

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0324

A PHASE II STUDY OF CETUXIMAB (C225) IN COMBINATION WITH CHEMORADIATION IN PATIENTS WITH STAGE IIIA/B NON-SMALL CELL LUNG CANCER (NSCLC)

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SCHEMA

R E G I S T E R	*Loading Dose C225: Week 1, Day 1	*Concurrent Cetuximab (C225) and Chemoradiation <u>Weeks 2-8</u> C225, weekly for 7 weeks, given 30-60 minutes before chemotherapy plus Paclitaxel and Carboplatin, weekly for 7 weeks plus RT: 63 Gy/7weeks/35 daily fractions	*Consolidation therapy <u>Weeks 9-11</u> C225, weekly for 3 weeks followed by <u>Weeks 12-17</u> C225, weekly, for 6 weeks, given 30-60 minutes before chemotherapy plus Paclitaxel and Carboplatin, every 3 weeks for 6 weeks
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*See Sections 6.0 and 7.0 for details.

Patient Population (See Section 3.0 for Eligibility)

Histologically or cytologically documented NSCLC; Patients must be MO. Patients with T1-T2 with N2 or T3N1-2 are eligible, if inoperable. Patients with T4 with any N or any T with N2 or N3 disease are eligible if unresectable.

Required Sample Size: 84

Institution # _____

RTOG 0324

ELIGIBILITY CHECKLIST (7/26/04)

Case # _____

(page 1 of 3)

- _____(Y) 1. Does the patient have histologically or cytologically documented NSCLC?
- _____(N) 2. Has the tumor been totally resected?
- _____(Y) 3. Is the patient stage IIIA/B with no evidence of metastasis (MO)?
- _____(Y) 4. Is disease measurable, as defined in Section 11.3?
- _____(Y) 5. Is the patient ≥ 18 years of age?
- _____(Y) 6. Is the Zubrod performance status 0-1?
- _____(Y) 7. Are the pre-treatment laboratory values within the parameter of eligibility per section 3.1.5?
- _____(Y) 8. Is the FEV1 ≥ 1200 cc?
- _____(N) 9. Has the patient had weight loss $> 5\%$ over the past 3 months?
- _____(Y) 10. Has the patient recovered from exploratory thoracotomy?
- _____(Y) 11. Were required pretreatment evaluations administered as specified in Section 3.1.11?
- _____(N) 12. Has the patient had prior systemic chemotherapy and/or thoracic/neck radiotherapy for any reason and/or surgical resection of present cancer?
- _____(N) 13. Has patient had prior treatment with any drugs that target the EGFR pathway or prior therapy with a chimerized monoclonal antibody?
- _____(N) 14. Does the patient have a known allergy to murine protein or Cremophor EL?
- _____(N) 15. Does the patient have active pulmonary infection not responsive to conventional antibiotics?
- _____(N) 16. Does the patient have a history of interstitial pneumonitis?
- _____(N) 17. Does the patient have a history of severe COPD requiring ≥ 3 hospitalizations with the past year?
- _____(N) 18. Does the patient have a significant history of cardiac disease as per section 3.2.9 of the protocol?
- _____(N) 19. Does the patient have a $>$ grade 1 neuropathy?
- _____(N) 20. Is there evidence of other malignancy within the past two years other than those stated in Section 3.2.11?
- _____(N) 21. If female, is the patient pregnant or nursing?
- _____(Y) 22. Is the patient (male or female) willing and able to practice effective contraception throughout the study and for four weeks after completion of treatment?

(Continued on next page)

Institution # _____

RTOG 0324

ELIGIBILITY CHECKLIST (3/8/04)

Case # _____

(page 2 of 3)

_____(N) 23. Is there evidence of pleural effusion on CXR?

_____(Y/N) 24. Is there evidence of pleural effusion on CT scan?

_____(Y) If yes, is the pleural effusion transudate, cytologically negative, and non-bloody; or determined to be too small to tap?

The following questions will be asked at Study Registration:

_____ 1. Name of institutional person registering this case?

_____(Y) 2. Has the Eligibility Checklist (above) been completed?

_____(Y) 3. Is the patient eligible for this study?

_____ 4. Date the study-specific Consent Form was signed? (must be prior to study entry)

_____ 5. Patient's Initials (First Middle Last) [May 2003. If no middle initial, use hyphen]

_____ 6. Verifying Physician

_____ 7. Patient's ID Number

_____ 8. Date of Birth

_____ 9. Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)

_____ 10. Race

_____ 11. Gender

_____ 12. Patient's Country of Residence (U.S. residents)

_____ 13. Zip Code

_____ 14. Patient's Insurance Status

_____ 15. Will any component of the patient's care be given at a military or VA facility?

_____ 16. Treatment Start Date

_____ 17. Medical Oncologist

_____(Y/N) 18. Tissue/Blood kept for current study?

(Continued on next page)

Institution # _____

RTOG 0324

ELIGIBILITY CHECKLIST (3/8/04)

Case # _____

(page 3 of 3)

_____ (Y/N) 19. Tissue/Blood kept for cancer research?

_____ (Y/N) 20. Tissue/Blood kept for medical research?

_____ (Y/N) 21. Allow contact for future research?

_____ (Y/N) 22. Was a PET scan performed on this patient?

_____ (NA/Y/N) 23. Was the PET scan used in staging?

_____ (NA/Y/N) 24. Was the PET scan used in treatment planning for radiation therapy?

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

Completed by _____

Date _____

1.0 INTRODUCTION

1.1 Non-small Cell Lung Cancer

1.1.1 *Background on Non-small Cell Lung Cancer (NSCLC) Therapy*

Lung cancer is the second most common cancer diagnosed for both sexes in the United States, second to prostate cancer for men and breast cancer for women. Approximately 171,900 new cases are estimated for 2003. It is the leading cause of cancer deaths in both men and women, with approximately 157,200 deaths estimated for 2003.¹ Upon initial presentation, fewer than one-half of patients will have surgically resectable lung cancer with the potential for cure. Approximately one-quarter of patients will present with locally advanced disease involving either the ipsilateral mediastinal or subcarinal lymph nodes (American Joint Committee on Cancer [AJCC] T1-3 N2 MO, Stage IIIA) or contralateral mediastinal, hilar or ipsilateral or contralateral scalene or supraclavicular nodes (AJCC T1-2 N3 MO, Stage IIIB) without evidence of extrathoracic metastases. A smaller number of patients will have a centrally located primary tumor involving mediastinal structures (AJCC T4 Nx MO, Stage IIIB). These patients are generally not considered candidates for surgical resection. Until recently the standard therapeutic approach for these patients was a four to six week course of thoracic radiation therapy (RT). This approach resulted in excellent control of tumor-related thoracic symptoms such as hemoptysis, airway obstruction, dyspnea, and chest pain. However, with median survival times of 9-12 months and five-year survival rates of only 5-8% reported with this approach, exploration of alternative therapeutic choices is well justified. One approach involves the delivery of chemotherapy and/or radiotherapy in an attempt to render these tumors potentially resectable followed by thoracotomy and attempted surgical resection. Several pilot studies have yielded encouraging results with such regimens; however, the majority of patients with stage III non-small cell lung cancer (NSCLC) have tumors, which will not be rendered resectable for cure with any pre-operative approach. For these patients, the current therapeutic challenge is to optimize available non-operative strategies.

Since the 1970's, a number of investigators sought to improve the survival results of stage III NSCLC patients by combining chemotherapy with thoracic RT. While early randomized trials failed to demonstrate any advantage of such regimens over thoracic RT alone, two developments led to clinical trial designs that have yielded a positive result. These developments included the availability of cisplatin-containing regimens and the recognition that patients with a more favorable performance status are more likely to benefit from aggressive therapy. There now have been four randomized trials published that demonstrate a statistically significant survival advantage of a cisplatin-containing regimen with thoracic RT over thoracic RT alone.²⁻⁵ Two of these trials used two cycles of pre-RT full dose cisplatin and vinblastine,^{2,3} one trial alternated chemotherapy with RT,⁴ and the other delivered low dose daily and weekly single agent cisplatin during thoracic RT.⁵ Based on somewhat incomplete analyses of patterns of tumor failure location, it appears that sequential chemoradiation reduces or delays the development of extra-thoracic metastases, while low dose concurrent cisplatin appeared to improve the control rate of intra-thoracic tumor, i.e., acted as a potentiator of the radiation effect. The goal of many investigators in recent years has been to take advantage of both the benefits of full dose chemotherapy and the sensitizing effects of concurrent chemoradiation.

The Radiation Therapy Oncology Group (RTOG) has conducted several phase II trials seeking to exploit the advantages of both full dose chemotherapy and the concurrent delivery of chemotherapy and thoracic RT. The most promising of these trials combined two cycles of cisplatin and oral etoposide concurrently with twice-daily thoracic RT. A total of 76 patients were entered, and the estimated median survival time was a remarkable 19.6 months.⁶ This compared with a median survival time of 9.6 and 11.4 months with standard RT and 13.7 and 13.8 months with sequential chemoradiation in two previously cited randomized trials.²⁻³ The exciting phase II result led to the phase III trial (RTOG 94-10) that compared the regimen to an established sequential chemoradiation regimen of vinblastine and cisplatin followed by once-daily RT on Day 50 and another concurrent chemoradiation regimen in which once- or twice-daily RT and the same chemotherapy were used.⁷ Median survival times were 14.6

months for the sequential arm and 17 and 15.6 months for the concurrent arms with once-daily and twice-daily RT, respectively.

