | |
| | Cough | | Cough |
| | Dyspnea | | Dyspnea |
| | Hoarseness | | Hoarseness |
| | | Pneumonitis | |
| | | Respiratory, thoracic, and mediastinal disorders - Other (non-cardiogenic pulmonary edema) | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| | Alopecia | | Alopecia |
| Dry skin | | | Dry skin |
| | Nail loss | | Nail loss |
| | | Palmar-plantar erythrodysesthesia syndrome | |
| | Photosensitivity | | Photosensitivity |
| | Pruritus | | Pruritus |
| | Purpura | | |
| Rash acneiform | | | Rash acneiform |
| Rash maculo-papular | | | Rash maculo-papular |
| | Skin ulceration | | |
| | Urticaria | | Urticaria |
| VASCULAR DISORDERS | | | |
| | Hypotension | | Hypotension |
| | Thromboembolic event | | Thromboembolic event |

¹This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

²Infection could include all 75 sites of infections under the INFECTIONS AND INFESTATIONS SOC.
Also reported on cetuximab trials but with the relationship to cetuximab still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Chest pain - cardiac; Left ventricular systolic dysfunction; Myocardial infarction; Paroxysmal atrial tachycardia; Pericardial effusion; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired
EYE DISORDERS - Blurred vision; Extraocular muscle paresis; Eyelid function disorder; Keratitis; Photophobia; Vitreous hemorrhage
GASTROINTESTINAL DISORDERS - Colitis; Dysphagia; Esophagitis; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal hemorrhage (including Colonic or Gastric hemorrhage or hemorrhage in other sites under the GASTROINTESTINAL DISORDERS SOC); Gastrointestinal perforation (Colonic perforation, Duodenal perforation, or perforation in other sites under the GASTROINTESTINAL DISORDERS SOC); Gastrointestinal ulcer (ulcer includes Duodenal ulcer, Rectal ulcer, or ulcer in other sites under the GASTROINTESTINAL DISORDERS SOC); Ileus; Pancreatitis; Rectal fistula
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Sudden death NOS
HEPATOBIILIARY DISORDERS - Cholecystitis; Hepatic failure
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Wound dehiscence
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Creatinine increased; Platelet count decreased; Serum amylase increased

METABOLISM AND NUTRITION DISORDERS - Hyperkalemia; Hyperuricemia; Hypokalemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (myasthenia); Musculoskeletal and connective tissue disorder - Other (Sudeck's Atrophy)

NERVOUS SYSTEM DISORDERS - Ataxia; Dizziness; Dysgeusia; Extrapyrarnidal disorder; Intracranial hemorrhage; Nervous system disorders - Other (cholinergic syndrome); Neuralgia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Tremor

PSYCHIATRIC DISORDERS - Agitation; Depression

RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (acute renal failure)

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (balanitis); Vaginal inflammation

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Atelectasis; Bronchopulmonary hemorrhage; Epistaxis; Pleural effusion; Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans-organized pneumonia [BOOP])

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hirsutism; Skin hypopigmentation; Skin and subcutaneous tissue disorders - Other (skin fissures)

VASCULAR DISORDERS - Flushing; Hypertension; Lymphedema; Vasculitis

Note: Cetuximab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.6.7 Drug Ordering and Accountability (10/9/08)

Bristol-Myers Squibb (BMS) will supply cetuximab free of charge to patients on study. The drug will be distributed by a vendor, Biologics, Inc., under contract to RTOG.

All pre-registration requirements must be met before calling to register the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, www.rtog.org (next to the protocol). U.S. and Canadian institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified. After receipt of written approval of submitted LOI forms from RTOG Headquarters, International institutions must submit the SASF and documentation of IRB approval to RTOG Headquarters (Fax 215-574-0300). This must be done prior to registration of the institution's first case.

Biologics will ship a patient-specific supply of cetuximab with enough quantity to complete protocol treatment for a 200-pound individual (83 vials) once the site has registered the patient. Since doses are dependent on the patient's BSA, sites can obtain additional per-patient supply for individuals over 200 pound by contacting Biologics. It is possible that sites will have more than one cetuximab clinical study ongoing at the same time. **It is imperative that only product designated for RTOG 0617 be utilized for this study.** RTOG 0617 product must be segregated from other investigational or marketed product.

Cetuximab will be placed in a temperature controlled cooler with 6 pounds of gel packs. U.S. shipments will be sent via FedEx for Priority Overnight delivery and via FedEx International for Canadian sites. Biologics will ship the order "same day" for all orders received before 4 p.m. EST, Monday through Thursday. Orders received after 4 p.m. EST, Monday through Thursday and any time on Friday will be processed and shipped the next business morning. Drug deliveries are restricted during weekends and holidays. Biologics observes the following holidays: New Years Eve, New Years Day, Memorial Day, July 4th, Labor Day, Thanksgiving Day and the Friday following Thanksgiving Day, Christmas Eve, and Christmas Day. Sites should plan ahead to accommodate patients being treated during restricted times.

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/alarms 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, contact Biologics.

Upon notification of a new patient enrollment, Biologics will place an outbound call to the site contact to confirm that the site's shipment is being processed. Biologics' distribution team will monitor packages throughout the duration of transit via the FedEx web site and FedEx One Call Solution (live support). Real-time monitoring enables Biologics to mitigate potential delivery delays.

(9/22/09) Questions about supply and delivery should be directed to:

Karl Buer, Clinical Trials Manager
Biologics, Inc.
120 Westin Oaks Court
Cary, NC 27513-2256
(800) 693-4906
FAX (919) 256-0794
dbuer@biologicstoday.com

7.6.7.1 Non-Canadian International Institutions (3/9/09)

Please refer to your LOI Approval Notification. Your institution will be responsible for acquiring any drug noted in the protocol as commercially available and not provided for the study. Before drug can be provided your institution must comply with all pre-registration requirements and certifications and provide all necessary documentation listed in your LOI Approval Notification document.

7.6.8 Handling and Dispensing of Investigational Product (10/9/08)

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.

7.6.9 Drug Destruction (10/9/08)

Opened vials must be disposed of at the site as chemotherapy or biohazardous waste, provided documented procedures for destruction are in place. 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 Biologics at 800-850-4306.

7.7 Paclitaxel (6/18/08)

7.7.1 Formulation

Paclitaxel is a poorly soluble plant product from the Pacific yew, *Taxus brevifolia*. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. Vials will be labeled with shelf life. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

7.7.2 Preparation

A sterile solution concentrate, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. Paclitaxel for injection must be diluted before administration with 5% dextrose USP, 0.9% sodium chloride USP, or 5% dextrose in Ringer's injection to a final concentration of 0.3 to 1.2 milligrams/milliliter. This solution is stable for 27 hours under ambient temperature (25 degrees Celsius) and room lighting (Prod Info Taxol®, 1997). Use 5% polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration. NOTE: Formation of a small number of fibers in solution has been observed after preparation of paclitaxel (NOTE: acceptable limits established by the USP Particular Matter Test for LVP's). Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration

should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: Millex-GV Millipore Products) into the IV fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate formation should not be used.

7.7.3 Administration (12/16/08)

See Section 7.3 for administration of paclitaxel concurrently with cetuximab and radiation.

See Sections 7.5.1 and 7.5.2.2 for administration of paclitaxel in consolidation treatment.

7.7.4 Storage

Paclitaxel vials should be stored between 2° -25°C (36° -77°F).

7.7.5 Adverse Effects:

- Hematologic: Myelosuppression
- Gastrointestinal: Nausea and vomiting; diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis, increased liver function tests (SGOT, SGPT, bilirubin, alkaline phosphatase); hepatic failure, hepatic necrosis
- Heart: Arrhythmias, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia, hypotension, hypertension, lightheadedness
- Neurological: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights; blurred vision, scintillating scotoma
- Allergy: Anaphylactoid and urticarial reactions (acute); Stevens-Johnson Syndrome; flushing, rash, pruritus
- Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration); radiation recall reaction.

7.7.6 Supply (10/9/08)

Paclitaxel is commercially available in the U.S. and will be provided free of charge to Canadian sites.

7.7.6.1 Canadian Sites (10/9/08)

Paclitaxel will be distributed by a vendor, Biologics, Inc., under contract to RTOG. Biologics will place the paclitaxel in a Biologics logo box for easy identification at the site. Biologics will ship a patient-specific supply of paclitaxel with enough quantity to complete protocol treatment for a 200-pound individual (27 vials) once the site has registered the patient. Since doses are dependent on the patient's BSA, sites can obtain additional per-patient supply for individuals over 200 pounds by contacting Biologics.

All pre-registration requirements must be met before calling to register the first case. Institutions must electronically complete (versus hand write) a Study Agent Shipment Form (SASF) available on the RTOG web site, www.rtog.org (next to the protocol). Canadian institutions must fax the SASF to the CTSU Regulatory Office (Fax 215-569-0206) as soon as the individual responsible for the study agent has been identified.

Biologics will ship the order "same day" for all orders received before 4 p.m. EST, Monday through Thursday via FedEx International. Orders received after 4 p.m. EST, Monday through Thursday and any time on Friday will be processed and shipped the next business morning. Drug deliveries are restricted during weekends and holidays. Biologics observes the following holidays: New Years Eve, New Years Day, Memorial Day, July 4th, Labor Day, Thanksgiving Day and the Friday following Thanksgiving Day, Christmas Eve, and Christmas Day. Sites should plan ahead to accommodate patients being treated during restricted times.

Upon notification of a new patient enrollment, Biologics will place an outbound call to the site contact to confirm that the site's shipment is being processed. Biologics' distribution team will monitor packages throughout the duration of transit via the FedEx web site and FedEx One Call Solution (live support). Real-time monitoring enables Biologics to mitigate potential delivery delays.

(9/22/09) Questions about supply and delivery should be directed to:

Karl Buer, Clinical Trials Manager
Biologics, Inc.
120 Westin Oaks Court
Cary, NC 27513-2256
(800) 693-4906
FAX (919) 256-0794
dbuer@biologicstoday.com

7.8 Carboplatin (6/18/08)

7.8.1 Formulation

Carboplatin is supplied as a sterile lyophilized powder available in a single-dose vial containing 50 mg, 150 mg, and 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight of carboplatin and mannitol.

7.8.2 Preparation

Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP, according to the following schedule:

| <u>Vial Strength</u> | <u>Diluent Volume</u> |
|----------------------|-----------------------|
| 50 mg | 5 ml |
| 150 mg | 15 ml |
| 450 mg | 45 ml |

These dilutions all produce a carboplatin concentration of 10 mg/ml. When prepared as directed, Paraplatin solutions are stable for eight hours at room temperature; since no antibacterial preservative is contained in the formulation, it is recommended that Paraplatin solutions be discarded eight hours after dilution.

7.8.3 Administration (10/29/10)

Carboplatin will be administered after paclitaxel as an IV infusion over 30 minutes. The dose will be calculated based on the patient's actual body weight at each treatment visit and the AUC (area under curve) dosing. **Note:** For subsequent weekly doses, a >10% change in the serum creatinine, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose.

The dose of carboplatin is calculated (in mg, not mg/m²) as follows, using the modified Calvert formula based on creatinine clearance: (MAXIMUM CREATINE CLEARANCE ALLOWED WILL BE 125 ml/min)

$$\text{AUC dose} = \text{Target AUC} \times (\text{Creatinine clearance} + 25)$$

The *Target AUC for carboplatin treatment is AUC=2 (concurrent therapy) or AUC=6 (consolidation therapy).

The creatinine clearance used to calculate the carboplatin dose will be estimated, based on serum creatinine, using the Cockcroft-Gault formula:

For males:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine in mg/dL}}$$

For females:

$$\text{CrCl (mL/min)} = 0.85 \times \frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine in mg/dL}}$$

7.8.4 Storage

Unopened vials of Paraplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

7.8.5 Adverse Events

- Hematologic: Myelosuppression
- Gastrointestinal: Nausea and vomiting; hepatic toxicity; electrolyte imbalance; hypomagnesemia; hypercalcemia
- Neurological: Peripheral neuropathy, ocular changes
- Other: Ototoxicity, myalgia, fatigue, allergic reaction

7.8.6 Supply

Carboplatin is commercially available.

7.9 Dose Modifications (6/18/08)

7.9.1 Paclitaxel and carboplatin infusions will not be concurrently withheld if cetuximab is withheld. Likewise, if paclitaxel, carboplatin, or RT are delayed or withheld, cetuximab will not be concurrently delayed or withheld, unless required by parameters described in Sections 6 and/or 7.5.2.1.

7.9.2 Dose Levels

Patients will be treated at the following dose levels:

| Dose Levels of Paclitaxel, Carboplatin, and Cetuximab | | | |
|--|-----------------------|-----------------------|-----------------------|
| | Starting Dose | Dose Level -1 | Dose Level -2 |
| Concurrent Therapy^a | | | |
| Paclitaxel | 45 mg/m ² | NA | NA |
| Carboplatin | AUC=2 | NA | NA |
| Consolidation Therapy^b | | | |
| Paclitaxel | 200 mg/m ² | 150 mg/m ² | NA |
| Carboplatin | AUC=6 | AUC=4.5 | NA |
| Cetuximab Dose Levels (post loading dose) | | | |
| Cetuximab | 250 mg/m ² | 200 mg/m ² | 150 mg/m ² |

^a For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.

^b For consolidation therapy, dose reductions of paclitaxel and carboplatin below the -1 dose level will not be allowed. Dose reductions for cetuximab will not be allowed below the -2 dose level.

7.9.3 Cetuximab Dose Modifications

As stated in Section 7.5.2, cetuximab dose reductions below the -2 dose level will not be allowed. All dose reductions are permanent; that is, there will not be any re-escalation of cetuximab dose. If cetuximab is omitted for more than 4 consecutive infusions for toxicity due to cetuximab or for an intercurrent illness (e.g., infection) requiring interruption of therapy, the patient should be discontinued from further cetuximab therapy. If toxicities prevent the administration of cetuximab, the patient may continue to receive paclitaxel, carboplatin, and RT without cetuximab.

It is recommended that patients be closely monitored for treatment-related adverse events, especially infusion reactions, during the infusion and the post-infusion observation hour. For the initial cetuximab infusion, vital signs should be monitored pre-infusion, 1/2 hour into the

infusion, at the end of the infusion and 1 hour post-infusion. For subsequent infusions, vital signs should be taken pre- and post-infusion.

7.9.3.1 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.

Severe infusion reactions require the immediate interruption of cetuximab therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

In previous clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of cetuximab and by continued use of antihistamine pre-medications (e.g., diphenhydramine) in subsequent doses. If the patient experiences a mild or moderate (Grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced by 50%. For grade 1 or 2 reactions manifesting only as delayed drug fever, see paragraph below. Cetuximab should be immediately and permanently discontinued in patients who experience severe (Grade 3 or 4) infusion reactions.

7.9.3.2 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. If a patient experiences isolated drug fever, for the next dose, pretreat with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion), repeat antipyretic dose 6 and 12 hours after cetuximab infusion. The infusion rate will remain unchanged for future doses.

If a patient experiences recurrent isolated drug fever following premedication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate. If fever recurs following infusion rate change, the investigator should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further cetuximab.

7.9.3.3 Management of Pulmonary Toxicity

In the event of acute onset (grade ≥ 2) or worsening pulmonary symptoms which are not thought to be related to underlying cancer, cetuximab therapy should be interrupted and a prompt investigation of these symptoms should occur. Cetuximab retreatment should not occur until these symptoms have resolved to grade 1. If interstitial lung disease is confirmed, cetuximab should be discontinued and the patient should be treated appropriately.

7.9.3.4 Management of Dermatologic Toxicity

Patients developing dermatologic toxicities while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Dose modifications of any future cetuximab infusions should be instituted in case of severe (grade 3) acneform rash. Treatment with topical and/or oral antibiotics should be considered; topical corticosteroids are not recommended.

If a patient experiences severe acneform rash, cetuximab treatment adjustments should be made according to the following table. In patients with mild and moderate skin toxicity, treatment should continue without dose modification.

| Cetuximab Dose Modification Guidelines for Dermatologic Toxicity | | | |
|---|------------------------|----------------|-----------------------------------|
| Grade 3 Acneform Rash | Cetuximab | Outcome | Cetuximab Dose Mod |
| 1 st occurrence | Delay infusion 1-2 wks | Improvement | Continue at 250 mg/m ² |
| | | No improvement | Discontinue cetuximab |
| 2 nd occurrence | Delay infusion 1-2 wks | Improvement | Reduce *Dose Level -1 |
| | | No improvement | Discontinue cetuximab |
| 3 rd occurrence | Delay infusion 1-2 wks | Improvement | Reduce *Dose Level -2 |
| | | No improvement | Discontinue cetuximab |
| 4 th occurrence | Discontinue cetuximab | | |

*See Section 7.9.2 for cetuximab dose levels

7.9.3.5 *Management of Hypomagnesemia and Electrolyte Abnormalities*

Hypomagnesemia has been reported with cetuximab when administered as a single agent and in combination with multiple different chemotherapeutic regimens. The incidence of hypomagnesemia (both overall and severe [NCI CTC grades 3 & 4]) is increased in patients receiving chemotherapy and cetuximab as compared with those receiving chemotherapy alone based on controlled clinical trials. Patients receiving cetuximab therapy (Arms C & D) should be monitored for hypomagnesemia, hypocalcemia, and hypokalemia, weekly during concurrent and consolidation treatment and for at least 8 weeks following the completion of cetuximab. Replete electrolytes as necessary.