The West Japan Lung Cancer Group compared sequential to concurrent chemoradiation using Mitomycin, vindesine, and cisplatin, (MVC) chemotherapy among 320 patients with stage III NSCLC and demonstrated a survival advantage favoring the concurrent arm, with median survival times of 16.5 versus 13.3 months, respectively (P=0.047).⁸

1.1.2 Paclitaxel, Carboplatin, and RT in NSCLC

Paclitaxel acts as a mitotic inhibitor, blocking cells in G₂ and M phases of the cell cycle. The inhibition is unique in that the drug enhances the rate and yields of microtubular assembly and prevents microtubular depolymerization.⁹⁻¹⁰ It is well known that cells in the G₂ and M phase of the cell cycle are particularly sensitive to radiation.¹¹ Tishler et al. showed that 24-hour treatment with 10 nM paclitaxel resulted in a radiosensitivity enhancement in a radio-resistant astrocytoma cell line.¹² The enhanced level of cell kill was consistent with the greater radiosensitivity of G₂/M cells. A radiation sensitizing effect of paclitaxel was also observed with only one hour of treatment with 300 nM Taxol, in human leukemia cell line (HL-60) and human lung cancer cell line (Calu-3).¹³

Carboplatin also can be used as a radiation sensitizer. The mechanism of radiation sensitization with carboplatin is different from that of paclitaxel. Carboplatin potentially interferes with repair of sublethal radiation injury while paclitaxel recruits cells in the radiosensitive G₂/M phase. Laboratory data have suggested a possible synergistic relationship of paclitaxel and carboplatin.¹⁴

The Clinical Oncology Group of Rhode Island (COGRI) conducted a phase II study of paclitaxel and RT for non-small cell lung cancer.¹⁵ Thirty-three patients with unresectable stage IIIA and IIIB NSCLC entered this phase II clinical trial. Paclitaxel (60 mg/m²) was administered as a three-hour infusion, weekly for 6 weeks. Radiation therapy was given concurrently to the primary tumor and regional lymph nodes (40.0 Gy) followed by a boost to the tumor (20.0 Gy). Esophagitis was the principal toxicity. Grade 3 or 4 esophagitis occurred in 11 patients (37%). One patient died of pneumonia following completion of therapy. Additional grade 3 toxicities included pneumonitis (3%) and neutropenia (6%). One patient had a grade 3 hypersensitivity reaction. Twenty-nine patients were evaluable for response. Two patients achieved a complete response (7%) and twenty-three (79%) achieved a partial response, for an overall response rate of 86% (95% confidence interval, 68% to 96%). The one-year survival rate was 72% and median survival was 18.4 months. This study demonstrated promising activity with weekly paclitaxel and RT for patients with unresectable stage IIIA and IIIB NSCLC.

In order to further improve local control and distant metastasis, a phase II study of concurrent weekly paclitaxel (50 mg/m²/wkly/7wks), carboplatin (AUC 2 wkly/7wks), and RT (66.0 Gy in 33 fractions) followed by two additional cycles of adjuvant paclitaxel, (200mg/m²/q3wks X 2) and carboplatin (AUC 6 q3wksX 2) was designed at the COGRI.¹⁶ The goal was to determine the response rate and toxicity of the regimen. A total of 39 eligible patients with previously untreated, inoperable, locally advanced NSCLC were treated on the study. One-year and two-year survival rates were 56.3% and 38.3 % respectively, with a median overall survival of 20.5 months. One- and two-year progression-free survival were 43.6% and 34.7%, respectively. Thirty-seven patients were evaluable for response with an overall response rate (CR+PR) of 75.7%. The primary toxicity observed was esophagitis (46% grade 3 and 4).

Belani et al. conducted a phase II study of weekly low dose paclitaxel at 45 mg/m² (three-hour infusion) with carboplatin, 100 mg/m², and simultaneous standard-dose thoracic radiotherapy (total of 60.0-65.0 Gy) for patients with locally advanced NSCLC.¹⁷ Thirty-eight patients were enrolled, of which 16 were stage IIIa and 22 were stage IIIB. The main toxicities included nine grade 3 leukopenia; three grade 3 mucositis and esophagitis; two grade 3 fatigue; and two grade 3 nausea/vomiting. No grade 4 toxicities were reported. Overall, the regimen was well tolerated. There were

12 instances of dose reduction and a delay in treatment duration of ≥ 1 week in 5 patients. Three patients died as a result of rapidly progressive disease without any evidence of dose-limiting toxicities. The median survival had not been reached at the time of the report. The one, two and three-year actuarial survival rates for this group of patients with locally advanced NSCLC were 63% (95 CI: 44-77%); 54% (95 CI: 35-70%); and 54% (95 CI: 35-70%) respectively.

More recent multimodality studies involving paclitaxel, carboplatin, and RT were reported at the 2000 annual American Society of Clinical Oncology (ASCO) meeting.¹⁵⁻¹⁸ Choy et al. reported on three sequential studies, the first regimen being paclitaxel and RT (Trial 1),¹⁵ the second study adding carboplatin to that regimen (Trial 2),¹⁶ and the third study using paclitaxel, carboplatin, and hyperfractionated RT (Trial 3).¹⁸ One hundred and fifteen patients were enrolled in the three studies (Trial 1, n=33; Trial 2, n=39; and Trial 3, n=43). The patients in all three trials were similar in terms of age range, disease stage (IIIA/B), performance status, and pattern of failure. Response rates for the three studies were 76% Trial 1 (weekly paclitaxel 60 mg/m² x 6 and RT 60.0 Gy); 75.7% for Trial 2 (weekly paclitaxel 50 mg/m² and carboplatin AUC 2 x 7 plus RT 66.0 Gy); and 78.6% for Trial 3 (weekly paclitaxel 50 mg/m² and carboplatin AUC 2 x 6 plus RT 69.9 Gy as 1.2 Gy BID). Median survival was 20 months in Trial 1, 20.5 months in Trial 2, and 14.3 months in Trial 3; the differences between the studies were not statistically significant. Incidence of esophagitis was similar across the three trials. The investigators concluded that the survival times obtained with the regimens were important enough to encourage further evaluation.

The Cancer and Leukemia Group B (CALGB) reported on its study of induction chemotherapy with paclitaxel and carboplatin followed by concurrent RT, paclitaxel and carboplatin.¹⁹ Patients with unresectable stage III NSCLC were enrolled onto the study and received induction therapy consisting of two cycles of paclitaxel (200 mg/m²) and carboplatin (AUC 6) administered every 3 weeks. This was followed by weekly paclitaxel (50 mg/m²) and carboplatin (AUC 2) with RT (2.0 Gy/day for 66.0 Gy). Forty-one patients (61% males) were enrolled on the study, with median age 60 years and 61% performance status of 0. The primary toxicity was esophagitis, with 35% of patients experiencing grade 3 or 4. The response rate for the induction phase was 24% (all PRs) while the overall response rate (induction and concurrent therapy) was 56% (7% CRs). Median survival was 14 months and progression-free survival was 7.7 months. One and two year survival rates were estimated at 56% and 43%, respectively. The CALGB concluded that the induction and concurrent regimens could be delivered safely and is currently conducting a randomized phase III study to further evaluate the value of induction therapy prior to immediate concurrent paclitaxel, carboplatin, and RT.

1.2 Epidermal Growth Factor Receptor

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.²⁰ *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.²¹ 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.²² An antagonist directed against the ligand-binding site of EGFR offers an interesting approach to the therapy of cancers involving upregulated EGFR-dependent pathways. Among those cancers that overexpress EGFR are some of the most prevalent including: esophageal 92%, head and neck 90%, colorectal 72%,²³ prostate 65%, bladder 65%, ovarian 60%, cervical 60%, pancreatic 89%, renal cell 50%, and lung 50%.²⁴⁻²⁵ Prognosis

for many of these malignancies is poor if not diagnosed at an early stage, and therapy for advanced disease is limited.

1.2.1 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}.²⁶⁻²⁷ In addition to inducing G₁-phase arrest, EGFR blockade also was shown to lead to cell death via apoptosis in DiFi colon adenocarcinoma cells.²⁸

1.2.2 Cetuximab

Cetuximab (C225), 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.²⁹ 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.²² Cetuximab was created by chimerization of the murine monoclonal antibody M225 developed at the University of California, San Diego.³⁰ 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.

In an *in vitro* study, both cetuximab and M225 inhibited A431 cell growth to a similar extent, i.e., 30% of the control.²⁹ In addition, *in vivo* studies involving A431 tumor xenografts in nude mice suggested enhanced anti-tumor activity of cetuximab compared with M225. The enhanced anti-tumor activity was postulated to be associated with the increased capacity of cetuximab to compete with ligand compared to M225.²⁹

1.2.2.1 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.²³ 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.²³

1.2.2.2 Toxicology/Preclinical Pharmacokinetics of Cetuximab

A series of non-clinical toxicity studies has evaluated the single-and repeat-dose toxicity of cetuximab in laboratory animals. Detailed information can be found in the Investigator Brochure.²³ As a result of the previously described immunohistochemistry studies, cetuximab has been shown not to recognize EGFR in hepatic tissues of standard animal models. Nevertheless, the immunohistochemistry data evaluated with cryosections of urinary bladder, skin, and esophagus of Cynomolgus monkeys showed reactivity of the monoclonal antibody cetuximab with EGF receptors of this primate species. Therefore, the pharmacologic action of the product is considered to be appropriately modeled in Cynomolgus monkeys.

1.2.2.3 Dose Selection Criteria and Clinical Pharmacokinetics of Cetuximab (7/17/07)

At the time that clinical development of cetuximab was initiated, the goal was to administer doses of the antibody that would be safe and would maintain serum cetuximab concentrations greater than those needed to saturate the binding of tumor-associated EGFR in preclinical murine models (approximately 20 nM). As early clinical development proceeded, this criteria for dose selection was revised based on a new hypothesis that non-tumor-associated EGFR binding in patients (especially liver and skin) might represent a large sink for cetuximab, which could

limit availability of the antibody to tumor associated receptors. An extension of this hypothesis is that non-tumor binding of cetuximab and subsequent receptor internalization represented a major route of elimination for cetuximab that would theoretically become saturated. Thus, at some point, systemic clearance of cetuximab may become saturated, which might be detected by estimation of patient serum pharmacokinetic parameters (total body clearance and half-life). Based on this hypothesis, the target criteria for dose selection was revised to identify a dose at which systemic clearance (as determined by serum PK) became saturated.

The initial clinical development program of cetuximab was comprised of 14 studies of which 13 contributed to the pharmacokinetic database. Across all dose-ranging studies, as the dose of cetuximab was increased from 5 to 500 mg/m², a trend of decreasing cetuximab clearance was reported. At doses of > 200 mg/m², the clearance of cetuximab from the body appeared to level off and remained at approximately 0.02 L/h/m² through the highest dose tested, 500 mg/m². Estimates of mean serum cetuximab terminal half-life increased from 14 to 97 hours over the dose range of 5 to 300 mg/m² after which the half-life appeared to plateau. The mean serum cetuximab volume of distribution at steady state (V_{ss}) was independent of cetuximab dose and ranged from 1.96 to 2.52 L/m², suggesting that cetuximab distributes into a volume equal to or slightly greater than that of the vascular space. Based on all of the above and the finding of increased incidence of skin toxicity at the 500 mg/m² dose level, the Phase II regimen of cetuximab was identified to be an initial dose of 400 mg/m² followed by repetitive weekly doses of 250 mg/m². With this regimen, it was proposed that EGFR occupancy and pharmacologic activity would be sustained.

Cetuximab, administered as monotherapy or in combination with concomitant chemotherapy or radiotherapy, exhibits nonlinear pharmacokinetics. When given as monotherapy in patients with metastatic renal cell carcinoma, at an initial dose of 400 mg/m² followed by a weekly maintenance dose of 250 mg/m² (n = 37 patients), the median volume of distribution approximated the vascular space (2.6 L/m²; range of 1.3 to 6.8 L/m²). The median C_{max} was 1135 nM (range of 594 to 1738 nM), and the median half-life was 83 hours (range 40 to 346 hours, 3.5 days). With repeated weekly dosing at 250 mg/m², cetuximab concentrations were relatively stable by the third weekly dose with median peak and trough concentrations over three courses of therapy ranging from 926 to 1582 and 263 to 714 nM, respectively. In a study of cetuximab administered in combination with irinotecan in patients with metastatic colorectal carcinoma, the median trough levels ranged from 245 to 576 nM over six courses of therapy. When cetuximab was administered as monotherapy in patients with metastatic colorectal carcinoma, the median serum cetuximab trough levels ranged from 350 to 645 nM over four courses of therapy. These data support the concept that weekly administration of cetuximab provides continuous exposures of antibody without a clinically significant accumulation. Moreover, there does not appear to be a decrease in serum concentration with repeated dosing over periods of a year. This finding suggests that clearance of cetuximab does not appear to increase with repeated dosing, supporting that neutralizing antibodies to cetuximab (anti-C225 Abs) are not being formed in patients with repeated cetuximab dosing. The pharmacokinetics of cetuximab were similar in patients with squamous cell carcinoma of the head and neck (SCCHN) and those with colorectal cancer (Cetuximab [ErbixTM] package insert, 2006).

1.2.2.4

Anti-Cetuximab Antibody Response

A total of 606 subjects treated with cetuximab through February 2002 were tested for the presence of anti-cetuximab antibodies by analyzing pre- and post-treatment sera using a double antigen radiometric assay.²³ The incidence of an anti-cetuximab immune response in these subjects was 4.1%. When it occurred, the anti-cetuximab response was generally found to be weak (upper limit of normal is 10 ng/ml cetuximab binding). The anti-cetuximab antibodies from two subjects with the highest reactivity (4670 and 6516 ng/ml) did not interfere with the ability of cetuximab to inhibit proliferation in a cetuximab sensitive cell line, suggesting that the antibodies in these sera were non-neutralizing. Levels of reactivity in sera from other subjects were not high enough to perform this type of analysis. In order to

determine the specificity of the antibody response, sera from 15 subjects who had a positive anti-cetuximab response were further studied in the double antigen radiometric assay using unlabeled cetuximab as a competitor. This analysis demonstrated that sera from 14 of the 15 subjects contained cetuximab-specific antibodies.

1.3 Clinical Studies of Cetuximab in Head and Neck Cancer (7/17/07)

The efficacy and safety of cetuximab in combination with radiation therapy was studied in a randomized controlled trial of 424 patients with locally or regionally advanced squamous cell carcinoma of the head and neck (SCCHN) 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. Since expression of EGFR has been detected in nearly all patients with head and neck cancer, patients enrolled in the head and neck cancer clinical studies were not required to have immunohistochemical evidence of EGFR expression prior to study entry.

1.3.1 Randomized, Controlled Trial in SCCHN

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. In a multi-center controlled clinical trial, 424 patients with Stage III/IV SCC 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. The planned radiation therapy regimen was chosen by the investigator prior to enrollment. For patients with \geq N1 neck disease, a post-radiation therapy neck dissection was recommended. 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). All cetuximab-treated patients received a 20-mg test dose on Day 1. 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 \geq 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:

	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

1.3.2 Single-Arm Trials of SCCHN

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 a platinum-based chemotherapy. 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. Upon progression, patients were given the option of receiving cetuximab plus the platinum regimen that they failed prior to enrollment. Tumor response and progression were assessed by an Independent Radiographic Review Committee (IRC). 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).

1.4 Safety of Cetuximab in SCCHN Clinical Studies (7/17/07)

Except where indicated, the data described below reflect exposure to cetuximab in 208 patients with locally or regionally advanced SCCHN who received cetuximab in combination with radiation and as monotherapy in 103 patients with recurrent or metastatic SCCHN. Of the 103 patients receiving cetuximab monotherapy, 53 continued to a second phase with the combination of cetuximab plus chemotherapy. Patients receiving cetuximab plus radiation therapy received a median of 8 doses (range 1-11 infusions). The population had a median age of 56; 81% were male and 84% Caucasian. Patients receiving cetuximab monotherapy, received a median of 11 doses (range 1-45 infusions). The population had a median age of 57; 82% were male and 100% Caucasian. The most serious adverse reactions associated with cetuximab in combination with radiation therapy in patients with head and neck cancer were:

- Infusion reaction (3%);
- Cardiopulmonary arrest (2%);
- Dermatologic toxicity (2.5%);
- Mucositis (6%);
- Radiation dermatitis (3%);
- Confusion (2%);
- Diarrhea (2%).

Fourteen (7%) patients receiving cetuximab plus radiation therapy and 5 (5%) patients receiving cetuximab monotherapy, discontinued treatment primarily because of adverse events.

The most common adverse events seen in 208 patients receiving cetuximab in combination with radiation therapy were acneform rash (87%), mucositis (86%), radiation

dermatitis (86%), weight loss (84%), xerostomia (72%), dysphagia (65%), asthenia (56%), nausea (49%), constipation (35%), and vomiting (29%).

The most common adverse events seen in 103 patients receiving cetuximab monotherapy were acneform rash (76%), asthenia (45%), pain (28%), fever (27%), and weight loss (27%).

The data in the table below are based on the experience of 208 patients with locoregionally advanced SCCHN treated with cetuximab plus radiation therapy compared to 212 patients treated with radiation therapy alone (Cetuximab [Erbix™] package insert, 2006).

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/Malaise	56	4	48	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				
Mucositis/Stomatitis	93	56	94	52
Xerostomia	72	5	71	3
Dysphagia	65	26	63	30
Nausea	49	2	37	2
Constipation	35	5	30	5
Vomiting	29	2	23	4
Anorexia	27	2	23	2
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
Cough Increased	20	<1	19	0
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 reactions
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 on the first day of dosing described as “allergic reaction”, “anaphylactoid reaction”, “fever”, “chills”, “chills and fever” or “dyspnea”.
³ Acneform rash as defined as any event described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin” or “exfoliative dermatitis”.

1.4.1 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.

1.5 Summary of Results of Investigational Program

1.5.1 *Clinically Relevant Adverse Events Related to Cetuximab*

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

The development of acute interstitial pneumonitis in patients treated with EGFR-targeted agents has recently been described (See the Investigator Brochure, Section 11.5.5). A detailed list of Serious Adverse Events (SAE) is presented in the Investigator Brochure.²³ Note that 2 SAEs lead to death: one from allergic reaction/hypersensitivity and one from interstitial pneumonitis (described in Section 10.3 of the Investigator Brochure). All remaining patients completely recovered with adequate counteractive treatment.

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

Adverse Events in All Cetuximab Trials* (n = 1473, as of November 30, 2002)								
	All Adverse Events				Related Adverse Events**			
	Grades 1 - 4		Grades 3 & 4		Grades 1 - 4		Grades 3 & 4	
	N	(%)	N	(%)	N	(%)	N	(%)
Asthenia	821	(56)	160	(11)	435	(30)	59	(4)
Nausea	651	(44)	56	(4)	301	(20)	24	(2)
Rash	643	(44)	96	(7)	493	(34)	64	(4)
Acne	617	(42)	100	(7)	603	(41)	100	(7)
Diarrhea	509	(35)	92	(6)	210	(14)	33	(2)
Vomiting	481	(33)	67	(5)	206	(14)	21	(1)
Fever	451	(31)	16	(1)	262	(18)	2	(< 1)
Anorexia	414	(28)	42	(3)	147	(10)	13	(1)
Weight Loss	382	(26)	31	(2)	87	(6)	3	(< 1)
Dry Skin	321	(22)	13	(1)	285	(19)	12	(1)
Dyspnea	282	(19)	74	(5)	67	(5)	11	(1)
Mucous Membrane Disorder	269	(18)	109	(7)	96	(7)	28	(2)
Headache	245	(17)	15	(1)	128	(9)	9	(1)
Stomatitis	242	(16)	23	(2)	116	(8)	9	(1)
Chills	165	(11)	1	(< 1)	116	(8)	0	(0)
Pruritus	136	(9)	6	(< 1)	111	(8)	3	(< 1)
Nail Disorder	123	(8)	5	(< 1)	97	(7)	5	(< 1)
Allergic Reaction	80	(5)	24	(2)	57	(4)	20	(1)
Anaphylactoid Reaction	14	(1)	13	(1)	14	(1)	13	(1)

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

** Possible, probably or definite relationship to cetuximab as reported by investigator

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

Adverse Events in Single-Agent Cetuximab Trials* (n = 281, as of November 30, 2002)								
	All Adverse Events				Related Adverse Events**			
	Grades 1 – 4		Grades 3 & 4		Grades 1 - 4		Grades 3 & 4	
	N	(%)	N	(%)	N	(%)	N	(%)
Asthenia	127	(45)	21	(7)	71	(25)	8	(3)
Nausea	76	(27)	3	(1)	38	(14)	0	(0)
Rash	87	(31)	8	(3)	86	(31)	6	(2)
Acne	104	(37)	20	(7)	104	(37)	20	(7)
Diarrhea	53	(19)	3	(1)	26	(9)	3	(1)
Vomiting	66	(24)	9	(3)	26	(9)	2	(1)
Fever	99	(35)	2	(1)	75	(27)	0	(0)
Anorexia	53	(19)	8	(3)	13	(5)	1	(< 1)
Weight Loss	24	(9)	0	(0)	3	(1)	0	(0)
Dry Skin	35	(13)	2	(1)	33	(12)	2	(1)
Dyspnea	51	(18)	20	(7)	11	(4)	3	(1)
Mucous Membrane Disorder	17	(6)	3	(1)	9	(3)	1	(< 1)
Headache	64	(23)	3	(1)	40	(14)	2	(1)
Stomatitis	26	(9)	7	(3)	13	(5)	0	(0)
Chills	13	(5)	2	(1)	0	(0)	0	(0)
Pruritus	25	(9)	2	(1)	21	(8)	1	(< 1)
Nail Disorder	21	(8)	0	(0)	18	(6)	0	(0)
Allergic Reaction	24	(9)	8	(3)	18	(6)	8	(3)
Anaphylactoid Reaction	4	(1)	4	(1)	4	(1)	4	(1)

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

** Possible, probably or definite relationship to cetuximab as reported by investigator

1.5.2 Acne-Like Rash

The most common adverse event associated with cetuximab administration is acne-like rash. Acne-like rash usually occurs on the face, upper chest, and back, but occasionally extends to the extremities and is characterized by multiple follicular or pustular-appearing lesions characterized histologically as lymphocytic perifolliculitis or suppurative superficial folliculitis in subjects with metastatic carcinoma. The onset of the rash is generally within the first three weeks of therapy. In subjects who received cetuximab at doses less than 100 mg/m², acne-like rash was reported infrequently and was restricted to Grades 1 or 2. A number of therapeutic interventions have been attempted, including oral and topical antibiotics, topical steroids, and rarely, oral steroids. The value of these measures is unknown since definitive clinical trials have not been performed. The etiology of the acne-like skin rash is believed to be the result of cetuximab binding to EGFR in the epidermis.