7.9.3.6 Based on previous experience with cetuximab reactions, the following treatment guidelines may be applicable:

| CTCAE, v 3.0 |
|---|
| Grade 1 Allergic reaction/hypersensitivity (including drug fever): Transient flushing or rash; drug fever < 38° C (< 100.4° F) |
| or Grade 1 Cytokine release syndrome/infusion reaction : Mild reaction; infusion interruption not indicated; intervention not indicated |
| Treatment : Decrease the cetuximab infusion rate by 50%, and monitor closely for any worsening. |
| Grade 2 Allergic reaction/hypersensitivity (including drug fever): Rash, flushing, urticaria; dyspnea; drug fever ≥ 38° C (≥ 100.4° F) |
| or Grade 2 Cytokine release syndrome/infusion reaction : Requires therapy or infusion interruption but responds promptly to treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours |
| Treatment : Stop cetuximab infusion; administer bronchodilators, oxygen, etc. as medically indicated. Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or has decreased to Grade 1 in severity, and monitor closely for any worsening. |
| Isolated drug fever (Grade 1 or 2 Allergic reaction/hypersensitivity or Cytokine release syndrome/infusion reaction) : |
| Treatment : Pre-treat for next dose with acetaminophen or NSAID (Investigator's discretion). Repeat antipyretic dose 6 and 12 hours after cetuximab infusion. The infusion rate will remain unchanged. See Section 7.5.3.2 for dose modification of subsequent courses. |
| Grade 3 or Grade 4 Allergic reaction/hypersensitivity (including drug fever): |
| <u>Grade 3</u> : Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension |
| <u>Grade 4</u> : Anaphylaxis |
| or Grade 3 or Grade 4 Cytokine release syndrome/infusion reaction : |
| <u>Grade 3</u> : Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) |

| |
|---|
| Grade 4: Life-threatening; pressor or ventilatory support indicated |
| Treatment: Stop the cetuximab infusion immediately, and disconnect infusion tubing from the patient; administer epinephrine, bronchodilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated. Report as a serious adverse event (see Section 7.14). |
| For a CTCAE Grade 3 or 4 reaction, the patient is to receive no further cetuximab treatment. |

7.9.3.7 Retreatment with Cetuximab Following Allergic/Hypersensitivity or Cytokine Release Reactions (12/16/08)

Once a cetuximab infusion rate has been decreased due to an allergic/hypersensitivity or cytokine release reaction, it will remain decreased for all subsequent infusions. If the patient has a second allergic/hypersensitivity or cytokine release reaction with the slower infusion rate, the infusion should be stopped, and the patient should receive no further cetuximab treatment. If a patient experiences a Grade 3 or 4 allergic/hypersensitivity or cytokine release reaction at any time, the patient should receive no further cetuximab treatment. If there is any question as to whether an observed reaction is an allergic/hypersensitivity or cytokine release reaction of Grades 1 – 4, the Study Chair should be contacted immediately to discuss the reaction.

If the patient experiences recurrent isolated drug fever following pre-medication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of the previous rate. If fever recurs following infusion rate changes, the Investigator should assess the patient’s level of discomfort with the event and use clinical judgment to determine if the patient should receive further cetuximab therapy.

The first time a patient experiences a grade 3 acne/acneiform rash associated with pain, disfigurement, ulceration, or desquamation, cetuximab therapy is to be held for up to four consecutive infusions with no change in the dose level. The Investigator also can consider concomitant treatment with topical and/or oral antibiotics; topical corticosteroids are not recommended. If the toxicity resolves to Grade 2 or less by the following treatment period, treatment may resume. With subsequent occurrences of a Grade 3 acne/acneiform rash, cetuximab therapy again may be omitted for up to four consecutive weeks. Treatment may resume with reduced dose of cetuximab if skin toxicity has resolved to Grade 2 or less. **Cetuximab dose reductions are permanent.** Cetuximab will be discontinued if there are more than 4 consecutive infusions held or if there is a subsequent occurrence of a fourth episode of Grade 3 acne-like rash (rash/desquamation). The patient should be followed weekly until resolution of the rash.

If cetuximab is omitted for more than four consecutive infusions for toxicity due to cetuximab, patients should be discontinued from further cetuximab.

7.10 Dose Modifications During Concurrent Therapy (3/4/10)

7.10.1 Paclitaxel/Carboplatin/Cetuximab Dose Modifications for Hematologic Toxicity

| Toxicity NCI CTCAE Grade (CTCAE v3.0) | Paclitaxel Dose At Start of Subsequent Cycles of Therapy ^a | Carboplatin Dose at Start of Subsequent Cycles of Therapy ^a | Cetuximab Dose at Start of Subsequent Cycles of Therapy ^a |
|---|--|--|--|
| Neutropenia | | | |
| 1 (1500-1999/mm ³) | Maintain dose level | Maintain dose level | Maintain dose level |
| 2 (1000-1499/mm ³) | Maintain dose level | Maintain dose level | Maintain dose level |
| 3 (500-999/mm ³) | Hold therapy ^b | Hold therapy ^b | Hold therapy ^b |
| 4 (< 500/mm ³) | Hold therapy ^b | Hold therapy ^b | Hold therapy ^b |
| Neutropenic fever | Hold therapy ^b | Hold therapy ^b | Hold therapy ^b |
| Thrombocytopenia | | | |

| | | | |
|-------------------------------------|---|---------------------------|---------------------------|
| 1 (< LLN-75,000/mm ³) | Maintain dose level | Maintain dose level | Maintain dose level |
| 2 (50,000- 74,999/mm ³) | Hold therapy ^B | Hold therapy ^B | Maintain dose level |
| 3 (25,000- 49,999/mm ³) | Hold therapy ^B | Hold therapy ^B | Maintain dose level |
| 4 (< 25,000/mm ³) | Hold therapy ^B | Hold therapy ^B | Hold therapy ^B |
| Other Hematologic toxicities | There will be no dose modifications for changes in leukopenia or lymphopenia. | | |

^aDose levels are relative to the starting dose in the previous cycle. Dose reductions of cetuximab below the –2 dose level will not be allowed. For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.

^BRepeat lab work weekly and resume chemotherapy based on this table.

Doses that are missed during weekly schedule concurrent with radiation will not be made up but will be documented.

Radiation therapy will be held for grade 4 toxicities hematologic described in the table above.

7.10.2 If paclitaxel and/or carboplatin doses must be withheld for greater than two consecutive weeks, the drug(s) will be held permanently for the duration of concurrent therapy.

7.10.3 Paclitaxel/Carboplatin/Cetuximab Dose Modifications for Non-Hematologic Toxicity During Concurrent Therapy

| Worst Toxicity NCI CTCAE Grade (CTCAE v3.0) ^{a, d} | Paclitaxel Dose At Start of Subsequent Cycles of Therapy ^b | Carboplatin Dose At Start of Subsequent Cycles of Therapy ^b | Cetuximab Dose At Start of Subsequent Cycles of Therapy ^{b, c} |
|--|--|---|--|
| Nail changes (paronychia) Grade 2 | Maintain dose level | Maintain dose level | Decrease by 1 dose level |
| Neuropathy ≤ Grade 1 | Maintain dose level | Maintain dose level | Maintain dose level |
| Grade 2 | Hold therapy until Grade ≤ 1; restart at full dose ^e | Maintain dose level | Maintain dose level |
| Grade 3 | Discontinue therapy | Maintain dose level | Maintain dose level |
| Other non-hematologic toxicities ^c ≥ Grade 3 | Hold treatment until ≤ Grade 2 | Hold treatment until ≤ Grade 2 | Hold treatment until ≤ Grade 2 |

- For ≤ CTCAE Grade 2 non-hematologic toxicity not described above, excluding neuropathy, maintain dose level of all study. For neuropathy, follow the guidelines listed above.
- 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. For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.
- With the exception of allergic/hypersensitivity or cytokine release reaction (see Sections 7.9.3.6 & 7.9.3.7), acne-like rash (rash/desquamation) [see Section 7.9.3.4], anorexia, and viral infections. See Section 7.9.3.4 for treatment modifications for and skin toxicity management.
- Radiation therapy should continued to be delivered for ≤ Grade 3 non-hematologic toxicities in or outside the radiation treatment field. RT should be held for all Grade 4 non-hematologic toxicity in or outside the treatment field and resumed only when toxicity is ≤ Grade 2.

In any case of cetuximab treatment delay, there will be no reloading infusion, and all subsequent treatments will be at the current dose level.

7.10.4 Carboplatin Dose Modifications for Renal Toxicity (9/22/09)

A > 10% change in the serum creatinine, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose (see Section 7.11.3)

7.10.5 Paclitaxel for Neuropathy

If paclitaxel doses must be withheld for greater than two consecutive weeks, the drug will be held permanently for the duration of concurrent therapy (see Section 7.11.4).

7.10.6 If there is a decline in Zubrod performance status to ≥ 2 for greater than 2 weeks while under treatment, radiotherapy should be held with no further chemotherapy administered. Re-evaluate patient after one week for resumption of radiotherapy.

7.10.7 Paclitaxel/Carboplatin/RT Dose Modifications for In RT Field, Non-Hematologic Toxicity During Concurrent Therapy

| Treatment Modification for In-field Non-Hematologic Toxicity | | | | | |
|--|----------------------|--|-------------------------------------|-------------------------------------|--------------------------------------|
| In-field | CTCAE Toxicity Grade | XRT | Paclitaxel | Carboplatin | Cetuximab |
| Esophagus/pharynx (on day of XRT) | 4 | Hold treatment until \leq Grade 2 | Hold treatment until \leq Grade 2 | Hold treatment until \leq Grade 2 | Hold treatment until \leq Grade 2 |
| Esophagus/pharynx (on day of chemo) | 3 | No change or hold \leq 5 days (See Sections 7.10.4.9 & 7.10.4.11) | Hold treatment until \leq Grade 2 | Hold treatment until \leq Grade 2 | Hold treatment until \leq Grade 2 |
| Esophagus/pharynx (on day of chemo) | 2 | No change | No change | No change | No change |
| Pulmonary | 4 | Discontinue | Hold treatment until \leq Grade 2 | Hold treatment until \leq Grade 2 | Discontinue cetuximab |
| Pulmonary | 3 | Hold treatment until \leq Grade 2 | Hold treatment until \leq Grade 2 | Hold treatment until \leq Grade 2 | Discontinue cetuximab |
| Skin | 4 | Hold treatment until \leq Grade 2 | Hold treatment until \leq Grade 2 | Hold treatment until \leq Grade 2 | Follow guidelines in Section 7.9.3.4 |
| Skin | 3 | No change | No change | No change | Follow guidelines in Section 7.9.3.4 |

7.10.8 (12/16/08) For in-field esophagitis, see the table in Section 7.10.7. Re-evaluate patient weekly.

7.10.9 (12/16/08) For dermatitis or other in-field radiotherapy-related toxicity, see the table in Section 7.10.7. On day of chemotherapy administration during any treatment week, omit paclitaxel and carboplatin until toxicity resolves to grade ≤ 2 as detailed in the table above. For cetuximab skin toxicity management, follow the guidelines in Section 7.9.3.4.

7.10.10 (9/22/09) Radiotherapy should be interrupted for Grade 4 toxicity, including Grade 4 esophagitis or pulmonary toxicity and resumed according to the table in Section 7.10.7. If treatment is interrupted for > 2 weeks, protocol treatment should be discontinued. Follow up and data collection will continue as specified in the protocol. Further treatment off protocol is at the discretion of the treating physician. If the patient experiences esophagitis so that IV fluid support is needed, insertion of a feeding tube should be considered.

7.11 Dose Modifications During Consolidation Therapy (3/4/10)

7.11.1 Paclitaxel/Carboplatin/Cetuximab Dose Modifications for Hematologic Toxicity

| Toxicity NCI CTCAE Grade (CTCAE v3.0) | Paclitaxel Dose At Start of Subsequent Cycles of Therapy ^{a, c} | Carboplatin Dose at Start of Subsequent Cycles of Therapy ^{a, c} | Cetuximab Dose at Start of Subsequent Cycles of Therapy ^a |
|---|---|---|--|
| Neutropenia | | | |
| 1 (1500-1999/mm ³) | Maintain dose level | Maintain dose level | Maintain dose level |

| | | | |
|--|--|--|---|
| 2 (1000-1499/mm ³) | Hold therapy ^b . Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when $\geq 1,500 \text{ mm}^3$ | Hold therapy ^b . Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when $\geq 1,500 \text{ mm}^3$ | Maintain dose level |
| 3 (500-999/mm ³) | Hold therapy ^b . Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when $\geq 1,500 \text{ mm}^3$ | Hold therapy ^b . Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when $\geq 1,500 \text{ mm}^3$ | Maintain dose level, unless reoccurs after discontinuation of paclitaxel and carboplatin, then decrease by 1 dose level |
| 4 (< 500/mm ³) | Hold therapy ^b and decrease by 1 dose level when $\geq 1,500 \text{ mm}^3$ | Hold therapy ^b and decrease by 1 dose level when $\geq 1,500 \text{ mm}^3$ | Maintain dose level unless reoccurs after discontinuation of paclitaxel and carboplatin, then decrease by 1 dose level |
| Neutropenic fever | Hold therapy ^b and decrease by 1 dose level when $\geq 1,500 \text{ mm}^3$ | Hold therapy ^b and decrease by 1 dose level when $\geq 1,500 \text{ mm}^3$ | Maintain dose level unless reoccurs after discontinuation of paclitaxel and carboplatin, then decrease by 1 dose level |
| Thrombocytopenia | | | |
| 1 ($\geq 75,000/\text{mm}^3$) | Maintain dose level | Maintain dose level | Maintain dose level |
| 2 (50,000 - 74,999/ mm ³) | Hold therapy ^b . Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when $\geq 75,000 \text{ mm}^3$ | Hold therapy ^b . Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when $\geq 75,000 \text{ mm}^3$ | Maintain dose level |
| 3 (25,000- 49,999/ mm ³) | Hold therapy ^b . Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when $\geq 75,000 \text{ mm}^3$ | Hold therapy ^b . Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when $\geq 75,000 \text{ mm}^3$ | Maintain dose level unless reoccurs after discontinuation of paclitaxel and carboplatin, then decrease by 1 dose level |
| 4 (< 25,000/mm ³) | Hold therapy ^b and decrease by 1 dose level when $\geq 75,000 \text{ mm}^3$ | Hold therapy ^b and decrease by 1 dose level when $\geq 75,000 \text{ mm}^3$ | Maintain dose level unless reoccurs after discontinuation of paclitaxel and carboplatin, then decrease by 1 dose level |
| Other Hematologic toxicities | There will be no dose modifications for changes in leukopenia or lymphopenia. | | |

^aDose levels are relative to the worst toxicities in the previous cycle. For consolidation therapy, dose reductions of paclitaxel and carboplatin below the -1 dose level will not be allowed. Dose reductions of cetuximab will not be allowed below the -2 dose level.

^bRepeat lab work weekly and resume chemotherapy based on this table.

^cDose delays greater than 2 weeks will warrant discontinuation of chemotherapy for the consolidation cycles.