1.5.3 Nail Disorder

An uncommon adverse event reported is a nail disorder characterized as paronychia inflammation with associated swelling of the lateral nail folds of the toes and fingers. The most commonly affected digits are the great toes and thumbs. According to Investigators, the nail disorder may persist for up to 3 months after discontinuation of cetuximab. Preliminary analysis in subjects treated at the doses to be administered in this trial (400 mg/m² initial dose, followed by 250 mg/m² weekly) revealed that incidence of nail disorder is greater in subjects who received > 6 cetuximab infusions (~10%) compared with subjects treated with ≤ 6 infusions (~3%).

1.5.4 Allergic Reactions

As cetuximab is a protein, the potential exists for allergic reaction to occur during or following cetuximab administration. In clinical trials, severe hypersensitivity reactions (including allergic and anaphylactic reactions), characterized by the rapid onset of

airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension, have been observed in approximately 3% of patients treated with cetuximab. The large majority of these severe reactions occurred with the first infusion of cetuximab and were observed during or within one hour of the completion of dosing.

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

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

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

1.6 Rationale

At the 2002 annual meeting of the American Society of Clinical Oncology (ASCO), preliminary results from the American College of Radiology (ACR) Locally Advanced Multi-Modality Protocol (LAMP) study, ACR 427, were presented.³² This study enrolled patients with unresected stage III NSCLC and randomized them to one of three arms: sequential paclitaxel/carboplatin followed by RT (Arm 1); induction therapy with paclitaxel/carboplatin followed by concurrent paclitaxel/carboplatin/RT (Arm 2); or concurrent paclitaxel/carboplatin/RT followed by consolidation therapy with paclitaxel/carboplatin (Arm 3). The preliminary survival data led to the termination of accrual to Arm 2, but were sufficiently promising to continue accrual to Arms 1 and 3. Recently, the Southwest Oncology Group (SWOG) published updated results of a study (SWOG 9504) of concurrent therapy followed by consolidation therapy.³³ Patients with stage IIIB NSCLC were treated with a regimen of concurrent cisplatin/etoposide/RT followed by consolidation with docetaxel. The results presented were compared to an earlier study using the same concurrent regimen, but without consolidation therapy. Median survival and one-, two-, and three-year survival rates were substantially increased with the addition of the consolidation therapy.

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.³⁴ 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.³⁵ 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.³⁶⁻³⁸ Two of the trials, designated IDEAL 1³⁷ (n=210)

and IDEAL 2³⁷ (n=216), evaluated the activity of oral, single agent ZD 1839 in patients with NSCLC. 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 anti-tumor 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.³⁸

The question of whether overexpression of EGFR correlates with response to EGFR inhibiting therapies also has been examined. An exploratory analysis using tumour 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 tumour response.³⁹

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.⁴⁰ 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 C225 with chemotherapy.⁴¹ In a phase I/II study in untreated metastatic NSCLC combining C225 with paclitaxel and carboplatin (C225 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 C225 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.⁴² 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 C225 with systemic chemotherapy in NSCLC. Both regimens had acceptable safety profiles, and encouraging clinical activity.

While there are no published data on the combination of chemotherapy, RT, and C225, there have been phase I trials of chemotherapy, RT, and gefitinib (Iressa™) that have not had undue toxicities.⁴³ (Gefitinib is a small molecule inhibitor of EGFR, the same target affected by C225.)

The present study is based upon a combination of the data from the studies described above. The use of concurrent chemoradiation therapy followed by consolidation therapy builds upon Arm 3 of the LAMP study and the SWOG 9504 study. 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.

2.0 OBJECTIVES

2.1 Primary Objective

Determine the feasibility of concurrent cetuximab and chemoradiation as measured by safety and compliance. Safety is measured by the rate of grade 3 or worse non-hematological toxicities occurring prior to the beginning of consolidation therapy (including all toxicities attributed to chemoradiation occurring within 90 days of the start of radiation therapy); compliance is defined as the completion of the treatment regimen with no more than minor variations.

2.2 Secondary Objectives

- 2.2.1 Estimate the treatment response rate of patients on the study regimen (complete and partial response rates)
- 2.2.2 Estimate overall survival of patients on the study regimen (one and two year rates, median survival).
- 2.2.3 Estimate the time to disease progression of patients on the study regimen (one and two year rates)
- 2.2.4 Investigate associations between EGFR expression and toxicity, response, overall survival, and progression

3.0 PATIENT SELECTION

3.1 Eligibility

- 3.1.1 Histologically or cytologically documented NSCLC, including squamous cell carcinoma, adenocarcinoma (including bronchoalveolar cell), and large cell anaplastic carcinoma (including giant and clear cell carcinomas) and poorly differentiated (not otherwise specified, NOS) non-small cell lung cancer; totally resected tumors are excluded.
 - Patients must be M0;
 - Patients with T1 or T2 disease with N2 or T3N1-2 disease (Stage IIIA) are eligible if they are deemed inoperable. Patients with T4 with any N or any T with N2 or N3 disease are eligible if unresectable. Radiographic evidence of mediastinal lymph nodes > 2.0 cm in the largest diameter is sufficient to stage N2 or N3 disease. If the largest mediastinal node is < 2.0 cm in diameter and this is the basis for stage III disease, then at least one of the nodes must be proven positive cytologically or histologically;
 - Measurable disease is required. See Section 11.3 for RECIST definitions of measurable disease.
- 3.1.2 Patients with tumors adjacent to a vertebral body are eligible as long as all gross disease can be encompassed in the radiation boost field. The boost volume must be limited to < 50% of the ipsilateral lung volume.
- 3.1.3 Patients must be ≥18 years of age;
- 3.1.4 Patients with Zubrod performance status 0-1 (See Appendix 1);
- 3.1.5 Adequate hematologic function defined as: ANC ≥ 1,500/mm³, platelets ≥ 100,000/mm³, and hemoglobin ≥ 9 g/dL (prior to transfusions); adequate hepatic function defined as: total bilirubin ≤ 1.5 mg/dl, SGOT or SGPT ≤ 3 x ULN, adequate renal function defined as a serum creatinine level ≤ 2.0 mg/dl, alkaline phosphatase ≤ 2.5 x ULN, glucose ≤ 2 x ULN;
- 3.1.6 FEV1 with ≥ 1200 cc;
- 3.1.7 Patients with weight loss ≤ 5% over the past 3 months;
- 3.1.8 Patients with a pleural effusion that is a transudate, cytologically negative and non-bloody are eligible if the radiation oncologists feel the tumor can still be encompassed within a reasonable field of radiotherapy (See Sections 6.4 and 6.5). If a pleural effusion can be seen on the chest CT but not on CXR and is too small to tap, the patient is eligible.
- 3.1.9 Patients who have recovered from exploratory thoracotomy;
- 3.1.10 Women of childbearing potential and male participants must practice effective contraception throughout the study and for four weeks after completion of treatment.
- 3.1.11 Pretreatment evaluations required for eligibility include: (11/23/04)
 - A medical history, physical examination, assessment of Zubrod performance status within 2 weeks prior to study entry;
 - CBC with differential and platelet count, and laboratory profile must be completed within 2 weeks prior to study entry;

- FEV1, CT scan or MRI of the chest, an EKG, a bone scan (a PET scan, rather than a bone scan, is permitted to rule out bone metastases), and a CT scan or MRI of the brain (to rule out brain metastasis) within 4 weeks prior to study entry;
 - For women of childbearing potential, a serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) must be performed within 72 hours prior to the start of protocol treatment;
 - Medical Oncology and Radiation Oncology consults and approval.
- 3.1.12 Patients must sign a study-specific consent form prior to study entry.
- 3.2 Conditions for Patient Ineligibility (7/26/04)**
- 3.2.1 Prior systemic chemotherapy and/or thoracic/neck radiotherapy for any reason and/or surgical resection of present cancer;
- 3.2.2 Exudative, bloody, or cytologically malignant effusions;
- 3.2.3 Asymptomatic or symptomatic brain metastasis;
- 3.2.4 Prior therapy with any other drug that targets the EGFR pathway, or prior therapy with a chimerized monoclonal antibody;
- 3.2.5 Known allergy to murine proteins or Cremophor EL;
- 3.2.6 Active pulmonary infection not responsive to conventional antibiotics;
- 3.2.7 History of interstitial pneumonitis;
- 3.2.8 History of severe COPD requiring ≥ 3 hospitalizations over the past year;
- 3.2.9 Significant history of cardiac disease, i.e., uncontrolled hypertension, unstable angina, uncompensated congestive heart failure, myocardial infarction within the past year, or cardiac ventricular arrhythmias requiring medication; patients with left ventricular ejection fraction (LVEF) below the institutional range of normal on a baseline multiple gated acquisition (MUGA) scan or echocardiogram.
- 3.2.10 Patients with $>$ grade 1 neuropathy;
- 3.2.11 Evidence of malignancy in the past 2 years except for adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, or other *in situ* cancers;
- 3.2.12 Women who are pregnant or breast feeding, as treatment involves unforeseeable risks to the participant, embryo, fetus, or nursing infant; women with a positive pregnancy test on enrollment or prior to study drug administration;
- 3.2.13 Women of childbearing potential and male participants who are unwilling or unable to use an acceptable method of contraception throughout the study and for four weeks after completion of treatment or those who are using a prohibited contraceptive method.
- 3.2.14 Patients who currently are participating in other clinical trials and/or who have participated in other clinical trials in the previous 30 days.