7.11.2 Paclitaxel/Carboplatin/Cetuximab Dose Modifications for Non-Hematologic Toxicity During Consolidation Therapy

| Worst Toxicity NCI CTCAE Grade (CTCAE v3.0) ^{a, d} | Paclitaxel Dose At Start of Subsequent Cycles of Therapy ^b | Carboplatin Dose At Start of Subsequent Cycles of Therapy ^b | Cetuximab Dose At Start of Subsequent Cycles of Therapy ^{b, c} |
|--|---|---|---|
|--|---|---|---|

| Worst Toxicity NCI CTCAE Grade (CTCAE v3.0) a, d | Paclitaxel Dose At Start of Subsequent Cycles of Therapy ^b | Carboplatin Dose At Start of Subsequent Cycles of Therapy ^b | Cetuximab Dose At Start of Subsequent Cycles of Therapy ^{b,c} |
|---|---|---|--|
| Nail changes (paronychia) Grade 2 | Maintain dose level | Maintain dose level | Decrease by 1 dose level |
| Neuropathy | | | |
| ≤ Grade 1 | Maintain dose level | Maintain dose level | Maintain dose level |
| Grade 2 | Hold therapy until Grade ≤ 1; restart at full dose | Maintain dose level | Maintain dose level |
| Grade 3 | Discontinue therapy | Maintain dose level | Maintain dose level |
| Other non- hematologic toxicities^c Grade 3 | Hold treatment until ≤ Grade 2 | Hold treatment until ≤ Grade 2 | Hold treatment until ≤ Grade 2 |

- a. For ≤ CTCAE Grade 2 non-hematologic toxicity not described above, excluding neuropathy, maintain dose level of all study drugs. For neuropathy, follow the guidelines above.
- b. Dose levels are relative to the worst toxicities in the previous cycle. Dose reductions of cetuximab below the -2 dose level will not be allowed. For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.
- c. With the exception of allergic/hypersensitivity reaction (see Sections 7.9.3.6 & 7.9.3.7), acne-like rash (rash/desquamation) [see Section 7.9.3.4], anorexia, and viral infections. See Section 7.9.3.4 for treatment modifications for skin toxicity management.

When a chemotherapy dose reduction is required during the consolidation course of therapy, re-escalation of the chemotherapy dose will not be allowed for subsequent doses during that specific course.

In any case of cetuximab treatment delay, there will be no reloading infusion, and all subsequent treatments will be at the current level.

7.11.3 Carboplatin Dose Modifications for Renal Toxicity (9/22/09)

A > 10% change in the serum creatinine, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose.

7.11.4 Paclitaxel Dose Modifications for Neuropathy

If paclitaxel doses must be withheld for greater than two consecutive weeks, the drug will be held permanently for the duration of consolidation therapy.

- A delay in protocol treatment of greater than 15 days during the concurrent phase and more than 4 weeks in the consolidation phase.
- If protocol treatment is discontinued for any reason, follow up and data collection will continue as specified in the protocol

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, 12, and Appendix II.

7.12 Criteria for Discontinuation of Protocol Treatment (6/18/08)

Protocol treatment may be discontinued for any of the following reasons:

- Progression of disease (Further treatment will be at the discretion of the treating physician);
- Pregnancy;
- Any clinical adverse event, laboratory abnormality, or intercurrent illness that, in the opinion of the Investigator, indicates that continued treatment with all study therapy is not in the best interest of the patient;
- A delay in protocol treatment of greater than 15 days during the concurrent phase and more than 4 weeks in the consolidation chemotherapy phase.
- If protocol treatment is discontinued for any reason, follow up and data collection will continue as specified in the protocol.

7.13 Modality Review (6/18/08)

The Medical Oncology Co-Chairs, Gregory Masters, M.D., George Blumenschein, M.D., Alex Adjei, M.D., Ph.D., Mark Socinski, M.D., and Tien Hoang, M.D., will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. The scoring mechanism is: **Per Protocol/Acceptable Variation, Not Per Protocol, and Not Evaluable**. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

The Medical Oncology Co-Chairs, Gregory Masters, M.D., George Blumenschein, M.D., Alex Adjei, M.D., Ph.D., Mark Socinski, M.D., and Tien Hoang, M.D., will perform a Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Masters will perform the next review after complete data for the next 20 cases enrolled has been received at RTOG Headquarters. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received at RTOG Headquarters, whichever occurs first.

7.14 Adverse Events (11/27/07)

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, MedDRA version 9 for grading of all adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). 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, v 3.0.

All adverse events (AEs) as defined in the tables below will be reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site ([https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main\\$.startup](https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup)).

Serious adverse events (SAEs) as defined in the tables below will be reported via AdEERS. Sites also can access the RTOG web site (<http://www.rtog.org/members/toxicity/main.html>) for this information.

In order to ensure consistent data capture, serious adverse events reported on AdEERS reports also must be reported on an RTOG case report form (CRF). In addition, sites must submit CRFs in a timely manner after AdEERS submissions.

7.14.1 Adverse Events (AEs)

Definition of an AE: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [CTEP, NCI Guidelines: Expedited Adverse Event Reporting Requirements. December 2004.]

(6/18/08) The following guidelines for reporting adverse events (AEs) apply to all NCI/RTOG research protocols. AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). **Note: AEs indicated in the AdEERS Expedited Reporting Requirements in text and/or table in Section 7.15 also must be reported via AdEERS.**

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

7.14.2 Serious Adverse Events (SAEs) — All SAEs that fit any one of the criteria in the SAE definition below must be reported via AdEERS. Contact the AdEERS Help Desk if assistance is required.

Certain SAEs as outlined below will require the use of the 24 Hour AdEERS Notification:

- **Phase II & III Studies: All unexpected potentially related SAEs**
- **Phase I Studies: All unexpected hospitalizations and all grade 4 and 5 SAEs regardless of relationship**

Definition of an SAE: Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Any pregnancy occurring on study must be reported via AdEERS as a medically significant event.

Any late death (more than 30 days after last treatment) attributed to the protocol treatment (possible, probable or definite) should be reported via AdEERS within 24 hours of discovery. An expedited report, if applicable, will be required within 5 or 10 calendar days.

All supporting source documentation, if applicable or if being faxed to NCI, must be properly labeled with the study/case numbers and the date of the adverse event and must be faxed to the RTOG dedicated SAE FAX, 215-717-0990, before the five or ten-calendar-day deadline to allow RTOG to comply with the reporting requirements of the pharmaceutical company/companies supporting the RTOG trial. All forms (and supporting source documentation) submitted to RTOG Headquarters must include the RTOG study/case numbers; non-RTOG intergroup study and case numbers must be included, when applicable. Submitted AdEERS Reports are forwarded to RTOG electronically via the AdEERS system. Use the patient’s case number as the patient ID when reporting via AdEERS.

SAE reporting is safety related and separate and in addition to the Data Management reporting requirements as outlined in the previous AE reporting section. Any event that meets the above outlined criteria for an SAE but is assessed by the AdEERS System as “expedited reporting NOT required” must still be reported for safety reasons and to fulfill the obligations of RTOG to the pharmaceutical company/companies supporting the RTOG trial. Sites must bypass the “NOT Required” assessment and complete and submit the report. The AdEERS System allows submission of all reports regardless of the results of the assessment. Note: Sites must print the AdEERS report and fax it to the FDA, FAX 1-800-332-0178.

7.14.3 Acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) [11/9/10]
 AML or MDS that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported via the AdEERS system and **must be mailed to RTOG Headquarters (address below) within 30 days of AML/MDS diagnosis.**

| |
|--------------------------------|
| RTOG Headquarters |
| AML/MDS Report |
| 1818 Market Street, Suite 1600 |
| Philadelphia, PA 19103 |

7.15 Phase 2 and 3 Trials Utilizing an Agent under a non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that Occur within 30 Days¹ of the Last Dose of the Agents in this Study

| | Grade 1 | Grade 2 | Grade 2 | Grade 3 | | Grade 3 | | Grades 4 & 5 ² | Grades 4 & 5 ² |
|---------------------------|-------------------------|--------------|--------------|---------------------------------|-------------------------|-------------------------------|-------------------------|---------------------------|---------------------------|
| | Unexpected and Expected | Unexpected | Expected | Unexpected with Hospitalization | without Hospitalization | Expected with Hospitalization | without Hospitalization | Unex-pected | Expected |
| Unrelated Unlikely | Not Required | Not Required | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | 10 Calendar Days |

| Possible Probable Definite | Not Required | 10 Calendar Days | Not Required | 10 Calendar Days | 10 Calendar Days | 10 Calendar Days | Not Required | 24-Hour; 5 Calendar Days | 10 Calendar Days |
|---|-----------------|---------------------|-----------------|---------------------|------------------------|------------------------|-----------------|--------------------------------|------------------------|
| <p>¹ Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a non-CTEP IND require reporting as follows: AdEERS 24-hour notification followed by complete report within 5 calendar days for:</p> <ul style="list-style-type: none"> Grade 4 and Grade 5 unexpected events <p>AdEERS 10 calendar day report:</p> <ul style="list-style-type: none"> Grade 3 unexpected events with hospitalization or prolongation of hospitalization Grade 5 expected events <p>² Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.</p> <p>Please see exceptions below under section entitled "Additional Instructions or Exceptions."</p> <p style="text-align: right;">March 2005</p> | | | | | | | | | |

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided. "On study" is defined as during or within 30 days of completing protocol treatment.

- Expedited AE reporting timelines defined:
 - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
 - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Additional Instructions or Exceptions to AdEERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing Agents under a non CTEP-IND: Not applicable.

8.0 SURGERY

Not applicable

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

9.1.1 Anti-emetics (6/18/08)

See Section 7.5.2.2.

9.1.2 Hematopoietic Growth Factors

WBC growth factors (G-CSF/GM-CSF) will not be permitted during radiation. If a patient receives WBC growth factors during radiation, this constitutes a major protocol violation.

WBC growth factors may be used during consolidation chemotherapy in accordance with ASCO guidelines, but should not be given prophylactically.

Erythropoietin may be given at the treating physician's discretion in accordance with accepted guidelines.

10.0 TISSUE/SPECIMEN SUBMISSION

(6/18/08) For patients who have consented to participate in the tissue/blood component of the study (See Appendix I)

(3/9/09) Note: Patients must be offered the opportunity to participate in the correlative components of the study. If the patient consents to participate in the tissue/specimen component of the study, the site is required to submit the patient's specimens as specified below. **Sites are not permitted to delete the tissue/specimen component from the protocol or sample consent.**

10.1 Tissue/Specimen Submission (5/22/08)

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Specimens are preserved through careful storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for planned and future translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

In this study, it is strongly encouraged that tumor tissue, blood (serum/plasma/lymphocytes), and urine be submitted to the RTOG Biospecimen Resource for the purpose of tissue banking and translational research.

10.2 Specimen Collection for Tissue Banking (6/18/08)

The following must be provided in order for the case to be evaluable for the Biospecimen Resource:

10.2.1 One H&E stained slide

10.2.2 (10/29/10) 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 punch tool and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, instructions, and a shipping label can be obtained free of charge from the RTOG Biospecimen Resource (contact information provided in Section 10.2.6). Block or core must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

10.2.3 A Pathology Report documenting that the submitted block or core contains tumor. The report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

10.2.4 A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number.

10.2.5 (10/29/10) When serum/plasma/lymphocytes/urine are collected: The following materials must be provided to the RTOG Biospecimen Resource: A Specimen Transmittal Form documenting the date of collection of the serum; the RTOG protocol number, the patient's case number, collection time point, and method of storage, (e.g., stored at -80° C), must be included (see Appendices V & VI). Sites can access the form (no password required) at <http://www.rtog.org/members/forms/list.html> (under "Pathology").

10.2.5.1 Storage/Shipment of Blood Specimens (10/29/09)

Store all frozen biospecimens at -80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only).

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only).

10.2.6 (10/29/10) Submit materials for Tissue Banking and Translational Research as follows:

U.S. Postal Service Mailing Address: For Non-frozen Specimens Only
RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
1657 Scott Street, Room 223
San Francisco, CA 94143-1800

Courier Address (FedEx, UPS, etc.): For Frozen Specimens
RTOG Biospecimen Resource
University of California San Francisco
1657 Scott Street, Room 223
San Francisco, CA 94115

For questions and requesting tissue/blood kits: e-mail: RTOG@ucsf.edu, call 415-476-RTOG (7864) or fax 415-476-5271

10.3 Reimbursement (10/29/10)

RTOG will reimburse institutions for submission of protocol specified biospecimen materials sent to the Biospecimen Resource at the University of California San Francisco and other protocol-specified collection repositories/laboratories. After confirmation from the RTOG Biospecimen Resource or other designated repository/laboratory that appropriate materials have been received, RTOG Clinical Trials Administration will authorize payment according to the schedule posted with the Reimbursement and Case Credit Schedule found on the RTOG web site (http://www.rtog.org/pdf_document/RTOG_STUDY_LIST.pdf). Biospecimen payments will be processed quarterly and will appear on the institution's summary report with the institution's regular case reimbursement.

10.4 Confidentiality/Storage (5/22/08)

(See the RTOG Patient Tissue Consent Frequently Asked Questions, <http://www.rtog.org/biospecimen/tissuefaq.html> for further details.)

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

10.4.2 Specimens for tissue banking will be stored for an indefinite period of time. Specimens for the translational research component of this protocol will be retained until the study is terminated, unless the patient has consented to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

10.5 Translational Research (Highly recommended but not required)

10.5.1 Rationale (6/18/08)

The RTOG has been collecting pretreatment diagnostic tissue from lung cancer protocols. A number of histological, cell kinetic/proliferation, and molecular markers are under investigation, with several showing promise for the stratification of patients in future trials. This large randomized study presents an excellent opportunity for the collection of diagnostic biopsy specimens, serum/plasma, lymphocytes, and urine that will be assayed for various biological markers. Correlating these findings with clinical outcome in a group of patients treated with conventional radiation dose (60 Gy) or dose escalated radiation therapy (74 Gy) with concurrent chemotherapy with and without cetuximab may help increase our understanding of radiation sensitivity or resistance for both tumor and normal tissues and predict efficacy of molecular targeting therapy.

10.5.2 Research design (10/29/10)

Our initial goal for the current protocol is to collect and bank tissue specimen, blood and urine samples for all enrolled patients. To make sure the quality and quantity of samples collected will be appropriate for the future proposed studies, we describe a generic samples collection procedure below.

Although we cannot make a final decision about which markers will be analyzed and what the prioritization will be, we have listed the study strategy and a broad range of potential molecular markers that are considered state of art at this time for the purpose of sample collection/storage and preparation for the future analysis.

We propose using a two-stage design for determining the potential role of gene polymorphism, RNA expression, cytokines and growth factors in two tissue types (i.e., serum/plasma and WBC) obtained from individuals in the clinical trial. The selection of the two tissue types is based on the assumptions that serum proteins reflect compounded changes in both airways

and other organ systems and that RNA expression and protein levels in WBC more closely reflect the effects of the chemoradiation therapy at cellular levels whereas DNA polymorphism reflects the inherited genetic background. 30 ml peripheral blood will be taken from each individual before treatment, 20 ml at four weeks after initiation of treatment and at the first follow up after completion of concurrent chemoradiotherapy in order to determine baseline and short-term and long-term responses after concurrent chemoradiotherapy. 10-20 ml urine will also be collected in the morning of each day when blood is collected for potential biomarker related study.

Our current plan is to subject the samples to DNA polymorphism analysis using restriction fragment length polymorphism-polymerase chain reaction, global gene expression profiling and cytokine microarray analysis (RayBio human cytokine array; RayBiotech) that measures levels of 174 cytokines, and growth factors, implicated in human diseases. A newly available phosphor-protein antibody array (73 proteins) will also be used for WBC samples. Although the assays are relative quantification, it is adequate for initial comparative analysis because we will be comparing two groups of patients and samples from the same individuals before and after treatment

It is quite possible that any or all of these assays could be outdated by the time accrual to the study is complete and the data are analyzable with respect to clinical outcome. Therefore, if other methods are 'state of the art' at that time, they will be substituted.

The tissue submitted will be IHC tested for evidence of EGFR expression. EGFR represents one of the most promising biomarkers studied to date with regard to clinical outcome in cancer. The results of current studies will expand and refine investigation of EGFR relationship to clinical outcome 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 patients who receive an EGFR inhibitory agent.

We propose to select patients from the first half of the participants for screening DNA polymorphism, gene and proteins expression profiles or their changes during and after treatment and correlate with the clinical recurrence patterns and quality of life including toxicity. The profiles correlated with the clinical outcome based on the initial screening will be validated.

Once candidate DNA polymorphism, gene and proteins expression signatures are selected, our second step is to study the selected DNA polymorphism and measure the RNA, and protein levels in both the sera and/or WBC samples from the remaining clinical trial participants at the time points selected based on our first step results using the high-throughput reserve protein array analysis. Data obtained will be analyzed with treatment outcome including survivals, tumor responses, local control, regional lymph node control, distant metastasis and quality of life including toxicity. Because we have selected candidate markers to be tested in the second step, this stage should be considered as a validation step, which will give us sufficient confidence about potential utility of the markers should positive results be obtained.

We understand that the following list of potential biomarkers is subject to change based on information that is unknown at this time. However, at this time we propose:

1. DNA repairing gene polymorphism such as p53, XPD, XRCC1, ERCC1
2. Radiation-induced symptom related cytokines such as IL-1, IL-6 and growth factors such as TGF-beta, EGF
3. DNA repair related proteins: ERCC-1, XPA, XPC, XPD, XPF, XPG, SF-2, SNPs related to DNA repair gene
4. Apoptosis related RNA expression such as TRAIL, caspases, BCL-2, EGF receptor.
5. Radiation treatment related hypoxia markers such as osteopontin.

10.5.3 **Hypotheses**

Gene polymorphism in peripheral lymphocytes, levels of apoptosis related RNA gene expression and cytokines, growth factors, core DNA repair proteins, hypoxia markers in serum and/or white blood cells (possibly in urine) as well as the changes of the levels after chemoradiation therapy reflect the individual's intrinsic genomic background and response to the tumor/disease status. Therefore, either the baseline levels of the RNA, proteins and/or changes of the levels after chemoradiation therapy may be used as biomarkers to predict clinical outcome including survival, local regional recurrence, distant metastasis, and treatment related toxicity. These markers may help us in the future to classify patients for their probability to benefit from the therapeutic regimens, particularly dose escalated radiotherapy.

One of the critical issues in studying biomarkers is the availability of biological materials. For patients with advanced stage NSCLC, repeated biopsies from tumors are difficult and cannot be performed routinely. Serum circulating in the body and carrying proteins or peptides from tumors and their surrounding environment may be a candidate surrogate tissue that provides important information about the individual's intrinsic genetic background and its response to the disease in the lungs. It may be informative in assessing response and toxicity following treatment. Furthermore, an individual's serum is relatively stable in volume, and therefore more reliable for quantitative analyses. A major advantage of using serum is its accessibility as it can be obtained easily without invasive procedures, particularly if only a small volume is required. In fact, associations between levels of certain serum proteins and responses to chemotherapeutic regimens have been reported. Blood lymphocytes are cellular components easily accessible from patients. Although they are not cancer cells, their response to treatment may reflect their genomic background. Information obtained from these cells might provide additional information about treatment response and toxicity if the genomic background indeed plays a role.

10.5.4 **Specimen Collection for Translational Research (6/18/08)**

See Section 10.2 for specimen collection requirements for tissue banking.

10.5.4.1 **Lung cancer tissue specimen: (10/29/10)**

The following must be provided:

1. One H&E stained slide.
2. A paraffin-embedded tissue block of the tumor or a 2 mm diameter core of tissue, punched from the tissue block with a n punch tool, containing the tumor , and submitted in a plastic tube is recommended. Block or core must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.
3. A Pathology Report documenting that the submitted block or core contains tumor. The report must include the RTOG protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must not be removed from the report.
4. A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient's case number.

10.5.4.2 **Serum, lymphocytes and plasma collection (10/29/10)**

(See Appendix V for kit contents and detailed collection instructions)

Blood sample preparation

30 ml peripheral blood (two 10 ml EDTA tubes and one 10ml Red-top tube) will be taken from each individual before treatment, 20 ml peripheral blood (one 10 ml EDTA tube and one 10 ml red-top tube) also will be taken at four weeks after initiation of treatment, and the first follow-up visit after completion of concurrent chemoradiotherapy. **Note:** If a site missed collecting the pre-treatment whole blood samples for lymphocytes, this sample can be collected at any other collection time point or at any follow-up appointment. Use sterile techniques to avoid contamination.

10.5.4.3 **Frozen Plasma Samples for Biomarker Analysis (10/29/10)**

- a. Collect one 10 ml tube of blood using one EDTA (purple top) tube.
- b. Invert six to seven times to ensure adequate mixing with anticoagulant

- c. Centrifuge within one hour of collection in a standard clinical centrifuge at 3000g at 4° Celsius for 10 minutes
- d. If the interval between specimen collection and processing is anticipated to be greater than one hour, keep specimen on ice until centrifuging is done.
- e. Carefully pipette and transfer 1.0 ml aliquots of plasma (up to ten 1.2 ml cryovials) taking care to avoid collecting any blood cells or buffy coat (red/white blood cells)
- f. Place tops on cryovials and make sure tops of cryovials are on securely.
- g. All tubes should be clearly labeled as indicated in Section 10.5.4.3.
- h. Place tubes in a plastic biohazard zip lock bag.
- i. Store plasma cryovials at -80°C until ready to be shipped (ship on dry ice).

10.5.4.3.1 Blood Sample for Isolation of Lymphocytes (10/29/10)

- a. Collect one 10 ml tube of blood using one EDTA (purple top) tube.
- b. Invert 6-7 times to ensure adequate mixing with anticoagulant.
- c. Carefully pipette and transfer 0.5 ml aliquots of whole blood (up to five 1.2 ml cryovials)
- d. Tubes should be clearly labeled as indicated in Section 10.5.4.3.
- e. Place all three cryovials in a Styrofoam holder and then place into a zip lock bag
- f. (Store whole blood in cryovials at -80°C until ready to be shipped (ship on dry ice).

10.5.4.3.2 Frozen Serum Samples for Biomarker Analysis (10/29/10)

- a. Collect one 10 ml tube of blood without coagulants (Red top).
- b. Sit at room temperature for 30 min to allow clot formation.
- c. Centrifuge in a standard clinical centrifuge at 3000g at 4° Celsius for 10 minutes.
- d. Transfer ~1ml aliquots of separated serum into up to ten 1.2 ml cryovials
- e. Place tops on cryovials and make sure tops of cryovials are on securely.
- f. Tube should be clearly labeled as indicated in Section 10.5.4.3
- g. Place tubes in a plastic biohazard zip lock bag.
- h. Store serum cryovials at -80°C until ready to be shipped.

10.5.4.3.3 Urine sample collection (10/29/10)

- a. 10-20 ml urine will also be collected in the morning of each day when blood is collected for potential biomarker related study. See Appendix VI for detailed collection instructions
- b. Tubes should be clearly labeled as indicated in Section 10.5.4.3.
- c. Place tubes in a Styrofoam holder and then place into a zip lock bag.
- d. Store urine tubes at -80°C until packed and shipped (ship on dry ice).

10.5.4.3.4 Sample Labeling (10/29/10)

Each label will contain the following:

RTOG Protocol Number:
 Patient ID number (Case number):
 Date of Sampling: (mm/dd/yy)
 Time of collection:
 Collection time point:
 Sample Type:
 Site ID Number:

10.5.4.3.5 Sample Shipping Instructions (10/29/10)

Specimens should be sent with a Specimen Transmittal Form documenting the date of collection of the serum; the RTOG protocol number, the patient's case number, and method of storage, for example, stored at -80° C, must be included. Questions regarding blood collection or shipment should be directed to the RTOG Biospecimen Resource (see contact information Section 10.2.6). Ship by express overnight service, Monday through Wednesday; the RTOG Biospecimen Resource is unable to accept weekend or holiday arrival dates, and DO NOT ship on Friday.

All serum, plasma, and blood should be placed into individual biohazard zip lock bags. Use separate zip lock bags for each patient's samples. For frozen tissue samples, use an appropriate amount of dry ice (minimum of 7 lbs); use dry ice, sample biohazard labels, etc. as required by carrier. Do not put sample shipment log on top of dry ice unless it is in a zip lock bag.

10.5.5 Specimen Collection Summary (10/29/10)

| Specimens for Tissue Banking/Central Review/Translational Research | | | |
|---|--|--|--|
| Specimens taken from patient: | Collected when: | Submitted as: | Shipped: |
| Representative H&E stained slides of the primary tumor | Pre-treatment | H&E stained slide Pre-treatment | Slide shipped ambient |
| A paraffin-embedded tissue block of the primary tumor taken before initiation of treatment or a 2 mm diameter core of tissue, punched from the tissue block with a punch tool | Pre-treatment | Paraffin-embedded tissue block or punch biopsy | Block or punch shipped ambient |
| SERUM: 5-10 mL of whole blood in 1 red-top tube and centrifuge. | Pre-treatment, 4 weeks during treatment, and post-treatment at first followup. | Frozen serum samples containing 0.5 mL per aliquot in 1 mL cryovials (up to ten) | Serum sent frozen on dry ice via overnight carrier (Mon-Wed) |
| PLASMA: 5-10 mL of anticoagulated whole blood in EDTA tube (#1 purple/lavender top) and centrifuge | Pre-treatment, 4 weeks during treatment, and post-treatment at first followup. | Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (up to ten) | Plasma sent frozen on dry ice via overnight carrier (Mon-Wed) |
| DNA: 5-10 mL of anticoagulated whole blood in EDTA tube (#2-purple/lavender top) and mix | Pre-treatment. (Note if site missed this collection timepoint they may collect whole blood at any timepoint or follow up visit). | Frozen whole blood samples containing 1 ml per aliquot in 1ml cryovials (up to five) | Whole blood sent frozen on dry ice via overnight carrier (Mon-Wed) |
| 10-20 mL clean-catch urine | Pre-treatment, 4 weeks during treatment, and post-treatment at first followup. | Two 5-10 mL urine aliquots in 2 sterile 15 ml polypropylene centrifuge tubes. Store frozen at -20 or 80° C | Urine sent frozen on dry ice via overnight carrier. (Mon-Wed) |

10.5.6 Specimen Submission

See Section 10.2.6 for the address information for sending specimens.

11.0 PATIENT ASSESSMENTS

11.1 (9/22/09) Study Parameters: See Appendix II for a summary of patient assessments. See details and exceptions below in Sections 11.1.1-11.1.9. Since the overall endpoint is patient survival, patients will be followed until death.

- 11.1.1** Vital signs will be checked midway through cetuximab infusion, at the completion of infusion, and at one hour post-infusion.
- 11.1.2** CT scans or MRIs will be performed at a minimum of 1 cm slice thickness to include the lung apices through the adrenals. In addition, a consistent evaluation (CT or MRI) should be used throughout the study.
- 11.1.3** If the patient experiences > 10% weight loss, the BSA will be recalculated.
- 11.1.4** (3/4/10) PFTs (including DLCO and FEV1) will be done at 6 months after completion of consolidation therapy, then at 1 year after completion of consolidation treatment.
- 11.1.5** CBC and serum creatinine will be collected weekly prior to each chemotherapy treatment (and cetuximab treatment, if given).
- 11.1.6** For patients on Arms C & D: Patients should be monitored for hypomagnesemia, hypocalcemia, and hypokalemia weekly during concurrent and consolidation treatment and for at least 8 weeks following the completion of cetuximab. Repeat electrolytes as needed.
- 11.1.7** (3/4/10) The CT scan or MRI of the chest, upper abdomen and adrenal glands should be done within 6 weeks after completion of consolidation treatment, then every 6 months after the completion of consolidation treatment for 2 years, then annually.

- 11.1.8 (3/4/10) Unless otherwise specified, post-treatment follow up will take place every 3 months for the first year, every 4 months for year 2, every 6 months for years 3-5, then annually from the date of registration.
- 11.1.9 Quality of life assessments will be done at the completion of concurrent treatment, then 3, 12, and 24 months from baseline.
- 11.1.10 The swallowing diary will be collected weekly during concurrent treatment and twice during consolidation treatment (see Section 12.1.).
- 11.2 Prospective Health-Related Quality of Life (HRQOL) Analysis (3/9/09)

Note: Patients must be offered the opportunity to participate in the correlative components of the study. If the patient consents to participate in the quality of life component of the study, sites are required to administer the baseline assessments prior to the start of protocol treatment. **Sites are not permitted to delete the quality of life component from the protocol or sample consent.**

The study design is to prospectively analyze the QOL among patients with stage III NSCLC randomized between standard radiotherapy (60 Gy) versus high-dose conformal radiation therapy (74 Gy), each with concurrent chemotherapy. While dose escalation is hypothesized to yield greater tumor cell kill, it may also increase the normal tissue toxicity, in which case there may be a decrease in HRQOL. The primary normal tissue toxicities in patients receiving chemoradiation for lung cancer are esophagitis and pneumonitis. Prior studies have demonstrated that the most sensitive and clinically meaningful method for accurately capturing the normal tissue toxicities is via patients reported outcomes (PROs), such as HRQOL.

In this randomized trial, we plan to assess the FACT-TOI and the EQ-5D in all arms at 5 specific time points to minimize patient burden: baseline (pretreatment), at the end of chemoradiation (week 7), at the first follow-up (3 months), and at 12 months and 24 months from baseline. A brief patient swallowing diary will also be utilized weekly (on Fridays) throughout the course of concurrent chemoradiation treatment and then at the f/u visits during consolidation chemotherapy (for a total of 4 months).

In order to analyze the difference in QOL between all arms, we plan to use a brief, validated instrument that is user friendly and has clinical relevance (the Lung Cancer Subscale of the FACT-TOI). FACT-TOI is a measure that sums the functional well being (FWB), physical well being (PWB), and the lung cancer subscale (LCS) of the Functional Assessment of Cancer Therapy - Lung (FACT-L) QOL instrument, which has been extensively used for measuring QOL in patients with lung cancer.⁹² In a review of the literature reported that the FACT-L scale has been used in more than 5,000 patients and has been found to be sensitive to changes in performance status, treatment response.⁹³ FACT has been translated into 26 languages and is available free of charge to institutions with the completion of an agreement to share data, accessible at <http://www.facit.org/translation/licensure.aspx>. The full FACT-L questionnaire can be completed in less than 10 minutes.⁹⁴ This instrument has not only been shown to be prognostic for survival, but also sensitive to changes in QOL on serial evaluations throughout treatment.⁹³ Importantly, the FACT-TOI has been associated with clinically meaningful changes in patients with lung cancer.⁹⁵ The lung cancer sub-scale (LCS) consists of 9 items, involving lung cancer specific symptoms. All items are rated on a 5 item (point) Likert Scale, from 0 (not at all) to 4 (very much). It has been determined that a 3-point difference on the FACT-G subscales is associated with a meaningful difference in clinical and subjective indicators.⁹⁵ Thus, a difference of 3 LCS points will be considered clinically significant. As the LCS focuses on lung cancer symptoms, this will be used for the primary endpoint; however, the more general subscales of physical and functional well-being (on the brief FACT-TOI) will also be collected.

In order to analyze together both the potential benefits of dose escalation (in terms of survival), as well as its risks (in terms of toxicity and HRQOL), a quality-adjusted survival analysis can be performed. The EQ-5D is a method for obtaining valuations of health-related QOL which also can be used for quality-adjusted survival and cost-utility analyses.⁹⁶⁻⁹⁹ It is a two-part questionnaire that takes approximately 5 minutes to complete.¹⁰⁰ The first part of the EQ-5D consists of five items addressing five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on three levels: 1-no problems, 2-moderate problems, and 3-extreme problems. Health states are defined by the combination of the response levels for each of the five dimensions, generating 243 health states to which unconsciousness

and death are added.¹⁰¹ The second part of the EQ-5D is a visual analogue scale (VAS) valuing current health state, measured on a 20-cm 10-point-interval scale. Worst imaginable health state is scored as 0 at the bottom of the scale, and best imaginable health state is scored as 100 at the top. Both the five-item index score and the VAS score are transformed into a utility score between 0-“worst health state” and 1-“best health state.” Either the index score or the VAS score can be used in the quality-adjusted survival analysis, or the cost-utility equation can be entered, depending on the health state(s) of interest.¹⁰²

Although developed in Europe, the EQ-5D has been used in the United States and Canada.⁹⁶⁻⁹⁹ The EQ-5D web site, <http://www.euroqol.org/>, lists multiple languages in which the instrument has been validated. There have been few studies published reporting on the incorporation of the EQ-5D into the evaluation of patients with NSCLC. Trippoli et. al. used the EQ-5D in the evaluation of 95 patients with NSCLC treated at 15 Italian hospitals.¹⁰³ The mean utility score was 0.58 in the self-classifier version and 0.58 in the VAS version. Both the self-classifier version and the VAS version showed statistically significant correlation with each of the eight domains of the Short Form-36 (SF-36).

In this study, we plan to use the patient swallowing diary that was successfully used in RTOG 9801 and which takes 2-3 minutes to fill out. The RTOG 9801 swallowing diary was modified from a Medical Research Council (MRC) swallowing diary card for lung cancer.¹⁰⁴ This swallowing diary will be filled out by patients weekly during concurrent chemoradiation (on Fridays) and then at the follow-up visits during adjuvant chemotherapy.

The patients will be given the FACT-TOI and EQ5D instruments to be completed in the clinic at specified visits. A research assistant will be available to answer any questions that the patients have and review the questionnaire for completeness. If the questionnaires are not complete, patients will be asked if they left out answering the question by mistake or because they did not wish to answer the question. If the former, patient will be asked to answer those questions; if the latter, patients would not be asked anything further. If a patient does not come in to clinic (and/or if requested), the questionnaires will be mailed to the patient. If the questionnaires have not been received in two weeks after the due date, another set will be sent to the patients, reminding them to complete the questionnaire. If the patient prefers, he or she will be interviewed by the research assistant over the telephone at that time. For the swallowing diary, the diary will be given to the patients at the beginning of treatment and the patients will be reminded to fill this out on a weekly basis (each Friday) through the course of radiation and then at the f/u visits during adjuvant chemotherapy. Reminder notices will be routinely sent to the clinical research associates whose institutions are accruing to the trial that the HRQOL instruments need to be distributed to the patients at the prescribed time frames.