4.0 RECOMMENDED PRETREATMENT EVALUATIONS

(In addition to required evaluations in Section 3.0)

- 4.1 PET scan of chest at pretreatment and 4 weeks after completion of concurrent therapy to assess acute toxicity;
- 4.2 For all patients for whom tumor tissue is available and who have consented to participate in the tissue component of the study, specimens will be sent for immunohistochemistry assay for evidence of EGFR expression (see Section 10.0). Unavailability of tissue is not a criterion for exclusion. If tissue is unavailable, the reason(s) should be documented in the site's source documentation.

5.0 REGISTRATION PROCEDURES

5.1 Pre-Registration Requirements (3/24/04)

- 5.1.1 **U.S. sites** must mail or send overnight the completed, signed, **original**, study-specific FDA 1572 form to Coalition of National Cancer Cooperative Groups, 1818 Market Street, Suite 1100, Philadelphia, PA 19103. **(4/2/04)**

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

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

Financial disclosure forms are not required.

- 5.1.2 (7/26/04) Canadian sites** must mail or send overnight the completed, signed, **original** study-specific FDA 1572 form to RTOG Headquarters, 1818 Market Street, Suite 1600, Philadelphia, PA, 19103.

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

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

Financial disclosure forms are not required.

- 5.1.3 (3/25/05)** For the initial shipment of Cetuximab, **U.S. and Canadian institutions** must email the shipment form for this study (available at <http://www.rtog.org/members/protocols/0324/0324shipmentform.doc>) to RTOG_BMS@phila.acr.org as soon as the individual responsible for the study agent has been identified and prior to registration of the institution's first case. (Fax 215-574-0300 if unable to email). Allow adequate processing time (7-10 days) before calling to randomize your first patient. See Appendix IV for the procedure for resupply requests.

5.2 Registration

5.2.1 Online Registration

Patients can be registered only after eligibility criteria are met. The RA will register the patient by logging onto the RTOG web site (www.rtog.org), going to "Data Center Login" and selecting the link for new patient registrations. A username and password is required. The system triggers a program to verify that all regulatory requirements (OHRP assurance, IRB approval) have been met by the institution. The registration screens begin by asking for the date on which the eligibility checklist was completed, the identification of the person who completed the checklist, whether the patient was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the patient is eligible and that the institution has met regulatory requirements, it assigns a patient-specific case number. The system then moves to a screen that confirms that the patient has been successfully enrolled. This screen can be printed so that the registering site will have a copy of the registration for the patient's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the patient-specific calendar. The system creates a case file in the study's database at the DMC (Data Management Center) and generates a data submission calendar listing all data forms, images, and reports and the dates on which they are due.

If the patient is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the patient. This screen can be printed.

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

5.2.2 Dial-in Registration

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

6.0 RADIATION THERAPY Note: Intensity Modulated RT (IMRT) is not allowed.

6.1 Radiation Dose

Patients will receive a total dose of 63 Gy in 35 fractions over 7 weeks, 1.8 Gy x 25 fractions, then 1.8 Gy x 10 fractions utilizing standard fractionated radiotherapy.

Standard fractionated radiotherapy is defined as 1.8-2.0 Gy once-daily radiation to a dose of 70.2 Gy or less, including 2D and 3D conformal radiotherapy.

Non-standard fractionated radiation therapy is treatment administered using brachytherapy, radiopharmaceuticals, high LET radiation, radiosurgery, intensity modulated radiation therapy (IMRT), and conventional radiotherapy with fraction size or total dose not within the parameters specified above.

6.2 Treatment Techniques and Target Volumes

6.2.1 All doses are to be prescribed and calculated assuming a homogeneous patient. There will be no heterogeneity corrections used in the definitions of these doses.

6.2.2 The doses shall be prescribed and calculated according to the following ICRU recommendations for external beam treatments using photons and electrons:

- At mid-separation on the central ray for two opposed coaxial equally weighted beams
- At the center of the target volume on the central rays for two opposed coaxial unequally weighted beams
- At the point of intersection of the central rays for two or more intersecting beams which are not coaxial
- At the center of the target volume for complex treatment arrangements which are not covered above
- At the depth of maximum dose for a single-electron beam with an electron beam energy chosen such that the minimum percent dose at 3.0 cm depth is 90%.

6.2.3 The clinical target volume (CTV) includes the area of subclinical involvement around the GTV. The CTV is the GTV plus the margin for micro extensions of the tumor, which is 1.0 cm. More than one CTV can be defined. For this protocol CTV = GTV + 1.0 cm. Ipsilateral supraclavicular irradiation is allowed when necessary for primary tumor coverage. Contralateral hilar or supraclavicular treatment is not allowed. The lower field border will be 3.0 cm below the carina for upper and middle lobe tumors for the large fields and 1.0 cm as CTV beyond GTV for the boost fields. If there is a gross subcarinal node, the margin needs to be 1.0 cm beyond the nodal involvement (GTV) for both the large and boost fields. Any mediastinal node detected by CT scan > 1.5 cm should be included with at least a 1 cm margin as CTV. Simulation is mandatory.

6.2.4 The planning target volume (PTV) is the CTV plus a margin to ensure that the prescribed dose is actually delivered to the GTV. This margin accounts for variations in treatment delivery, including variations in set-up between treatments, patient motion during treatment, movement of the tissues that contain the GTV (e.g. respiration), and size variations in the tissue containing the GTV. The PTV is a geometric concept, which is 0.5 cm (e.g., upper lobe or proximal lesion) – 1.5 cm (e.g., lower lobe lesion) depending on the motion of the tumor detected by the fluoroscope. PTV = CTV + 0.5-1.5 cm.

6.3 Target Volumes/Doses

6.3.1 Initial Target Volume (CTV1/PTV1): This will include all gross tumor (GTV) + microscopic margin + selected elective nodal irradiation (see section 6.2.3). The prescribed dose to this volume will be 45 Gy.

6.3.2 Boost Target volume (CTV2/PTV2): This will include all gross tumor (GTV) + microscopic margin + grossly involved nodes (see section 6.2.3). This will receive an additional prescribed dose of 18 Gy, to bring the total dose to 63 Gy.

6.3.3 In all regimens, no part of the primary lesion and ipsilateral hilar and mediastinal lymph nodes (within a 2.0 cm margin) will receive a dose less than 45.0 Gy from the initial fields. In cases in which the central rays of the initial fields do not intercept the center of the boost target volume, the primary lesion should not exceed the prescribed dose by more than 15%.

6.3.4 Deviations of the daily dose of up to 5% are allowed. In patients for whom the difference in dose to the initial target volume and to the boost target volume is smaller than 5%, a change in the boost dose is allowed. As an example of the above, assume

that a patient receives 43.0 Gy to the center of the boost target volume when 45.0 Gy has been delivered at the intersection of the central rays of the initial fields. The center of the target volume has received 2.0 Gy less than prescribed. This patient could then receive one extra fraction of 1.8 Gy to the boost field (See Section 6.10 for Compliance Criteria).

6.4 Irradiation Portals

Three-dimensional, CT-planned conformal radiotherapy is very highly recommended for this protocol. This protocol does not mandate the radiation field arrangements that are to be used in order to fulfill the target volume/dose requirements of section 6.3 and minimize normal tissue exposure. It is anticipated that AP-PA fields will be used for a large portion or all of the treatment of CTV1/PTV1 (45 Gy) and that a multifield arrangement to minimize cord and lung dose will be used for the boost field treatment (CTV2/PTV2).

6.5 Technical Factors

- 6.5.1 **Beam Energy:** Megavoltage equipment is required with minimum peak photon energies of 6 MeV. Electrons with at least 90% dose at 3 cm depth may be used to boost supraclavicular lymph nodes. The dose should be specified at dmax.
- 6.5.2 **Treatment Distance:** Minimal treatment distance to skin should be 100 cm for SSD technique and isocenter distance should be 100 cm for SAD techniques.
- 6.5.3 **Blocking:** In the case of x-ray beams, the primary collimation may be used, and blocking will be required only for shaping of the ports to exclude volume of tissues that are not to be irradiated.
- 6.5.4 **Filter or Wedges:** In the case of a large sloping contour, such as usually encountered when treating upper lobe tumors in large patients, compensating filters are recommended. A wedge may also be used as a 2 dimensional tissue compensator. If necessary, appropriate reduction in field size must be done to avoid excessive irradiation of critical structures.

6.6 Radiation Therapy Interruptions

- 6.6.1 **Total dose, number of fractions, and elapsed days** should be carefully reported. Every effort should be made to minimize the length of treatment interruptions. Radiotherapy interruptions or delays only will be permitted for Grade 4 esophagitis/mucositis or skin toxicity and/or \geq Grade 3 pulmonary toxicity. Interruptions longer than 5 days should be discussed with the Study Chair. Also see Sections 7.5.4.6 through 7.5.4.11.

6.7 Treatment Planning

Treatment planning should be performed in accordance with the prescribing doses to each target volume, together with restrictions in dose to normal tissues. Treatment planning simulation is required. It is recommended that CT-based treatment planning be utilized whenever possible.

One set of composite isodose distributions in the transverse plane passing through the midlevel of the boost target volume should be submitted. Sagittal dose distributions are encouraged.

In addition to the isodose distribution, the following specific points of dose calculations should be included:

- 6.7.1 **Spinal Cord Dose:** If compensating filters are not used, the point at which the spinal cord dose to be calculated is 2 cm below the superior margin of the posterior field. If compensating filters or wedges are used, then the point of maximum dose to the spinal cord must be determined. Maximal spinal cord dose should not exceed 48.0 Gy at any level.
- 6.7.2 **Subcarinal Nodes:** Are assumed to be at mid-plane.
- 6.7.3 **Ipsilateral Normal Lung Dose:** This is to be calculated at the level of the central rays of the boost fields at the point of maximum dose in the lung which lies at least 2 cm outside the projected border of the initial treatment fields in the ipsilateral lung.
- 6.7.4 **Contralateral Normal Lung Dose:** This is to be calculated at the level of the central rays of the boost fields at the point of maximum dose in the lung which lies at least 2 cm outside the projected border of the initial treatment fields in the contralateral lung.
- 6.7.5 **Maximum Normal Tissue Dose:** This is to be calculated at level of the central rays of boost fields as the maximum total dose at least 2 cm outside of the target volume.

6.8 Localization Films:

All fields treated require filming on simulator (conventional or CT sim) units. Portal verification shall be done for all treatment fields. Copies of both simulator and portal fields will be submitted.