11.3 Response Assessment (RECIST Criteria)

11.3.1 Measurement of Response (10/29/10)

Response will be evaluated in this study using the international criteria proposed in the Revised Response Evaluation Criteria in Solid Tumors (RECIST) Guideline version 1.1 [*Eur J Cancer*. 2009;45:228-247.] See http://ctep.info.nih.gov/protocolDevelopment/docs/recist_guideline.pdf for further details.

Response Criteria: Evaluation of target lesions

- *Complete Response (CR): Disappearance of all target lesions
- *Partial Response (PR): At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
- *Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
- *Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

12.0 DATA COLLECTION

Data should be submitted to:

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

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

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

12.1 Summary of Data Submission (10/9/08)

| Item | Due |
|--|---|
| Demographic Form (A5) Initial Evaluation Form (I1) Pathology Report (P1) Slides/Blocks (P2) | 2 weeks after registration |
| Functional Assessment Cancer Therapy-Lung Trial Outcome Index (TOI) [FA] EQ-5D (HP) | Pretreatment, at completion of chemoradiation, then at 3, 12 and 24 months from baseline |
| Patient Swallowing Diary (DP) | Pretreatment, weekly during concurrent treatment, weeks 11 and 14 |
| Chemoradiation Treatment Summary Form (TS) | 1 week after completion of chemoradiation treatment |
| Consolidation Treatment Form (SF) | 1 week after completion of consolidation treatment |
| Radiotherapy Form (T1) [Copy sent to HQ and ITC] Complete Daily Treatment Record (T5) [Copy sent to HQ and ITC] | At completion of radiation therapy |
| Follow-up Form (F1) | Every 3 months for first year, every 4 months for year 2 and every 6 months for year 3-5; then annually |

12.2 Summary of Dosimetry Digital Data Submission for 3D-CRT or IMRT (Submit to ITC; see Section 12.2.1) [6/18/08, 10/29/09]

| Item | Due |
|--|------------------------------|
| Preliminary Dosimetry Information <ul style="list-style-type: none">▪ Digital Data Submission Information Form (DDSI) (submitted online at http://atc.wustl.edu)▪ CT data, critical normal structures, all GTV, CTV and PTV contours▪ Digital beam geometry for initial and boost beam sets▪ Doses for initial and boost sets of concurrently treated beams▪ Digital DVH data for all required critical normal structures, | Within 1 week of start of RT |

- GTV, CTV, and PTVs for total dose plan (**DV**)
- Hard copy or JPEG color isodose distributions for total dose plan as described in the QA Guidelines (**T6**)

NOTE: Sites must notify ITC via e-mail (itc@wustl.edu) after digital data is submitted. The e-mail must include study and case numbers or, if the data is phantom, “dry run” or “benchmark”.

Final Dosimetry Information

Within 1 week of RT end

- Copy of Radiotherapy Form (**T1**)
- Daily Treatment Record (**T5**) [**Copy to HQ and ITC**]
- Modified digital patient data as required through consultation with Image Guided Therapy QA Center

12.2.1

Digital Data Submission to ITC (10/29/09)

Digital data submission may be accomplished using media or the Internet.

For network submission: The secure FTP account assigned to the submitting institution by the ITC shall be used, and e-mail identifying the data set(s) being submitted shall be sent to:

itc@wustl.edu

For media submission: Please contact the ITC about acceptable media types and formats.

Hardcopies accompanying digital data should be sent by mail or Federal Express and should be addressed to:

**Image-Guided Therapy Center (ITC)
ATTN: Roxana Haynes
4511 Forest Park, Suite 200
St. Louis, MO 63108
314-747-5415
FAX 314-747-5423**

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint

13.1.1.1 Overall survival (Failure: death from any cause);

13.1.2 Secondary Endpoints

13.1.2.1 Progression-free survival (Failure: occurrence of local or regional progression, distant metastases, or death from any cause);

13.1.2.2 Local-regional failure (Failure: occurrence of local or regional progression);

13.1.2.3 Grade 3-5 esophagitis and pneumonitis adverse events;

13.1.2.4 Other grade 3-5 adverse events;

13.1.2.5 Death during or within 30 days of discontinuation of protocol treatment;

13.1.2.6 Quality of life (lung cancer subscale [LCS] of FACT-TOI);

13.1.2.7 Patient-reported swallowing ability;

13.1.2.8 Quality adjusted survival based on EQ5D derived health utility score;

13.1.2.9 Correlation of tumor markers with overall survival, local-regional failure, and QOL;

13.1.2.10 Prognostic and predictive effects of gross tumor volume on overall survival;

13.1.2.11 Prognostic value of pre-treatment SUV of PET scan in predicting survival, distant metastasis, and local-regional control.

13.2 Treatment Comparison: Background and Sample Size Determination

In accordance with NCI Cooperative Group Program Guidelines, this phase III trial will be reviewed by RTOG Data Monitoring Committee (DMC) on a semi-annual basis prior to the January and the June RTOG group meeting.

(6/18/08) This study has been redesigned as a 2x2 factorial with radiation dose as one factor and cetuximab as the other factor, and a primary endpoint of overall survival. The sample size calculations are based on increasing median survival time (MST) from 17.1 months to 24 months. For the sample size estimation, this study is viewed as a two-arm study in which the radiation

(RT) dose question [primary endpoint (1)] will be tested by combining the with and without cetuximab arms (Arms A & C versus Arms B & D), and the cetuximab question [primary endpoint (2)] will be tested by combining the high RT dose and standard RT dose arms (Arms A & B versus Arms C & D). The MST of 17.1 months for the control arm is based on RTOG 9410, which showed this MST in the once daily RT with concurrent chemotherapy arm.

The required sample size for each question [(1) RT dose and (2) cetuximab] of the primary endpoint of overall survival is based on the following conditions:

- Survival times are exponentially distributed with (at least approximately) constant hazards in both treatment arms;
- The MST of the control group will be 17.1 months (translates to monthly hazard $\lambda = 0.04053$);
- The MST of the experimental group will be 24 months (translates to monthly hazard $\lambda = 0.02888$);
- A one-sided test at $\alpha = 0.0125$ (familywise $\alpha = 0.025$);
- Statistical power of 80%;
- Fifty months of accrual and an additional 18 months of follow-up;
- Three interim significance tests and a final test are planned using Haybittle-Peto boundaries¹⁰⁵⁻¹⁰⁶ for rejecting the null hypothesis (efficacy) and Rule C in Freidlin and Korn¹⁰⁷ for rejecting the alternative hypothesis (futility).

Using a group sequential design, we will require a total sample size of 450 to be accrued uniformly over 50 months with an additional 18 months of follow up.¹⁰⁸ Guarding against up to a 10% ineligibility and lost to follow up rate, **the final targeted accrual for this study will be 500 cases.**

13.3 Tumor Markers: Background and Statistical Power Considerations (6/18/08)

At the time of data maturity of this study, we will propose specific details of the markers to be investigated. We will address the assays that will be used and will provide a list of specific correlative aims along with appropriate statistical considerations.

For planning purposes, it is assumed that the patient accrual will not be discontinued in the trial before reaching its target. Based on other RTOG trials, it is projected that 60% to 80% of randomized patients will be analyzable for tumor marker evaluation, giving a total of 270-360 analyzable patients. A two-step design will be used. All patients eligible for the treatment comparison will be randomly divided into training and test subsets. A randomization will be performed within strata defined by specimen submission (yes vs. no) and assigned treatment. Each set will have 135-180 patients. Since this analysis will occur after the primary treatment analysis, there should be at least 339 deaths. So it is projected that there will be between 101 and 135 deaths in patients with submitted specimen in the training subset. This number of deaths is based upon 60% or 80% of the patients having a biomarker]. Possible biomarkers [will be initially identified as potentially having prognostic value in the training subset and then validated in the test subset. The biomarkers will be categorized into subgroups e.g., two subgroups (overexpressed and underexpressed) or three subgroups (mutation in two alleles, one allele, or no mutation).

The equation described by Schoenfeld¹⁰⁹ was used to calculate statistical power for various scenarios with training set for a biomarker with two subgroups:

Number of failures = $(z_{1-\alpha/2} + z_{1-\beta})^2 / (\ln HR)^2 w (1 - w)$, where

$z_{1-\alpha/2}$ = normal deviate for the significance level

$z_{1-\beta}$ = normal deviate for the statistical power

HR = hazard ratio comparing favorable risk subgroup to unfavorable risk for subgroup

w = prevalence rate of risk subgroup

Table 1 below shows statistical power to detect hazard ratios for survival of 1.50, 1.75, and 2.00 for prevalence rates between 10-90%. The proposed analysis will be done when there are projected between 101 and 135 deaths. The significance level was set at 0.05. As seen in the table, there will be good statistical power (≥ 0.80) with 101 deaths to detect a hazard ratio ≥ 2.00 and with 135 deaths to detect a hazard ratio ≥ 1.75 .

Table 1: Statistical Power with 101 and 135 Events (Deaths) and 5% Alpha

| Hazard Ratio | 1.50 | | 1.75 | | 2.00 | |
|-----------------|------|------|------|------|------|------|
| # deaths/ | 101 | 135 | 101 | 135 | 101 | 135 |
| Prevalence rate | | | | | | |
| 10% or 90% | 0.23 | 0.29 | 0.39 | 0.49 | 0.55 | 0.67 |
| 20% or 80% | 0.37 | 0.46 | 0.61 | 0.73 | 0.79 | 0.89 |
| 30% or 70% | 0.46 | 0.57 | 0.73 | 0.84 | 0.89 | 0.95 |
| 40% or 60% | 0.51 | 0.63 | 0.78 | 0.88 | 0.92 | 0.97 |
| 50% | 0.53 | 0.65 | 0.80 | 0.90 | 0.93 | 0.98 |

13.4 Patient Accrual (6/18/08)

The study design is based on a 50-month accrual period with approximately 9 patient entries per month. This includes a projection of 2 patients per month from NCCTG based on their most current experience participating in SWOG 0023, and the balance from RTOG. CALGB has also indicated that some of their institutions will participate in this trial. Currently, there are no data available to project their additional accrual to the study.

During the first 6 months following activation, little accrual is anticipated while the trial is approved by institutional IRBs. If the total accrual during months 13 through 18 of the study is $\leq 20\%$ of the targeted accrual, the protocol will be discontinued per NCI-CTEP accrual guidelines for phase III studies. If the total accrual is between 21-49%, the protocol will continue to accrue for an additional 6 months. If continued, the study has to accrue at least 50% of targeted accrual during these months in order to remain open beyond two years.

13.5 Randomization (6/18/08)

Patients will be stratified before randomization with respect to PET imaging used in staging; (yes vs. no), dose delivery (3D CRT vs. IMRT), Zubrod (0 vs. 1), and histology (squamous vs. non-squamous). The treatment allocation scheme described by Zelen will be used because it balances patient factors other than institution.¹¹⁰ Patients will be randomized to 1 of 4 Arms:

Arm A): Radiation to 60 Gy given concurrently with weekly carboplatin and paclitaxel

Arm B): Radiation to 74 Gy given concurrently with weekly carboplatin and paclitaxel

Arm C): Radiation to 60 Gy given concurrently with weekly carboplatin and paclitaxel + cetuximab

Arm D): Radiation to 74 Gy given concurrently with weekly carboplatin and paclitaxel + cetuximab

13.6 Analysis Plan (6/18/08)

13.6.1 Statistical Methods

All eligible patients randomized will be included in answering each question [(1) RT dose and (2) cetuximab] of the primary endpoint (intent-to-treat analyses). The major analysis will take place after a boundary is crossed in any of the interim analyses or after all the patients have been entered in the study and 339 deaths have occurred. Critical values used in the sequential analyses will preserve an overall alpha level of 0.025 for the study. Overall survival, progression-free survival, and local-regional failure rates will be measured from the date of randomization to the event of interest otherwise censored at last follow-up. In the primary

analysis, for each of the two questions, overall survival will be estimated by the Kaplan-Meier method.¹¹¹ The distribution of overall survival estimates between the control and experimental groups will be compared using the log rank test.¹¹² The same estimation method and statistical test will be used for progression-free survival. The cumulative incidence method will be used to estimate local-regional failure rates and the failure rates between the control and experimental groups will be compared using the failure-specific log-rank test.¹¹³ Associations between time-to-event endpoints and covariates of interest that are of secondary interest will be investigated using the Cox proportional hazards model.¹¹⁴ As appropriate, these analyses will use time-dependent covariates or the landmark method to eliminate time bias.

For endpoints 13.1.2.3 and 13.1.2.4, only adverse events assessed to be definitely, probably, or possibly related to protocol treatment will be considered. The rates of Grade 3-5 esophagitis and pneumonitis adverse events, all Grade 3-5 adverse events, and death during or within 30 days of discontinuation of protocol treatment will be tested for equality using a two-sided z-test with a 0.05 significance level after transforming the proportions in each arm to an approximate standard normal random variable

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 quality adjusted survivals. The log-rank test will compare those survivals between the treatments.

The Hochberg procedure will be used to preserve the overall significance level of 0.05 for multiple tests associated with the QOL and the tumor marker secondary endpoints.¹¹⁵

13.6.2 Early Stopping Rules (6/18/08)

13.6.2.1 Unacceptable Adverse Events on Arms B, C, and D (3/4/10)

Early stopping of this trial will be based on the following unacceptable adverse events (AEs) occurring within ≤ 30 days after the end of treatment defined as possibly, probably, or definitely related to treatment (per CTCAE, v.3.0):

- The following grade 3-5 cardiac arrhythmia/cardiac general AES:
 - Cardiac arrhythmia (supraventricular, ventricular)
 - Left or right ventricular dysfunction
 - Pericardial effusion
 - Pericarditis
 - Restrictive cardiomyopathy
- The following grade 4-5 gastrointestinal AES:
 - Dysphagia
 - Esophagitis
 - Fistula (esophagus)
 - Obstruction (esophagus)
 - Perforation (esophagus)
 - Stricture/stenosis (esophagus)
 - Ulcer (esophagus)
- The following grade 3-5 neurological AES:
 - Brachial plexopathy
 - Laryngeal nerve dysfunction
 - Myelitis
 - Phrenic nerve dysfunction
- The following grade 3-5 (except if noted) pulmonary/upper respiratory AES:
 - Atelectasis (grade 4-5 only)
 - FEV1 (provided grade 3 is worse than baseline)
 - Fistula
 - Hypoxia (provided grade 3 is worse than baseline)
 - Obstruction/stenosis of the airway
 - Pleural effusion
 - Pneumonitis
 - Pulmonary fibrosis
 - Vital capacity (provided grade 3 is worse than baseline)
- Grade 3-5 hemorrhage (pulmonary or upper respiratory) AES

- Any Grade 5 AE attributed to treatment

All of the above AEs will be immediately monitored and queried for source documentation and then reviewed by the study chairs. If a patient has more than one unacceptable AE, they will only be counted as one unacceptable AE for this analysis.

(3/4/10) Three interim analyses of AEs are planned after 20, 40, and 80 evaluable patients have been accrued to each of Arms B, C, and D (high-dose RT and/or cetuximab arms) and have been followed for a minimum of 30 days after the end of treatment. Patients will be considered evaluable if they are eligible and receive a single dose of cetuximab or at least one fraction of RT. The interim analysis will include all of the above specified unacceptable treatment-related AEs reported at the time of the interim analysis. The rate of the above specified unacceptable treatment-related AEs occurring within 90 days from the start of treatment in RTOG 0324 was 11%. For the purposes of these early stopping rules, a rate of 40% or greater will be considered too excessive.

According to Fleming's method¹⁰⁵ with a maximum overall significance level of 0.05

1. If there are 11 or more of the specified treatment-related AEs out of the first 20 evaluable patients or
2. If there are 16 or more of the specified treatment-related AEs out of the first 40 evaluable patients or
3. If there are 25 or more of the specified treatment-related AEs out of the first 80 evaluable patients;

Then it will be concluded that the particular treatment arm has a specified treatment-related AE rate greater than or equal to 40%. These stopping rules provide > 98% power for concluding that the unacceptable adverse event rate is equal to or exceeds 40% when in fact that is the true rate. If this occurs, the study chairs, RTOG Lung Cancer Committee Chair and the statistician will review the AE data and make appropriate recommendations to the RTOG Executive Committee and Research Strategy Committee about the study. Some possible recommendations include the following:

- If the specified treatment-related AE rate is greater than or equal to 40% in Arm B, then the high-dose RT arms will close (B and D), and arms A and C will remain open to answer the cetuximab question [primary endpoint (2)].
- If the specified treatment-related AE rate is greater than or equal to 40% in Arm C, then the cetuximab arms will close (C and D), and arms A and B will remain open to answer the RT dose question [primary endpoint (1)].
- If the specified treatment-related AE rate is greater than or equal to 40% in Arm D, then Arm D will close, and the study chairs, the RTOG Lung Cancer Committee Chair, and the statistician will meet to determine how to proceed with this study. If needed, the protocol will be appropriately amended.

RTOG HQ will send the results of the interim SAE analyses to the Protocol Information Office (PIO) at NCI.

Even if all the arms are within the acceptable boundaries set above, treatment completion will be evaluated at each AE interim analysis. There are two main concerns:

Concern #1 is the potential that the addition of cetuximab will limit the ability to complete a reasonable amount of the high-dose RT treatment course defined in the protocol. This could create a negative interaction if the higher dose of radiation is actually more effective than the standard dose. A negative interaction would compromise the ability of this trial to answer the radiation question. In order to address this concern, the completion of the high-dose RT treatment course will be evaluated and reported using the following definition of completion:

- Patients must receive $\geq 93\%$ of the prescribed dose to $\geq 95\%$ of the PTV. This comes from Section 6.1.6.2 in the protocol. It is the definition of an acceptable deviation.

Concern #2 is the potential that the delivery of high-dose RT will limit the ability to complete a reasonable amount of the cetuximab treatment course defined in the protocol. This could create a negative interaction if the cetuximab arm is actually more effective than the no

cetuximab arm. A negative interaction would compromise the ability of this trial to answer the cetuximab question. In order to address this concern, the completion of the cetuximab treatment course will be evaluated and reported using the following definition of completion:

- Patients must receive 70% of the total cetuximab dose that they are expected to receive, allowing for protocol specified dose modifications. If a patient has a protocol permitted dose modification (Section 7.9.2: -1 dose level = 200 mg/m² or -2 dose level = 150 mg/m²) then the total expected dose will be calculated based on these levels. For patients who miss a dose, the expected dose for that day will be calculated using the current dose level they should be receiving, which will be either 250, 200, or 150 mg/m².

13.6.2.2 Deaths on All Arms

All deaths reported as related to treatment will be reviewed by an independent reviewer, Dr. Ross Abrams, RTOG's Vice-Chair of Disease Sites. In addition, deaths reported as not related to treatment occurring while a patient is on protocol treatment or within 30 days after stopping protocol treatment will be reviewed by Dr. Abrams.

13.6.3 Interim Analysis to Monitor the Study Progress (6/18/08)

Interim reports with statistical analyses will be prepared twice per year until the initial treatment results have been presented or published. In general, the interim reports will contain the following information:

- patient accrual rate with a projected completion date (while the study is still accruing)
- total patients accrued
- distributions of important pretreatment and prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm
- compliance rates of treatment delivery

The interim reports will not contain the results from the treatment comparisons with respect to the primary endpoint, overall survival, or any secondary endpoints.

13.6.4 Significance Testing for Early Termination and Reporting

13.6.4.1 Primary Endpoint: Overall Survival (6/18/08)

A group sequential test with 3 planned interim analyses and a final analysis will be performed. The timing of the interim analyses will be based on primary endpoint events as defined in 13.1. The maximum number of events required for the study is 339. For each of the two primary study endpoints, under the alternative hypothesis that the higher RT or additional treatment will increase survival from MST = 17.1 months to MST = 24 months, the projected numbers of deaths and the nominal significance levels for rejecting the H₀ or the H₁ at each of these interim analyses, along with the projected timing and accrual, are shown in Table 2 below:

Table 2: Nominal Significance Levels for Interim Analyses

| Interim Analysis | Efficacy: Reject H ₀ if p (H ₀) ≤ | Futility: Reject H ₁ if p (H ₁) ≤ | # Events |
|------------------|--|--|----------|
| #1 | 0.001 | 0.005 | 85 |
| #2 | 0.001 | 0.005 | 170 |
| #3 | 0.001 | 0.005 | 255 |

At each planned interim analysis, the 1-sided p-value from the tests for assessing treatment efficacy and futility with respect to overall survival will be compared to the nominal significance levels in Table 2. For efficacy, Haybittle-Peto boundaries are used.¹⁰⁴⁻¹⁰⁵ For futility, the alternative hypothesis will be tested using Rule C from Freidlin and Korn¹⁰⁶ at a significance level of 0.005. Table 3 shows the actions to be taken based on the results of the interim analyses.

Table 3: Outcome Possibilities and Corresponding Actions for Interim Analyses

| Primary Endpoint (1) (RT dose question) | Primary Endpoint (2) (cetuximab question) | Action |
|--|--|--|
| Reject H_0 | Reject H_0 | Stop accrual (if applicable), conclude (1) the OS rate of high dose RT is higher than standard dose RT <u>and</u> (2) the OS rate with cetuximab is higher than without it. |
| Reject H_1 | Reject H_1 | Stop accrual (if applicable), <u>cannot</u> conclude (1) the OS rate of high dose RT is higher than standard dose RT, <u>nor</u> that (2) the OS rate with cetuximab is higher than without it. |
| Do not reject H_0 or H_1 | Do not reject H_0 or H_1 | Continue accrual (if applicable) and follow to the next scheduled analysis. |
| Reject H_0 | Reject H_1 | Stop accrual (if applicable), conclude that (1) the OS rate of high dose RT is higher than standard dose RT, but <u>cannot</u> conclude that (2) the OS rate with cetuximab is higher than without it. |
| Reject H_0 | Do not reject H_0 or H_1 | Randomize rest of patients only to arms B & D (if still accruing), conclude that (1) the OS rate of high dose RT is higher than standard dose RT. For (2) follow to the next scheduled analysis. |
| Reject H_1 | Reject H_0 | Stop accrual (if applicable), <u>cannot</u> conclude that (1) the OS rate of high dose RT is higher than standard dose RT, but can conclude that (2) the OS rate with cetuximab is higher than without it. |
| Reject H_1 | Do not reject H_0 or H_1 | Randomize rest of patients only to arms A & C (if still accruing), <u>cannot</u> conclude that (1) the OS rate of high dose RT is higher than standard dose RT. For (2) follow to the next scheduled analysis. |
| Do not reject H_0 or H_1 | Reject H_0 | Randomize rest of patients only to arms C & D (if still accruing). For (1) follow to the next scheduled analysis. Conclude that (2) the OS rate with cetuximab is higher than without it. |
| Do not reject H_0 or H_1 | Reject H_1 | Randomize rest of patients only to arms A & B (if still accruing). For (1) follow to the next scheduled analysis. <u>Cannot</u> conclude that (2) the OS rate with cetuximab is higher than without it. |

In addition to reporting results as listed in 13.6.2, at the first RTOG DMC meeting following the required number of deaths for each planned interim analysis, blinded efficacy results will be reported to the RTOG DMC.

13.6.5 Analysis For Reporting the Initial Treatment Results (6/18/08)

The primary objectives of this study are to determine whether high-dose RT in addition to concurrent chemotherapy will increase the MST from 17.1 months to 24 months and whether the addition of cetuximab to concurrent radiation therapy and chemotherapy will increase the MST from 17.1 months to 24 months. This major analysis will occur after at least 339 failures have been observed, unless an early stopping rule is satisfied. It will include:

- tabulation of all cases entered and those excluded from the analyses with the reasons for exclusion given
- distributions of important prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm
- compliance rate of treatment delivery
- observed results with respect to the primary and secondary endpoints

All eligible patients randomized will be included in the comparison and will be grouped by assigned treatment in the analysis. The primary hypothesis of treatment benefit for each primary endpoint question will be tested using the log-rank statistic with a 1-sided significance level of 0.0125, given that the 3 interim analyses were carried out per Section 13.6.4.1. If a

futility boundary is crossed for only 1 of the primary hypotheses, then the primary hypothesis for the remaining treatment question will be tested using the log-rank statistic with a 1-sided significance level of 0.025. Additional analyses of treatment effect will be performed using the Cox proportional hazard model with the stratification factors included as fixed covariates, as well as other possible modifying factors, such as age, gender, race, and other patient characteristics that are imbalanced between the treatment arms. If feasible, treatment comparisons with respect to the primary endpoint (OS) will be compared within each ethnic and racial category.

13.6.6 Clinical Data Update System (CDUS) Monitoring

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

13.6.7 Tumor Marker Analysis

The bio-assays will be performed at study chair's laboratory without knowledge of clinical outcome, and the results will be forwarded to the RTOG Department of Statistics for correlation with clinical outcome. All tumor marker analyses will occur after the analysis reporting the results from the treatment comparison.

A two-stage analysis will be used. All patients who are used in the treatment analysis will be randomly divided into training and test subsets. The randomization will be performed within strata defined by specimen submission (yes vs. no) and assigned treatment. The biomarkers will be categorized into subgroups, e.g., two subgroups (overexpressed and underexpressed) or three subgroups (mutation in two alleles, one allele, or no mutation). In the first stage, the log-rank test will be used to test for overall survival and local-regional failure differences among subgroups of potential markers using the training subset. Those markers found to be statistically significant at $p < 0.05$ will be further tested in the test subset of patients using the Cox proportional hazards model for both outcomes. Potential covariates evaluated for the multivariate models are assigned treatment, age, Zubrod performance status, and stage (IIIA vs. IIIB). A stepwise procedure will be used to develop the base model for each outcome endpoint prior to evaluating the prognostic impact of the tumor markers. This approach will be employed to account for as much variation as possible for each outcome before they are tested. It is entirely possible that factors shown to be prognostic in other published series may not be found prognostic here. Then the tumor marker or combination of markers will be added to the model to test for significance. If the hypothesized cut points do not yield statistical significance, other cut points may be evaluated. The analysis of one individual marker will include only patients with that marker. However, the analysis of two or more markers will include all patients with at least one determination of the tumor markers being tested. The assumption is made that the other tumor marker values are missing completely at random. The missing tumor values will be imputed 5 times, and the average value along with the pooled standard error associated with the parameter estimates for each tumor marker in the Cox model analysis will be reported.¹¹⁶

13.6.8 Health-related Quality of Life (HRQOL) and Health Utility Analysis (6/18/08)

These HRQOL and health utility analyses will be carried out with respect to the radiation (RT) dose question (Arms A & C versus Arms B & D). We will use two instruments to measure HRQOL: FACT-TOI, including the lung cancer subscale (LCS) and EQ-5D. FACT-TOI is a measure that sums the functional well being (FWB – 7 items), physical well being (PWB – 7), and the lung cancer subscale (LCS – 9 items) of the Functional Assessment of Cancer Therapy - Lung (FACT-L). Patients eligible for the treatment comparison will be included in the QOL analysis only if they have provided baseline and at least one subsequent measurement. The difference in the LCS and the FACT-TOI score between the baseline and each follow-up evaluation will be computed for each patient. These differences of the means between the two treatments will be compared at 3, 12 and 24 months with t-tests and will be considered to be clinically meaningful if they are > 3.0 for LCS and > 7.0 for FACT-TOI.

The primary QOL hypothesis is that patients on the more intensive chemoradiation arm (the higher radiation dose arm) will have clinically meaningfully lower QOL as measured by the LCS subscale of the FACT-TOI instrument at 3 months post completion of treatment. Secondly, this lower QOL score will be maintained at longer follow up as well (at twelve and 24 months from the start of treatment).

Quality-adjusted survival is the sum of the products generated by multiplying a patient's health utility score for each specific time period by the length of that time period. The five-item index score and VAS score from EQ5D will be used to generate utility scores that will lie between 0 (Worst health state) and 1 (Best health state). Quality-adjusted survivals between the two treatments will be compared by log rank test.

The area under curve (AUC) will be employed to compare the individual patient scores derived from their swallowing diaries over time between the two arms. A Z-test will be used for this comparison. This analysis will be restricted to patients who have at least 15 entries in their swallowing diary.

To inspect the missing data mechanism, we will use at least a graphical method. A missing completely at random (MCAR) mechanism exists when missing values are randomly distributed across all observations. A missing at random (MAR) mechanism exists when values are not randomly distributed across all observations, rather than one or more sub-samples.

If the cause of missing data is MCAR, listwise deletion (complete case analysis) will be done. If the MAR assumption is supported by the data, then an imputation method such as multiple imputation will be applied to impute missing data.

If the MAR assumption is not supported by the data, then adjusting for covariates (such as the baseline QOL score) might reduce the conditional association between outcomes and missing values. If missing data patterns look similar when stratified by such covariate(s), then an analysis that adjusts for such covariate(s) will be conducted and an imputation method such as multiple imputation will be applied. If approximate conditional independence cannot be obtained with any set of covariates, then MNAR (missing not at random) must be addressed by an explicit model for the missing data mechanism¹¹⁷ and then an imputation method such as multiple imputation will be applied. All results from the imputed analysis using the multiple imputation will be compared to the complete case analysis results to assess any potential biases.

We will describe the distributions of QOL data collection patterns over all collection points in each treatment arm. The distribution of pretreatment characteristics, such as performance score and treatment assignment, will be compared between the patients with available QOL data and the patients without QOL data.

13.7 Gender and Minorities

Some investigators have shown gender to be a prognostic factor in non-small cell lung cancer; however, the RTOG did not show this to be the case. An analysis of race also did not indicate an association with outcome.¹¹⁸⁻¹¹⁹ 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 also considered the possible interactions between gender and treatments and race and treatments. Participation rates of men and women will be examined in the interim analyses. Based on accrual statistics from RTOG 9410, the following table lists projected accrual by gender and race/ethnicity.

Projected Distribution of Gender and Minorities

| Ethnic Category | Gender | | |
|---|----------------|--------------|--------------|
| | Females | Males | Total |
| Hispanic or Latino | 2 | 4 | 6 |
| Not Hispanic or Latino | 170 | 324 | 494 |
| Ethnic Category: Total of all subjects | 172 | 328 | 500 |
| Racial Category | | | |
| American Indian or Alaskan Native | 0 | 1 | 1 |
| Asian | 2 | 5 | 7 |
| Black or African American | 11 | 40 | 51 |
| Native Hawaiian or other Pacific Islander | 1 | 4 | 5 |
| White | 158 | 278 | 436 |
| Racial Category: Total of all subjects | 172 | 328 | 500 |

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APPENDIX I

Sample Informed Consent

RTOG 0617/NCCTG N0628/CALGB 30609/ECOG R0617

A RANDOMIZED PHASE III COMPARISON OF STANDARD- DOSE (60 Gy) VERSUS HIGH-DOSE (74 Gy) CONFORMAL RADIOTHERAPY WITH CONCURRENT AND CONSOLIDATION CARBOPLATIN/PACLITAXEL +/- CETUXIMAB (IND #103444) IN PATIENTS WITH STAGE IIIA/IIIB NON-SMALL CELL LUNG CANCER

This is a clinical trial, a type of research study. Your study doctor (and/or people on your doctor's team who are familiar with this study) will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have lung cancer that has spread to regional lymph nodes and are not a candidate for surgery.

Why is this study being done?

(For patients enrolled on or before [6/18/08])

The purpose of this study is to compare the effects, good and/or bad, of high-dose radiation therapy with standard dose radiation therapy on you and your Stage III non-small cell lung cancer to find out which is better. In this study, you will get either the high-dose or the standard-dose radiation therapy. You will not get both. Everyone will get the chemotherapy with the same drug combination and schedule, consisting of paclitaxel and carboplatin.

(For patients enrolled after [6/18/08])

One purpose of this study is to compare the effects, good and/or bad, of high-dose radiation therapy and chemotherapy with standard dose radiation therapy and chemotherapy on you and your cancer to find out which is better. In this study, you will get either the high-dose or the standard-dose radiation therapy. The high-dose radiation therapy is considered experimental in this study. Everyone will get the chemotherapy with the same drug combination and schedule, consisting of paclitaxel and carboplatin.

In addition, this study will compare the effects, good and/or bad, of adding cetuximab to radiation and chemotherapy. In this study, you will get either radiation and chemotherapy or radiation, chemotherapy, and cetuximab.

Cetuximab is a drug that may delay or prevent tumor growth by blocking certain cellular chemical pathways that lead to tumor development. It has been approved by the FDA as a treatment for patients with colorectal and head and neck cancer. Cetuximab has not yet been approved as a treatment for patients with lung cancer and is considered experimental in this study.

How many people will take part in the study? (6/18/08)

About 500 people will take part in this study. About half of the patients will receive high-dose radiation therapy and about half will receive standard dose radiation therapy.