6.9 Suggested Maximum Doses to Critically Sensitive Normal Structures

<u>Organ</u>	<u>Maximum Dose</u>
Spinal Cord (Maximum Dose)	48.0 Gy
Heart: Entire Organ	45.0 Gy
Heart: < 50%	50.0 Gy
Esophagus	60.0 Gy

The dose to the spinal cord must be limited to 48.0 Gy. A posterior spinal cord shield will not be an acceptable technique. Oblique or lateral field arrangements with custom shielding are recommended to limit spinal cord dose.

6.10 Compliance Criteria

The Radiation Oncology Co-Chair, Ritsuko Komaki, M.D., will perform an RT Quality Assurance Review after complete data for the first 20 cases enrolled has been received at RTOG Headquarters. Dr. Komaki 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. These reviews will be on going and performed at the RTOG semi-annual meetings as well as at RTOG Headquarters.

Total Dose Criteria:

≤ 5%	Per Protocol
> 5% to ≤10%	Variation Acceptable
> 10%	Deviation Unacceptable

Field Borders:

2 cm to < 2.5 cm		Per Protocol
<u>Min.</u>	<u>Max.</u>	
1-2 cm	2.5-3.5 cm	Variation Acceptable
< 1 cm	>3.5 cm	Deviation Unacceptable

6.11 Radiation Toxicity

6.11.1 Reversible alopecia, bone marrow toxicity, skin pigmentation and esophagitis are expected side effects of radiation therapy, while radiation-induced myocarditis or transverse myelitis rarely will occur at doses lower than 50.0 Gy. Radiation pneumonitis will occur in 100% of patients within the first six months after initiation of treatment so it is essential to spare as much normal lung as possible. Radiation treatment interruptions are strongly discouraged; however, radiation therapy may be interrupted under the conditions described in Sections 6.6.1 and 7.5.4.6 through 7.5.4.11.

6.12 Radiation Toxicity Reporting RTOG AE TELEPHONE LINE: (215) 717-2762

6.12.1 All acute and late adverse events from protocol radiation therapy will be reported and scored for severity using the NCI Common Terminology Criteria for Adverse Events (CTCAE) v3.0. A copy of the CTCAE can be downloaded from the CTEP homepage (<http://ctep.info.nih.gov>).

6.12.2 *Documentation*

Radiation therapy is being combined with chemotherapy administration in this protocol, therefore ALL serious adverse events are reported using AdEERS, as stated in Section 7.7 of this protocol.

6.12.3 *Summary of AE Reporting Involving Radiation Treatment With Chemotherapy Administration*

- Report Grade 4/Grade 5 AE's;
- Telephone report within 24 hours of discovery;

- Document using AdEERS within 10 days (a dictated summary and CRF's may also be indicated);
- Institutional reporting as required.

DEATH WITHIN 30 DAYS OF COMPLETION OF TREATMENT

- Telephone report to RTOG within 24 hours of discovery;
- Follow guidelines outlined in section 7.7 of this protocol for AE reporting.

7.0 DRUG THERAPY

7.1 Treatment Plan

7.1.1 Cetuximab Loading Dose (Week 1, Day 1)

Patients will receive a loading dose of cetuximab (C225), 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 similar agent) IV 30-60 minutes prior to the first dose of cetuximab in an effort to prevent an allergic/hypersensitivity or cytokine release reaction.** Premedication is recommended prior to subsequent doses, but at the Investigator's discretion, the dose of diphenhydramine may be reduced.

The medical staff must closely observe patients for signs of anaphylaxis or any other potential adverse events. Vital signs (blood pressure, heart rate, respiratory rate, and temperature) should be checked and recorded prior to the administration of cetuximab, midway through the infusion, at the completion of the infusion, and 60 minutes post the infusion in an area with resuscitation equipment and other agents (epinephrine, prednisone equivalents, etc.) available. A nurse must be present in the immediate treatment area throughout the infusion and observation period. A physician must be in close proximity to the patient treatment area. In the event that a patient experiences an allergic/hypersensitivity or cytokine release reaction, see Section 7.5.3.1 for proper management. **Patients should be instructed to report any delayed reactions to the investigator immediately.**

7.1.2 Concurrent Cetuximab and Chemoradiation (Weeks 2-8) [7/26/04]

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 7 weeks (see Section 7.2.4 for details of administration). **Pre-medication with diphenhydramine hydrochloride 50 mg (or similar agent) IV 30-60 minutes is recommended prior to cetuximab administration to prevent an allergic/hypersensitivity or cytokine release reaction, but at the Investigator's discretion, the dose of diphenhydramine 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 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 must be administered on either Monday or Tuesday of each week.

7.1.3 Consolidation Therapy (Weeks 9-17)

Beginning week 9, following the completion of concurrent cetuximab and chemoradiation, patients will receive three weeks of single agent cetuximab given 250 mg/m² IV over 60 minutes on a weekly schedule (See Section 7.2.4 for details of administration).

Beginning on week 12 (week 4 of consolidation therapy), cetuximab administration will be continued weekly at 250 mg/m² IV over 60 minutes. **Pre-medication with diphenhydramine hydrochloride 50 mg (or similar agent) IV 30-60 minutes is recommended prior to cetuximab administration to prevent an allergic/hypersensitivity or cytokine release reaction, but at the Investigator's discretion, the dose of diphenhydramine may be reduced.** Following 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. The paclitaxel and carboplatin will be delivered every 3 weeks for 6 weeks. 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.**

7.2 Cetuximab (C225)

7.2.1 Formulation: Cetuximab is an anti-EGFR receptor humanized chimeric monoclonal antibody. Cetuximab is expressed in SP2/0 myeloma cell line, grown in large scale cell culture bioreactors, and purified to a high level purity using several purification steps including protein A chromatography, ion exchange chromatography, low pH treatment, and nanofiltration. Cetuximab is not known to be a vesicant. To obtain a copy of the C225 Investigator Brochure (Version 9.0), please contact Bristol-Myers Squibb (BMS) via Allison Hunt at (609) 897-3637 or allison.hunt@bms.com or Randy Gardner-McQuade at (609) 897-3922 or randy.gardner-mcquade@bms.com.

7.2.2 Supply

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

7.2.3 Safety Precautions

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

7.2.4 Preparation and Administration

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

The dose and volume of the study drug to be infused are dependent upon the patient's actual BSA. **The infusion rate must never exceed 10 mg/minute (5 mL/minute).** The dose may subsequently be reduced for individual patients, depending on a patient's toxicity. For the duration that patients are on cetuximab therapy, adverse event monitoring should be done continuously. Patients will be evaluated for adverse events at each visit and are to be instructed to call their physician to report any adverse events between visits.

Cetuximab may be administered via an infusion pump, or syringe pump with in-line filtration. Cetuximab requires in-line filtration during administration. The 0.22 µm in-line filters in both the recommended Baxter Healthcare and Abbott Laboratories infusion sets have identical in-line filters composed of polyethersulfone. Calculate and draw the appropriate volume of cetuximab into a sterile syringe based on either the 400 mg/m² initial dose or 250 mg/m² weekly dose, and administer via one of the options detailed below:

1) In-line Filtration by Infusion Pump

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

2) In-line Filtration by Syringe Pump

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

Studies have been conducted to demonstrate the compatibility of cetuximab drug product with various infusion systems. Some examples of materials, IV containers, infusion sets, and filters tested and recommended for use with cetuximab are listed below. For further examples of approved materials, please see Section 3.4.1 in the Investigator Brochure (Version 9.0).

Recommended IV Containers

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

Recommended Infusion Sets

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

Recommended Filters

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

Normal saline or D5W should be use to clear the infusion set of residual cetuximab. The delivered drug product is > 95% for all recommended infusion sets when flushed with 50 mL of normal saline. Use a separate line for cetuximab infusion.

7.2.5 Storage Requirements/Stability

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

7.2.6 Adverse Events

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

7.2.7 Drug Ordering and Accountability (5/6/04)

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

<http://www.rtog.org/members/protocols/0324/0324shipmentform.doc>) to RTOG_BMS@phila.acr.org as soon as the individual responsible for the study agent has been identified and prior to registration of the institution's first case. (Fax 215-547-0300 if unable to email). Allow adequate processing time (7-10 days) before calling to randomize your first patient. See Appendix IV for the procedure for resupply requests.

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

All product will be shipped via Federal Express in a temperature-controlled container. Shipments will be made from BMS on Monday through Thursday for delivery to sites on Tuesday through Friday. There will be no weekend or holiday delivery of drugs. Each drug box (4 vials) will contain a large label on the side of the box with the RTOG protocol number. It is possible that sites may have more than one cetuximab clinical study ongoing at the same time. It is imperative that only product designated for RTOG 0324 be utilized for this study.

Inside each shipping container will be a disposable electronic unit (TagAlert™) to ensure the product has remained at the appropriate temperature during shipping. This unit will be attached to an information card. The LCD display will show OK (indicating no alarm has been triggered) or a black bar and the number(s) 1-4 (indicating an alarm/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 or shipment, contact BMS at 800-743-9224 or 609-252-4973.

Important Reorder Instructions

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

Receipt Of Drug Shipment

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

7.2.8 Handling and Dispensing of Investigational Product

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

7.2.9 Drug Destruction and Return

Opened vials must be disposed of at the site as chemotherapy or biohazardous waste, provided documented procedures for destruction are in place. Otherwise, opened vials must be returned to the BMS for disposal. At the completion of the study, all unused drugs will be destroyed at the site according to the institution's policy for drug destruction. It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed, including dates and quantities. If approved procedures for destruction are not in place and/or for questions regarding cetuximab destruction, please contact BMS at 800-743-9224 or 609-252-4973.

7.3 Paclitaxel

7.3.1 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.

7.3.2 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 matter formation should not be used.

7.3.3 Administration

Paclitaxel will be administered as a 60 minute IV infusion using non-PVC tubing and connectors, such as the IV administration sets (polyethylene or polyolefin) that are used to infuse parenteral nitroglycerin and/or fat emulsion. A 22 micron filter must be placed on the distal end of the infusion line. Nothing else is to be infused through the line where paclitaxel is being administered.

Patients will receive prophylactic anti-allergy premedication prior to paclitaxel administration as follows:

Dexamethasone: 20 mg IV approximately 30 minutes prior to paclitaxel

Diphenhydramine: 50 mg IV x 1 dose 30 min prior to paclitaxel (Note: if diphenhydramine is administered prior to cetuximab, repeat administration prior to paclitaxel is not required when given on the same day.)

Ranitidine: 50 mg IV x 1 dose 30 minutes prior to paclitaxel

The premedication schedule can be altered at the discretion of the treating physician after the first paclitaxel dose.

7.3.4 Storage

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

7.3.5 Adverse Effects

- Hematologic: Myelosuppression
- Gastrointestinal: Nausea and vomiting; diarrhea, stomatitis, mucositis, pharyngitis, typhilitis, 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.