What will happen if I take part in this research study? (3/9/09)

Before you begin the study ...

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Physical examination by several doctors
- Evaluation of your height, weight, blood pressure and overall physical condition
- Evaluation of your ability to carry out daily activities
- A biopsy of your tumor proving that you have cancer
- CT scan of the chest and upper abdomen; a CT (Computed Tomography) scan is a study using x-rays to look at one part of your body
- MRI scan of the brain (or CT scan if the MRI cannot be performed for medical reasons); an MRI (Magnetic Resonance Imaging) is imaging using a strong magnetic field to look at one part of your body
- Body FDG-PET or PET-CT scan; a PET scan is a computerized image that looks at the activity of tumor cells in your entire body and that requires injection of a special marker into your vein, such as sugar (glucose) combined with a low-dose radioactive substance (a tracer). A camera records the tracer's signal as it travels through your body.
- A bone scan (if a PET scan isn't available); A bone scan is a study using x-rays in which a small amount of radioactive material is injected and travels through the bloodstream. It collects in the bones and is detected by special instrument called a scanner.
- Routine blood tests (about 1-3 teaspoons of blood will be taken from your vein)
- Studies of your lung function
- For women able to have children, a pregnancy test
- If your doctor recommends: An EKG, a test of your heart function

During the study ...

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Evaluation of your weight and ability to carry out daily activities weekly during chemotherapy
- Routine blood tests weekly during chemotherapy (about 1-3 teaspoons of blood will be taken from your vein)
- Evaluation of any side effects you may be having during chemotherapy

- For patients receiving cetuximab, evaluation of blood pressure and overall physical condition each time cetuximab is given: midway through receiving the cetuximab, at the completion of cetuximab, and after receiving cetuximab

When you are finished with radiation therapy, chemotherapy (and cetuximab if you receive it)...

- Physical examination
- Evaluation of your weight and ability to carry out daily activities
- Evaluation of any side effects you may be having
- Routine blood tests (about 1-3 teaspoons of blood will be taken from your vein)

At the end of all treatment...

- Physical examination
- Evaluation of your weight and ability to carry out daily activities
- Evaluation of any side effects you may be having
- Routine blood tests (about 1-3 teaspoons of blood will be taken from your vein)
- Studies of your lung function
- An EKG, a test of your heart function
- CT scan of the chest and upper abdomen

You will need these tests and procedures in follow-up visits. They are being done to see how you and your cancer were affected by the treatment you received.

- You will be seen by your doctor every 3 months for the first year, every 4 months for year 2, every 6 months for years 3-5, then once a year for your lifetime
- You will have a CT scan or MRI of the chest and upper abdomen every 6 months for 2 years then once a year
- You will have studies of your lung function at 6 months from the end of all treatment and at 1 year

(3/9/09) 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 study doctor can choose the group you will be in. You will have a 25% chance of being placed in one of four groups.

If you are in group 1 (called "Arm A"):

You will receive the standard or usual dose of radiation therapy. You will receive radiation therapy 5 days per week for about 6 weeks. Chemotherapy consisting of paclitaxel and carboplatin will be given on days 1, 8, 15, 22, 29, and 36 during radiation therapy. You will receive two additional cycles of chemotherapy on days 64 and 85 after completion of the combined chemotherapy and radiation.

If you are in group 2 (called "Arm B"):

You will receive a higher than standard dose of radiation therapy. You will receive radiation therapy 5 days per week for 7½ weeks. Chemotherapy consisting of paclitaxel and carboplatin will be given on days 1, 8, 15, 22, 29, 36, and 43 during radiation therapy. You will receive two additional cycles of chemotherapy on days 71 and 92 after completion of the combined chemotherapy and radiation.

If you are in group 3 (called “Arm C”):

You will receive the standard or usual dose of radiation therapy. You will receive radiation therapy 5 days per week for about 6 weeks. Chemotherapy consisting of paclitaxel and carboplatin will be given on days 8, 15, 22, 29, 36, and 43 during radiation therapy. You also will receive cetuximab on these days. After completion of the radiation, chemotherapy, and cetuximab, you will receive two additional cycles of chemotherapy on days 71 and 92, and you will receive cetuximab on days 50, 57, 64, 71, 78, 85, 92, 99, and 106.

If you are in group 4 (called “Arm D”):

You will receive a higher than standard dose of radiation therapy. You will receive radiation therapy 5 days per week for 7½ weeks. Chemotherapy consisting of paclitaxel and carboplatin will be given on days 8, 15, 22, 29, 36, 43, and 50 during radiation therapy. You also will receive cetuximab on these days. After completion of the radiation, chemotherapy, and cetuximab, you will receive two additional cycles of chemotherapy on days 78 and 99, and you will receive cetuximab on days 57, 64, 71, 78, 85, 92, 99, 106, and 113.

All groups will receive chemotherapy with the same drug combination, dose, and schedule. Paclitaxel and carboplatin are given by vein before radiation therapy. The paclitaxel takes one hour to be given after you have been pre-medicated with medicines to ease possible side effects. After the paclitaxel, the carboplatin is given over 30 minutes along with drugs used to prevent or reduce upset stomach and vomiting.

Groups 3 and 4 (Arms C and D): Before the first dose of cetuximab, you will be given some medicine through your vein to prevent an allergic reaction to cetuximab. Then you will be given the first dose of cetuximab through your vein for approximately two hours. You will not receive chemotherapy or radiation therapy on the day you receive the first dose of cetuximab. You will receive chemotherapy or radiation therapy the following week.

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

If you tolerate the first dose of cetuximab well, the following week you will begin receiving cetuximab before radiation therapy and chemotherapy.

How long will I be in the study? (6/18/08)

You will receive radiation therapy for either 6 or 7 ½ weeks (depending on the radiation dose you are assigned). You will receive with chemotherapy (and cetuximab if you are assigned to the group receiving it) during radiation therapy.

Groups 1 and 2: After you finish radiation therapy, you will be given additional chemotherapy (carboplatin and paclitaxel), twice over 6 weeks. You will receive treatment for a total of about 16 to 17 weeks.

Groups 3 and 4: After you finish radiation therapy, you will be given additional chemotherapy (carboplatin and paclitaxel) twice over 6 weeks and cetuximab weekly over 9 weeks. You will receive treatment for a total of about 19 to 20 weeks.

Your doctor will see you in follow-up visits every 3 months for first year, every 4 months for year 2 and every 6 months for year 3-5; then annually for your lifetime.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the treatment can be evaluated by him/her. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the radiation or chemotherapy. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death from either radiation therapy or chemotherapy.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to radiation therapy to the chest: (10/29/10)

Risks and side effects on Arms B and D may be greater than on Arms A and C.

Specifically, side effects with swallowing, cough, and/or lung damage may be greater on Arms B and D.

Likely

- Difficulty, pain, or a burning sensation when swallowing, which is temporary
- Fatigue, which is temporary
- Tanning, redness of the skin, and hair loss within the treatment area, which is temporary
- Skin in the treatment area may remain permanently dry, and chest hair may not grow back
- Decrease in blood counts while undergoing treatment that may result in bleeding, and bruising easily
- Cough and some difficulty in breathing due to lung damage

Less Likely

- Narrowing of the esophagus causing difficulty swallowing meals (requiring internal dilation or a feeding tube)
- Severe skin reactions (similar to a severe sun burn) are possible for patients receiving a higher than standard dose of radiation therapy (Groups 2 and 4 or Arms B and D)

Rare but serious (late)

- Pericarditis – irritation of the heart sac causing a rapid heart rate, chest discomfort, or chest pain
- Myocarditis – irritation of the heart muscle causing shortness of breath, chest pain, or permanent heart muscle damage
- Transverse myelitis – irritation of the spinal cord causing weakness or paralysis
- Bleeding from the airway
- Narrowing of the airway causing shortness of breath
- Death

Risks and side effects associated with Paclitaxel (3/9/09)

Likely

- Low pulse
- Low blood pressure
- Loss of hair
- Tingling, numbness, burning pain in hands and feet
- A decrease in white blood cells, which could lead to infection
- A decrease in platelets, which could lead to bleeding
- Skin redness or rash
- Fatigue
- Nausea and/or vomiting
- Mouth sores
- Diarrhea
- Anemia, a lower than normal number of red blood cells
- Swelling of the legs, arms, or feet
- Cardiovascular changes on EKG (test that measures electrical signal of heart)

Less Likely

- Injection site reaction
- Blurred vision
- Skin or nail darkening
- Aches and pains in muscles and joints
- Fever

Rare but serious

- Temporary changes in blood tests measuring liver function
- Abnormal heart rhythms, which could be life threatening
- Severe allergic reactions

- Temporary “bright spots” in vision
- Severe rash called “Stevens- Johnson Syndrome” that can cause fever and severe eruptions of blisters which can occur on the skin of the trunk of the body, mouth, eyes, and genitals
- Death

Risks and side effects associated with Carboplatin

Likely

- A decrease in white blood cells, which could lead to infection
- A decrease in platelets, which could lead to bleeding
- Nausea and/or vomiting
- Diarrhea
- Fatigue
- Loss of hair
- Temporary changes in blood tests which measure kidney or liver function
- Low sodium in the blood, which could result in bloating and puffiness in the face and fingers, nausea, vomiting, muscle weakness, headache, and disorientation
- Low magnesium in the blood, which could result in increased irritability of the nervous system with spasms of the hands and feet, muscular twitching, and cramps
- Low calcium in the blood, which could result in numbness or tingling around the mouth or in the feet and hands, as well as in muscle spasms in the face, feet, and hands
- Low potassium in the blood, which could result in muscle weakness, cramping, muscle limpness, and/or irregular heartbeat

Less Likely

- Weakness, loss of strength
- Pain
- Mouth sores
- Tingling, numbness, burning pain in hands and feet, which may be persistent or permanent
- Inflammation of the lung, which could lead to cough and shortness of breath

Rare but serious

- Blurred vision
- Hearing loss
- Allergic reactions
- Irregular heartbeats
- Shortness of breath
- Hemolytic-uremic syndrome (HUS), a disorder that results in the destruction of red blood cells and platelets with decreased kidney function
- A risk of developing a second cancer unrelated to the treated lung cancer, which may occur months or years after initial treatment
- Death

Risks Associated with Cetuximab (6/9/10)

Likely

- Diarrhea
- Nausea or the urge to vomit
- Fatigue or tiredness
- Fever
- Headache or head pain
- Dry skin
- Acne
- Skin rash with the presence of flat discolored areas (macules) and raised bumps (papules)

Less Likely

- Lack of enough red blood cells (anemia)
- Swelling and redness (inflammation) of the skin of outer ear and canal
- Noise in the ears, such as ringing, buzzing, roaring, clicking
- Swelling and redness (inflammation) of the outermost layer of the eye and the inner surface of the eyelids (conjunctiva); commonly called "pink eye".
- Dry eye
- Swelling and redness (inflammation) of the middle layer of the eye (uvea)
- Excessive tearing in the eyes
- Belly pain
- Swelling and redness (inflammation) of the lip
- Constipation
- Dry mouth
- Heartburn
- Irritation or sores in the lining of the mouth
- Vomiting
- Chills
- Swelling of the arms and/or legs
- Flu-type symptoms (including body aches, fever, chills, tiredness, loss of appetite, cough)
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Chest pain not heart-related
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing. 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.
- Infection
- Decreased number of a type of white blood cell (neutrophil/granulocyte)
- Weight loss
- Decrease in the total number of white blood cells (leukocytes)
- Loss of appetite
- Dehydration (when your body does not have as much water and fluid as it should)
- Decreased blood level of calcium
- Decreased blood level of magnesium
- Joint pain
- Back pain

- Muscle pain
- Fainting
- Stuffy or runny nose, sneezing
- Sudden constriction of the small airways of the lung that can cause wheezing and shortness of breath
- Cough
- Shortness of breath
- Hoarseness
- Hair loss
- Loss of some or all of the finger or toenails
- Increased skin sensitivity to sunlight
- Itching
- Area of bleeding within the skin causing a reddish purple discoloration
- Sores or destruction of skin
- Hives
- Low blood pressure
- Formation of a blood clot that plugs the blood vessel; blood clots may break loose and travel to another place, such as the lung

Rare but Serious

- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness. 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.
- Inflammation of the lining of the brain and spinal cord
- Inflammation of the lungs that may cause difficulty breathing and can be life-threatening
- Fluid build-up in the lungs that is not due to a heart problem and that can be life-threatening
- Swelling and redness of the skin on the palms of the hands and soles of the feet

Risks Associated with Cetuximab, Radiation Therapy, and Chemotherapy (10/29/10)

The combination of cetuximab with radiation and chemotherapy may increase the risk of life-threatening complications for patients with advanced, non-small cell lung cancer. Some of these complications may be fatal in elderly patients (65 years old or more), particularly those patients with pre-existing cardiac disease.

(6/18/08) Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Some of the drugs used in the study may make you unable to have children in the future. Pregnancy testing will be required if you are female and are able to have children.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study? (10/29/10)

The participants that are assigned to the higher dose of radiation therapy may or may not benefit from the extra treatments. We do know that the information from this study will help researchers learn more about whether or not the extra treatment offers any further benefit.

Researchers also will learn if adding cetuximab to radiation and chemotherapy provides better tumor control or improved survival compared to the radiation and chemotherapy alone.

Taking part in this study may or may not make your health better, but information from this study could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- **Getting treatment or care for your cancer without being in a study**
- **Taking part in another study**
- **Getting no treatment**

Talk to your study doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

Data are housed at RTOG Headquarters in a password-protected database. We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

(6/18/08) Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The local institutional review board at the center where you are treated
- Auditors and researchers from the RTOG, CALGB, and/or NCCTG that are associated with the study
- Qualified representatives of Bristol-Myers Squibb, makers of cetuximab
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study? (6/18/08)

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Phase III studies like this one are generally covered by insurance. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Bristol-Myers Squibb is supplying cetuximab at no cost to you. However, you or your health plan may need to pay for costs of the supplies for drug administration and personnel who give you the cetuximab.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ [investigator's name(s)], if you feel that you have been injured because of taking part in this study. You can tell the study doctor in person or call him/her at _____ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

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

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

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.

A Data Safety Monitoring Board will be regularly meeting to monitor safety and other data related to this study. The Board members may receive confidential patient information, but they will not receive your name or other information that would allow them to identify you by name.

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

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ [name(s)] at _____ [telephone number].

For questions about your rights while taking part in this study, call the _____ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

***You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*Only applies to sites using the CIRB.]**

Please note: This section of the informed consent form is about additional research that is being done with people who are taking part in the main study. You may take part in this additional research if you want to. You can still be a part of the main study even if you say ‘no’ to taking part in this additional research.

You can say “yes” or “no” to [each of] the following study[ies]. Below, please mark your choice [for each study].

Quality of Life Study (6/18/08)

We want to know your view of how your life has been affected by cancer and its treatment. This “Quality of life” study looks at how you are feeling physically and emotionally during your cancer treatment. It also looks at how you are able to carry out your day-to-day activities.

This information will help doctors better understand how patients feel during treatments and what effects the medicines are having. In the future, this information may help patients and doctors as they decide which medicines to use to treat cancer.

You will be asked to fill out two questionnaires at the following five time points in order to assess the impact of this therapy on your quality of life: before treatment, at the end of chemoradiation (and cetuximab, if you receive it) therapy, at 3 months, 12 months, and at 2 years. There are two questionnaires per time point; one called the FACT-TOI that takes

approximately 10 minutes to complete and one called the EQ-5D that takes approximately 5 minutes to complete.

You will also be given a swallowing diary and asked to enter a daily score of your swallowing symptoms (ability to swallow) during the course of chemoradiation and twice more during the follow-up chemotherapy. This will take a few minutes per week. You will be asked to turn in your swallowing diary at the end of the treatment.

If any questions make you feel uncomfortable, you may skip those questions and not give an answer.

If you decide to take part in this quality of life study, you will be asked to fill out the two questionnaires (at the five time points above) and the weekly swallowing diary. You may change your mind about completing these forms at any time.

Just like in the main study, we will do our best to make sure that your personal information will be kept private.

Please circle your answer.

I choose to take part in the Quality of Life Study. I agree to fill out the two Quality of Life Questionnaires and the swallowing diary.

YES

NO

Use of Tissue for Research and Collection of Blood and Urine

Consent Form for Use of Tissue for Research

About Using Tissue for Research

You will have had a biopsy to see if you have cancer. Your doctor will remove some tumor 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 is left over for future research.

In addition to the tumor tissue, we would like to collect some blood and urine.

You will be asked to provide about 4 teaspoons of blood and about 2 teaspoons of urine at the following time points: before treatment, four weeks after the start of treatment, and at your first follow-up visit after completion of chemoradiotherapy

If you agree, this tissue, blood, and urine will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. This information sheet is available to all at the following web site:

<http://www.cancerdiagnosis.nci.nih.gov/specimens/patient.pdf>

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.

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 part of the 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. Then any tissue that remains will no longer be used for research and will be returned to the institution that submitted it and leftover blood and urine will be destroyed.

In the future, people who do research may need to know more about your health. While the doctor/institution may give them reports about your health, it will not give them 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 and will not be sold. The research done with your tissue may help to develop new treatments for cancer in the future.

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

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice (9/22/09)

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My specimens may be kept for use in research to learn about, prevent, or treat cancer, as follows:
 - Tissue Yes No

- Urine Yes No
- Blood Yes No

2. My specimens 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), as follows:

- Tissue Yes No
- Urine Yes No
- Blood Yes No

3. Someone may contact me in the future to ask me to take part in more research.
Yes No

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

APPENDIX II: STUDY PARAMETER TABLE (9/22/09)

**See Section 11.1 for details and exceptions

| Assessments | Pre-Treatment | During concurrent & consolidation treatment | End of concurrent treatment | End of all treatment | Follow up |
|---|--|---|-----------------------------|----------------------|------------|
| Medical History Physical Examination, | Within 8 wks prior to registration | | X | X | X** |
| Zubrod Performance | X | Weekly | X | X | X** |
| Vital signs | X | X** | | X | X** |
| Height, weight and BSA | X | Weight only, weekly** | Weight only** | Weight only** | |
| Rad Onc and Med Onc Consults | Approval required prior to initiation of treatment | | | | |
| PFTs (including FEV1) | Within 12 wks prior to registration | | | X | X** |
| EKG | Recommended 4 wks prior to registration | | | X | |
| Adverse event eval | | X | X | X | X** |
| CBC with differential and ANC; serum creatinine | Within 2 wks prior to registration | Weekly** | X | X | X** |
| Electrolytes, Mg++ | | Weekly for Arms C & D** | | | |
| Total bilirubin, AST/ALT, | X | | X | X | X** |
| Alk phos., glucose | Recommended | | | | |
| Pregnancy test (urine or serum), if applicable | Within 72 hours prior to initiation of treatment | | | | |
| CT scan or MRI of chest & upper abdomen, adrenal glands | Within 6 wks prior to registration | | | X | X** |
| FDG-PET, PET/CT or Bone scan | Within 6 wks prior to registration | | | | At relapse |
| CT scan or MRI, with contrast of Brain | Within 6 wks prior to registration | | | | At relapse |
| EGFR Assessment | If tissue is available and patient consents | | | | |
| Swallowing diary | X | Weekly** | X | | |
| QOL:FACT-TOI, EQ-5D, | X | | X | | X** |

APPENDIX III (3/9/09)

ZUBROD PERFORMANCE SCALE

- 0 Fully active, able to carry on all predisease activities without restriction**
- 1 Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
- 2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours**
- 3 Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
- 4 Completely disabled. Cannot carry on self-care. Totally confined to bed or**
- 5 Death**

APPENDIX IV

AJCC Staging Lung, 6th Edition, 2002

Primary Tumor (T)

- TX** Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.
- T0** No evidence of primary tumor.
- Tis** Carcinoma *in situ*
- T1** Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus,* (i.e., not in the main bronchus)
- T2** Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension; Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura; Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
- T3** Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung.
- T4** Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion.**

***Note:** The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.

****Note:** Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is non-bloody and is not an exudate. Such patients may be further evaluated by videothoracoscopy (VATS) and direct pleural biopsies. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged T1, T2, or T3.

Regional Lymph Nodes (N)

- NX** Regional lymph nodes cannot be assessed.
- N0** No regional lymph nodes metastasis
- N1** Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor
- N2** Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
- N3** Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

APPENDIX IV (continued)

**AJCC Staging
Lung, 6th Edition, 2002**

Distant Metastasis (M)

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

Note: M1 includes separate tumor nodule(s) in a different lobe (ipsilateral or contralateral)

STAGE GROUPING

| | | | |
|-------------------------|-------|-------|----|
| Occult Carcinoma | TX | N0 | M0 |
| Stage 0 | Tis | N0 | M0 |
| Stage IA | T1 | N0 | M0 |
| Stage IB | T2 | N0 | M0 |
| Stage IIA | T1 | N1 | M0 |
| Stage IIB | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| Stage IIIA | T1 | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N1 | M0 |
| | T3 | N2 | M0 |
| Stage IIIB | Any T | N3 | M0 |
| | T4 | Any N | M0 |
| Stage IV | Any T | Any N | M1 |

APPENDIX V (10/29/10)
RTOG BLOOD COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of serum, plasma, or whole blood

Kit contents:

- One Red Top tube for serum (A)
- One Purple Top EDTA tube for plasma (B)
- One Purple Top EDTA tube for Whole Blood (C)
- Twenty five (25) 1 ml cryovials
- Absorbent shipping material (3)
- Biohazard bags (3)
- Styrofoam container (inner)
- Cardboard shipping (outer) box
- Kit Instructions
- Specimen Transmittal Form
- UN1845 DRY Ice Sticker
- UN3373 Biological Substance Category B Stickers

Preparation and Processing of Serum, Plasma and Whole Blood:

A) Serum (if requested): Red Top Tube

- Label as many 1ml cryovials (up to 10) as necessary for the serum collected. Label them with the RTOG study and case number, collection date, time, and time point, and clearly mark cryovials “serum”.

Process:

1. Allow one red top tube to clot for 30 minutes at room temperature.
2. Spin in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the STF.
3. Aliquot 0.5 ml serum into as many cryovials as are necessary for the serum collected (up to 10) labeled with RTOG study and case numbers, collection date/time, protocol time-point collected (e.g. pretreatment, post-treatment), and clearly mark specimen as “serum”.
4. Place cryovials into biohazard bag and immediately freeze at -70 to -90° C, and store frozen until ready to ship. See below for storage conditions.
5. Store serum at -70 to -90° C until ready to ship on dry ice. See below for storage conditions.

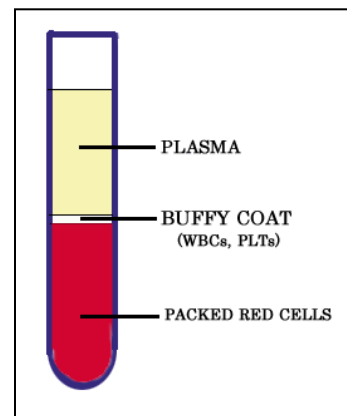
PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED, and include collection Time point on STF.

B) Plasma (If requested): Purple Top EDTA tube #1

- Label as many 1ml cryovials (up to 10) as necessary for the plasma collected. Label them with the RTOG study and case number, collection date and time, and clearly mark cryovials “plasma”.

Process:

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the STF.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (up to 10) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as “plasma”. Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70 to -90°C
6. Store frozen plasma -70 to -90° C until ready to ship on dry ice.
7. See below for storage conditions.



PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED, and include collection time point on STF.

RTOG Blood Kit Instructions- continued- (page 2 of 2)

C) Whole Blood For DNA (If requested): Purple Top EDTA tube #2

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

Process:

1. After collection, invert tube(s) multiple multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (up to 5) labeled with RTOG study and case numbers, collection date/time, time point collected and clearly mark specimen as "blood".
3. Place cryovials into biohazard bag and freeze immediately at -70 to -80° Celsius.
4. Store blood samples frozen -70 to -90° C until ready to ship on dry ice.
5. See below for storage conditions.

PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED, and include collection Time point on STF.

Storage and Shipping:

Freezing and Storage:

- Freeze Blood samples in a -80C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- Store at -80°C (-70°C to -90°C) until ready to ship.
If a -80°C Freezer is not available,
 - Samples can be stored short term in a -20° C Freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only- Canada Mon-Tues).
 - OR:
 - Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only- Canada Mon-Tues).
 - OR:
 - Samples can be stored in liq. nitrogen vapor phase (ship out Monday-Wednesday only- Canada Mon-Tues).
- Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified
- Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). Add padding to avoid the dry ice breaking the tubes.
- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.*
- For questions regarding collection, shipping or to order a Blood Collection Kit, please Email RTOG@ucsf.edu or call (415)476-7864 or fax (415) 476-5271

Shipping Address : FedEx/UPS/Courier address (For all frozen samples)

**RTOG Biospecimen Resource at UCSF
1657 Scott Street, Room 223
San Francisco, CA 94115
Contact Phone 415.476.7864**

APPENDIX VI (10/29/10)

RTOG URINE COLLECTION KIT INSTRUCTIONS

This Kit is for collection, processing, storage, and shipping of Urine Specimens.

Kit Contents:

- One (1) Sterile Urine collection cup
- Two 7 ml disposable pipets
- Absorbent Paper Towel
- Two 15 ml polypropylene centrifuge tubes
- Biohazard bags
- Parafilm for sealing outside of tubes

Preparation and Processing of Urine Specimens:

- ❑ A clean catch urine specimen will be collected. To collect the specimen, use the following instructions:
 - Males should wipe clean the head of the penis and females need to wipe between the labia with soapy water/ cleansing wipes to remove any contaminants.
 - After urinating a small amount into the toilet bowl to clear the urethra of contaminants, collect a sample of urine in the collection cup.
 - After 10-25 mL urine has been collected, remove container from the urine stream without stopping the flow of urine.
 - Finish voiding the bladder into the toilet bowl.
- ❑ Aliquot 5-10 mls of Urine into each of two 15 ml polypropylene centrifuge tubes (disposable pipets are provided in the kit). Do not fill with more than 10 mls to avoid cracking of tubes due to expansion during freezing. Replace the cap and tighten on the tubes. Make sure the cap is not cross-threaded or placed on incorrectly or leaking will occur.
- ❑ Use parafilm to seal the cap around the outside rim of the urine tube to prevent leakage.
- ❑ Discard remaining Urine and collection cup.
- ❑ Label the specimen with the RTOG study and case number, collection date and time, time point of collection, and clearly mark specimens as "urine".
- ❑ Wrap Urine Tubes with absorbent material (paper towels) and place into biohazard bag and seal the bag. Freeze and store Urine samples in a -20°C or -80°C Freezer until ready to ship

Storage and Shipping:

Freezing and Storage

- ❑ Urine specimens may be sent in batches or with other frozen biospecimens, if within 30-60 days of collection. Store at -20°C or 80°C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available,
 - Samples can be stored short term in a -20° C Freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only- Canada Mon-Tues).

OR:

- Samples can be stored in plenty of Dry Ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only- Canada Mon-Tues).
- Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

Shipping/Mailing:

- ❑ Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- ❑ Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
- ❑ Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- ❑ Place sealed specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). Add padding to avoid the dry ice breaking the tubes.
- ❑ Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- ❑ *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice. Add padding to avoid the dry ice from breaking the tubes.*
- ❑ For questions regarding ordering, collection, or shipping a Urine Collection Kit, please Email RTOG@ucsf.edu or call (415)476-7864 or fax (415) 476-5271

Shipping Address : **FedEx/UPS/Courier address (For all frozen samples)**
RTOG Biospecimen Resource at UCSF
1657 Scott Street, Room 223
San Francisco, CA 94115
Contact Phone 415-476-7864

APPENDIX VII (5/22/08)

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

| To submit site registration documents: | For patient enrollments: | Submit study data directly to the RTOG unless otherwise specified in the protocol: |
|--|---|--|
| CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone - 1-888-823-5923 Fax – 215-569-0206 | CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays) [For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.] | RTOG Headquarters 1818 Market Street, Suite 1600 Philadelphia, PA 19103 Please do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions. |
| <u>For patient eligibility questions:</u> Contact the RTOG Research Associate for Protocol, Data Management section at 215-574-3214. | | |
| <u>For treatment-related questions:</u> Correspond by e-mail (preferred) or by phone with the study chair designated on the protocol cover page. | | |
| <u>For questions unrelated to patient eligibility, treatment, or data submission</u> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com . All calls and correspondence will be triaged to the appropriate CTSU representative. | | |
| The CTSU Public Web site is located at: www.ctsu.org | | |
| The CTSU Registered Member Web site is located at: http://members.ctsu.org | | |
| | | |

REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site at <http://members.ctsu.org>

All forms and documents associated with this study can be downloaded from the RTOG 0617 Web page on the CTSU registered member Web site (<https://members.ctsu.org>). Patients can be registered

only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

Requirements for RTOG 0617 site registration:

- **All patients MUST be treated with either 3DCRT or IMRT on this trial and all institutions must be pre-credentialed.** Credentialing requirements for IMRT and 3DCRT are outlined in protocol sections 5.1.1 and 5.1.2 respectively. The NCI Thoracic IMRT guidelines may be found at the RPC website <http://rpc.mdanderson.org/rpc> and information for 3DCRT can be found at <http://itc.wustl.edu>. Credentialing requirements are outlined in Section 5.1 and at <http://rpc.mdanderson.org/rpc>. Submission of digital data to the Image-Guided Therapy Center (ITC) requires advanced request for an FTP account with the ITC (itc@castor.wustl.edu). The ITC will notify the registering institution when that institution is eligible to enter patients on study. The status of the credentialing review will be reflected on the RSS Site Registration Status screen <http://members.ctsu.org/rss/>
- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- CTSU RT Facilities Inventory Form

Note: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC) monitoring program. For sites enrolling through the CTSU an RT Facilities Inventory Form must be on file with CTSU. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

Pre-study requirements for patient enrollment on RTOG 0617:

- Request initial specimen collection/shipping kits from LDS Hospital.
- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms
- All baseline laboratory tests and prestudy evaluations performed within the time period specified in the protocol.
- Baseline QOL forms completed prior to treatment start.

CTSU Procedures for Patient Enrollment

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.

2. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- RTOG 0617 Eligibility Checklist

3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 8:00 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that RTOG registration hours end at 4:30 pm Eastern Time. The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.

4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the RTOG within the confines of RTOG's registration hours to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.

Protocol treatment must begin within 4 weeks after patient registration to the trial.

DATA SUBMISSION AND RECONCILIATION (9/22/09)

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the RTOG 0617 web page located on the CTSU registered member Web site (<http://members.ctsu.org>). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.
2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals to RTOG Headquarters unless an alternate location is specified in the protocol. Do not send study data to the CTSU. See the Special Materials or Substudies section below for submission of dosimetry data.
3. The RTOG Headquarters will send query notices and delinquency reports to the site for reconciliation. Please send query responses and delinquent data to the RTOG and do not copy CTSU Data Operations. Each clinical site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and the RTOG.
4. Please affix the RTOG study/case label to all source documentation and redact the patient's name.

SPECIAL MATERIALS OR SUBSTUDIES

Radiation Therapy (section 6.0)

- Dosimetry data for 3DCRT and IMRT must be submitted to the Image-Guided Therapy Center (ITC), either by digital transmission using the ITC-assigned FTP account or tape submission (contact ITC for acceptable tape types and format). Hard copy materials accompanying digital data should also be sent directly to the ITC. See section 12.2 for a complete inventory of dosimetry items to be submitted.
- **Tissue/Specimen Submission – optional but highly recommended (section 10.0)**
 - 1. With patient's consent, tumor tissue and blood will be collected. Submit specimens, pathology report, and RTOG Specimen Transmittal Form to the RTOG Biospecimen Resource at University of California at San Francisco.
 - 2. See protocol section 10.0 for detailed instructions on collection kits, preparation, and shipment of samples. All reports must include the protocol number and patient's case number (or RTOG label attached). Surgical pathology numbers and information must not be removed from the report; however, the patient's name and/or other identifying information should be redacted. Do not send specimens, forms, reports, or transmittals to the CTSU.
 - 3. CTSU clinical sites qualify for specimen reimbursement in the amounts stated in section 10.3 of the protocol. Payments will be made in accordance with RTOG's pathology payment cycle and forwarded to the enrolling sites by the Cooperative Group credited with the accrual.

Quality of Life (protocol section 11.0):

QOL assessments will be administered according to the schedule in Appendix II.

SERIOUS ADVERSE EVENT(AE) REPORTING (10/29/10)

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.
2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (AdEERS) from either the Adverse Events tab of the CTSU member homepage (<https://members.ctsu.org>) or by selecting Adverse Event Reporting Forms from the document center drop down list on the RTOG 0617 Web page.
3. Do not send adverse event reports to the CTSU.
4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via AdEERS. Submit the completed form and supporting documentation as outlined in the protocol.

DRUG PROCUREMENT (SECTION 7.0)

Commercial agents: Paclitaxel, Carboplatin (paraplatin)

1. Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in section 7.0 of the protocol.
2. You may navigate to the drug forms by selecting Pharmacy Forms from the document center drop down list on the RTOG 0617 Web page.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.