7.3.6 Supply

Paclitaxel is commercially available.

7.4 **Carboplatin**

7.4.1 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.

7.4.2 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.

7.4.3 Administration

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.

The dose of carboplatin is calculated (in mg, not mg/m²) as follows, using the modified Calvert formula based on creatinine clearance:

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

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:

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

7.4.4 Storage

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

7.4.5 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

7.4.6 Supply

Carboplatin is commercially available.

7.5 **Dose Modifications**

7.5.1 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 Section 6.6, 6.11, 7.5.

7.5.2 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.			

7.5.3 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 four 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.

7.5.3.1 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.

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

had prior exposure to a murine monoclonal antibody or other murine products. Adverse events should be attributed accordingly.

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

CTCAE v3.0

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):

Grade 3: Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension

Grade 4: Anaphylaxis

or **Grade 3 or Grade 4 Cytokine release syndrome/infusion reaction:**

Grade 3: 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 7.7).

For a CTCAE Grade 3 or 4 reaction, the patient is to receive no further cetuximab treatment.

7.5.3.2 Retreatment with Cetuximab Following Allergic/Hypersensitivity or Cytokine Release Reactions

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.

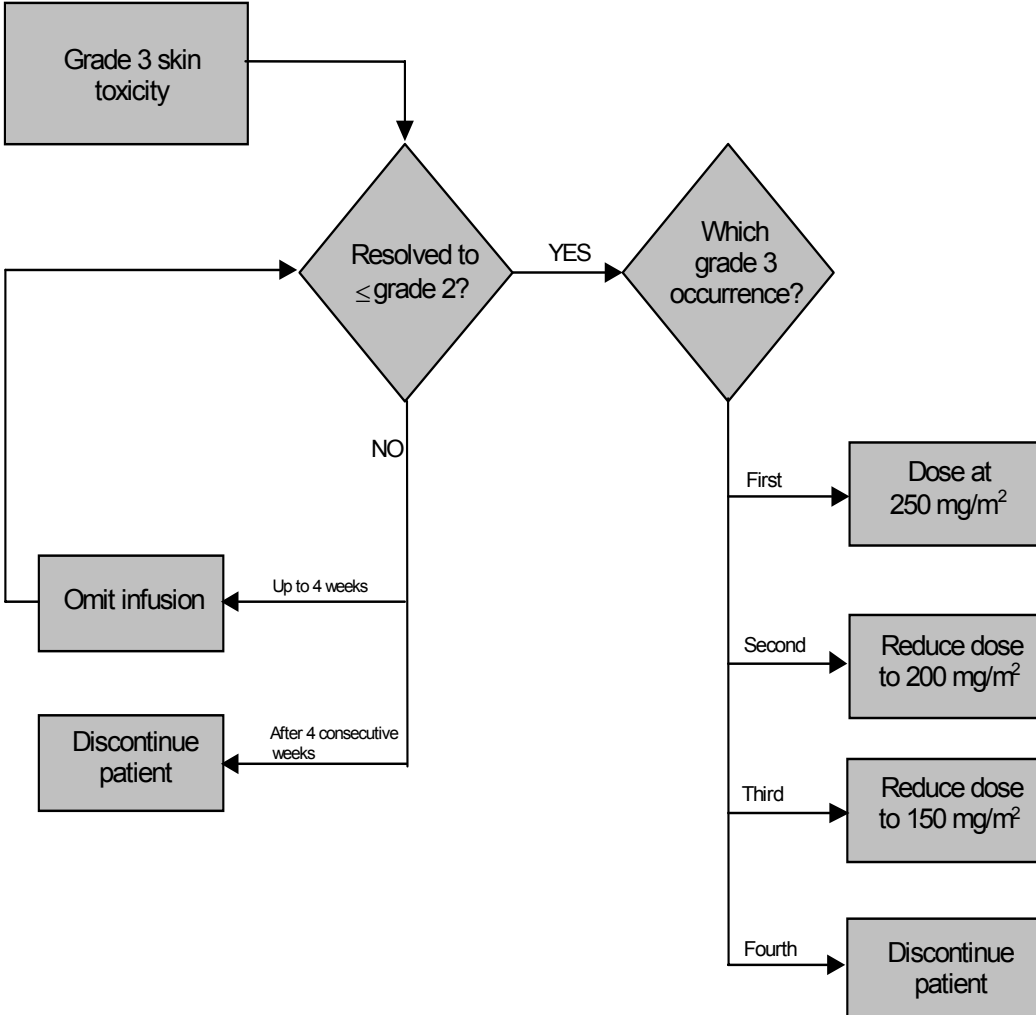
7.5.3.3 *Cetuximab Dose Modifications for Rash*

The cetuximab dose will be modified as follows for cetuximab-related Grade 3 acne-like rash. The severity of these events will be graded according to the criteria for the CTCAE v3.0 term "Rash: acne/acneiform." Local or generalized rash with erythema and/or desquamation other than acne/acneiform should be coded separately as "Rash/desquamation." A rash that occurs within the radiation field should be coded separately as "Rash: dermatitis associated with radiation."

The cetuximab dose alteration scheme for skin toxicity is outlined in the following figure. The first time a patient experiences a Grade 3 acne/acneiform rash, defined as 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 (see figure below) if skin toxicity has resolved to Grade 2 or less. **Cetuximab dose reductions are permanent.** Cetuximab will be discontinued if there are more than four 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 protocol therapy.

Management of C225 Skin Toxicity



7.5.4 Dose Modifications During Concurrent Therapy

7.5.4.1 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	Dose modifications for leukopenia are based on NCI CTCAE and are the same as recommended for neutropenia above.		

^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.

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

7.5.4.2 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.

7.5.4.3 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

^a 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.

- ^b 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.
- ^c With the exception of allergic/hypersensitivity or cytokine release reaction (see Section 7.5.3.2), acne-like rash (rash/desquamation) [see Section 7.5.3.3], anorexia, and viral infections. See Section 7.5.4.7 for treatment modifications for in-field GI and skin toxicity management.
- ^d 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.
- ^e See Section 7.5.4.5 for further neuropathy details.

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

- 7.5.4.4** Carboplatin Dose Modifications for Renal Toxicity
A > 25% change in the serum creatinine, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose.
- 7.5.4.5** 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 7.5.4.2).
- 7.5.4.6** 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.
- 7.5.4.7** 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 treatment)	4	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Esophagus/pharynx (on day of chemo)	3	No change or hold ≤ 5 days (See Section 7.5.4.10)	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Esophagus/pharynx (on day of chemo)	2	No change	No change	No change	No change
Pulmonary	4	Discontinue	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Pulmonary	3	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Skin	4	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Follow guidelines in Section 7.5.3.3
Skin	3	No change	No change	No change	Follow guidelines in Section 7.5.3.3

- 7.5.4.8** For Grade 4 infield esophagitis, radiotherapy and chemotherapy should be interrupted as detailed in the table above. Re-evaluate patient weekly.
- 7.5.4.9** For Grade ≥ 3 esophagitis/pharyngitis, dermatitis, or other in-field radiotherapy-related toxicity, 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 7.5.3.3.

7.5.4.10 Radiotherapy should be interrupted only for Grade 4 in-field toxicity and resumed when that toxicity has decreased to Grade ≤ 2 as detailed in the table above. If treatment is interrupted for > 2 weeks, the patient should be removed from study treatment. If the patient experiences esophagitis so that *IV* fluid support is needed, insertion of a feeding tube should be considered.

7.5.4.11 For Grade 3 esophagitis, radiotherapy can be continued with pain management and *IV* support, or radiotherapy can be held for ≤ 5 days until symptoms are $<$ Grade 3.

7.5.5 Dose Modifications During Consolidation Therapy

7.5.5.1 *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 $\geq 1,500$ mm ³	Hold therapy ^b . Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when $\geq 1,500$ 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 $\geq 1,500$ mm ³	Hold therapy ^b . Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when $\geq 1,500$ 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 $\geq 1,500$ mm ³	Hold therapy ^b and decrease by 1 dose level when $\geq 1,500$ 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 $\geq 1,500$ mm ³	Hold therapy ^b and decrease by 1 dose level when $\geq 1,500$ mm ³	Maintain dose level unless reoccurs after discontinuation of paclitaxel and carboplatin, then decrease by 1 dose level
Thrombocytopenia			
1 ($\geq 75,000$ /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 $\geq 75,000$ mm ³	Hold therapy ^b . Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when $\geq 75,000$ 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 $\geq 75,000$ mm ³	Hold therapy ^b . Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when $\geq 75,000$ 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 $\geq 75,000$ mm ³	Hold therapy ^b and decrease by 1 dose level when $\geq 75,000$ mm ³	Maintain dose level unless reoccurs after discontinuation of paclitaxel and carboplatin, then decrease by 1 dose level
Other Hematologic toxicities	Dose modifications for leukopenia are based on CTCAE, v3.0 and are the same as recommended for neutropenia above.		

^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.

7.5.5.2 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}
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

^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 Section 7.5.3.2), acne-like rash (rash/desquamation) [see Section 7.5.3.3], anorexia, and viral infections. See Section 7.5.4.7 for treatment modifications for in-field GI and skin toxicity management.

^d Radiation therapy should continue 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.

^eSee Section 7.5.5.4 for further neuropathy details.

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.

7.5.5.3 Carboplatin Dose Modifications for Renal Toxicity

A > 25% change in the serum creatinine, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose.

7.5.5.4 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 concurrent therapy (See Section 7.5.5)

7.6 Duration of Treatment

7.6.1 Discontinuation from Protocol Treatment

Study therapy MUST be immediately discontinued for the following reasons:

- Withdrawal of consent (patient's decision to withdraw for any reason);

- 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;
- Pregnancy;
- Progressive disease (Further treatment will be at the discretion of the treating physician).

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

7.6.2 Treatment Compliance

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

7.6.3 Modality Review

The Medical Oncology Co-Chair, Francisco Robert, 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 scoring mechanism is: **per protocol; variation, acceptable; deviation unacceptable; not evaluable for chemotherapy review, or, incomplete chemotherapy.** The review process is contingent on timely submission of chemotherapy treatment data as specified in Section 12.1. When complete data has been received at RTOG Headquarters for ten cases, these cases will be prepared and sent to Dr. Robert for review. Subsequent cases will be prepared and sent to Dr. Robert for review, in increments of 20-25 cases, after complete data for those cases is received at RTOG Headquarters. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

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

7.7.1 This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all treatment related adverse events. A copy of the CTCAE v3.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.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 v3.0. See the RTOG procedure manual for general Adverse Event Reporting Guidelines.

7.7.2 Reporting Requirements

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

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

7.7.4 **(7/26/04)** The following tables will outline the reporting requirements for this study. Follow the appropriate table as necessary.

Phase I Studies

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

Phase II/III Studies

UNEXPECTED EVENTS		EXPECTED EVENTS	
Grades 2 - 3 Attribution Possible, Probable, or Definite	Grades 4 and 5 Regardless of Attribution	Grades 1 - 3	Grades 4* and 5 Regardless of Attribution
Expedited report within 10 working days. (Grade 1 - Adverse Event Expedited Reporting NOT required.)	Report by phone to RTOG Headquarters within 24 hours of discovery. Expedited report to follow within 10 working days. Death—see below	Adverse Event Expedited Reporting NOT required.	Report by phone to RTOG within 24 hours of discovery. Expedited report within 10 working days. *Grade 4 Myelosuppression events submitted on case report forms.
Note 1	Telephone number available 24 hours daily: (215) 717-2762		
Note 2	Report the events using Common Terminology Criteria for Adverse Events (CTCAE) version 3.0		
Note 3	For Hospitalization only – Any medical event equivalent to CTCAE Grade 3, 4, 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported regardless of expected or unexpected and attribution.		

Note 4	A list of agent specific expected adverse events can be found in the protocol document and/or consent form.
Note 5	Reactions considered <i>definitely</i> not treatment-related should not be reported. However, a report should be submitted if there is reasonable suspicion of drug effect.

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

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

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

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

9.1 Prohibited Therapies

Patients should not receive any other anti-cancer drugs while receiving paclitaxel, carboplatin, or cetuximab, including hormonal and immunotherapy agents. Treatment with hormones or other chemotherapeutic agents will result in the patient's removal from the study. Exceptions are steroids administered for acute symptom management, adrenal failure, septic shock, or as antiemetics; or hormones administered for non-disease related conditions (e.g., insulin for diabetes). Colony stimulating factors (i.e., G-CSF, GM-CSF, etc.) should not be administered. In case of myelotoxicity, dose reductions will be made. In addition, treatment with amifostine is not allowed during radiation or within 3 months of completion of radiation therapy.

9.2 Supportive Therapy

Patients should receive full supportive care (except for colony stimulating factors) including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. The use of erythropoietin (i.e., Epogen®, Procrit®) is permitted. Sucralfate slurries may provide symptomatic relief of mucositis and esophagitis. Post-treatment pneumonitis attributed to radiation should be treated with prednisone after excluding microbial causes. It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving cetuximab therapy.

10.0 PATHOLOGY

(For Patients Who Have Consented to Participate in the Tissue Component of the Study; see Appendix IB)

10.1 Translational Research

Tissue submission for translational research is strongly encouraged but not required. Unavailability of tissue is not a criterion for exclusion. If tissue is unavailable, the reason(s) should be documented in the site's source documentation.

10.1.1 Rationale

The RTOG has been collecting pretreatment diagnostic tissue from cancer protocols over the last eight to ten years. A number of histologic, cell kinetic/proliferation, and molecular markers are under active investigation, with several showing promise for the stratification of patients in future trials.

The tissue submitted will be IHC tested for evidence of EGFR expression by the Translational Research Co-Chair, Dr. Ang, at MD Anderson Cancer Center. The 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.

10.1.2 Specimen Collection

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

10.1.2.1 One H&E stained slide

10.1.2.2 A paraffin-embedded tissue block of the tumor or a 2 mm diameter core of tissue, punched from the tissue block containing the tumor with a skin punch and submitted in a plastic tube labeled with the surgical pathology number. NOTE: A kit with the punch, tube, and instructions can be obtained from the Tissue Bank. If both of these tissue types are unavailable, 15 unstained slides may be submitted. Block, core, or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.

10.1.2.3 A Pathology Report documenting that the submitted block, core, or slides contain 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.

10.1.2.4 A Specimen Transmittal Form clearly stating that tissue is being submitted for the RTOG Tissue Bank; the form must include the RTOG protocol number and patient's case number.

10.1.3 (7/26/04) (7/17/07) Submit materials to:

**LDS Hospital
Dept. of Pathology
E.M. Laboratory
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10.2 Reimbursement

RTOG will reimburse submitting institutions \$300 per case for fresh or flash frozen tissue, \$200 per case for a block or core of material, or \$100 per case for unstained slides. After confirmation from the RTOG Tissue Bank that appropriate materials have been received, RTOG Administration will prepare the proper paperwork and send a check to the institution. Pathology payment cycles are run twice a year in January and July and will appear on the institution's summary report with the institution's regular case reimbursement.

10.3 Confidentiality/Storage

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

10.3.1 Upon receipt, the specimen is labeled with the RTOG protocol number and the patient's case number only. The Tissue Bank database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.

10.3.2 Specimens for translational research will be retained until the study is terminated, unless the patient consents to storage for future studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters (3/25/05)

Procedure	Pre-Treatment	During Therapy	End of Concurrent Therapy	End of all Protocol Therapy	Post Treatment Follow-up (See Section 11.2)
Medical History	X ^a		X	X	X
Physical Examination, Zubrod	X ^a	X ^d	X	X	X
RT and Med Onc Consults	X ^j				
Vital Signs	X ^{a,b}	X ^b		X	
Height and Weight and BSA	X ^a	X ^{a,e}	X ^e	X ^e	
FEV1	X ^c			X	X ^k
EKG	X ^c			X	
Toxicity Assessment/Adverse Events		X	X	X	X
CBC with differential and platelet count, serum creatinine	X ^a	X ^d	X	X	X ^f
Electrolytes, Mg ⁺⁺		X ^d			
Bilirubin, SGOT or SGPT, alk. Phos., glucose,	X ^a		X	X	X ^f
Pregnancy Test (urine or serum)	X ^h				
EGFR Assessment	X ⁱ				
CT Scan or MRI of Chest	X ^c			X	X ^g
Bone Scan ^m	X ^c				X ⁱ
CT Scan or MRI of Brain	X ^c				X ⁱ
PET Scan of chest	X ^l		X ^l		

- a. Within 2 weeks prior to study entry;
- b. Prior to cetuximab infusion, midway through infusion, at completion of infusion, and at one-hour post infusion;
- c. Within 4 weeks prior to study entry; perform CT scan or MRI at a minimum of 1 cm slice thickness to include the lung apices through the adrenals. It is recommended that a consistent evaluation (CT or MRI) be used throughout the study.
- d. Weekly;
- e. Assess weight only; recalculate the BSA if there has been > 10% weight loss;
- f. At relapse;
- g. Recommended every 6 months for 2 years, then annually;
- h. For women of childbearing potential; within 72 hours prior to start of protocol treatment;
- i. If tissue is available; availability must be documented in chart at time of registration.
- j. Approval to proceed must be received prior to initiation of study treatment.
- k. At 6 months after completion of consolidation therapy, then at 1 year
- l. Recommended at pretreatment and 4 weeks after completion of concurrent therapy to assess acute toxicity
- m. A pretreatment PET scan, rather than a bone scan, is permitted to rule out bone metastases.

11.2 Post-treatment Follow up

A follow-up evaluation will be performed approximately 30 days following completion of all protocol treatment. In addition, all patients will be followed for a minimum of 30 days after the last dose of study therapy or every 4 weeks until all study drug related

toxicities have resolved, returned to baseline, or are deemed irreversible, whichever is longer. Thereafter, patients will be seen for follow up every 3 months for 2 years, then every 4 months for 2 years.

11.3 Response Assessment (RECIST Criteria)

11.3.1 Measurement of Response

Response will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3): 205-216, 2000] See <http://ctep.info.nih.gov/guidelines/recist.html> for further details.

Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

- **Measurable disease** - the presence of at least one measurable lesion; If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan.
- **Non-measurable lesions** - all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques

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 (7/26/04)

Data should be submitted to:

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

NOTE: Prompt data submission is required for Phase I statistical analysis.

12.1 Summary of Data Submission (7/26/04)

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 weeks of study entry
Initial Evaluation Form (I1)	
Pathology Report (P1)	
Slides/Blocks (P2)	
<u>Preliminary Dosimetry Information:</u>	Within 1 week of start of RT
RT Prescription (Protocol Treatment Form) (T2)	
Films (simulation and portal) (T3)	
Calculations (T4)	
Treatment Planning CT Scan (C1) [if done]	

<u>Final Dosimetry Information:</u> Daily Treatment Record (T5) Isodose Distribution (T6) Boost Films (simulation and portal) (T8)	Within 1 week of RT end
Radiotherapy Form (T1)	Within 1 week of RT end
Treatment Summary Form (TF)	At 8, 12, and 18 weeks
Follow-up Form (F1)	Every 4 weeks x 2; Following completion of consolidation treatment, then every 3 months for 2 years; every 4 months x 2 years. Also at progression/relapse and at death, if these events occur between planned follow-up intervals.
Autopsy Report (D3)	As applicable

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint: Feasibility of concurrent cetuximab and chemoradiation as measured by safety and compliance. Safety is measured by the rate of grade 3 or worse non-hematological toxicities occurring prior to the beginning of consolidation therapy (including all toxicities attributed to chemoradiation occurring within 90 days of the start of radiation therapy); compliance is defined as the completion of the treatment regimen with no more than minor variations.

13.1.2 Secondary endpoints:

13.1.2.1 Response rate (complete and partial response rates)

13.1.2.2 Overall survival rates (one and two year rates, median survival)

13.1.2.3 Time to progression rates (one and two year rates)

13.1.2.4 Association between EGFR expression and toxicity, response, overall survival, and progression (exploratory analysis)

13.2 Sample Size

The overall grade 3 or worse non-hematological toxicity rate for patients receiving concurrent chemotherapy and radiation followed by chemotherapy on BMSO/ACR 427, a randomized trial comparing three regimens in the treatment of locally advanced non-small cell lung cancer, was observed as 60%. This rate with the addition of cetuximab to the treatment regimen is of greatest interest in this study. Using a Fleming one-sample multiple test procedure⁴⁴ with Type I and Type II errors each set at 10% we would require 63 analyzable cases to reject a null hypothesis that the true toxicity rate of adding cetuximab to this therapy is greater than 75% in favor of the alternative hypothesis that the true rate is no more than 60%. Adjusting that number of cases by 5% to adjust for patient ineligibility, the primary endpoint requires at least **67cases**.

In order to adequately assess the clinical endpoint of survival, the sample size necessary to detect an increase median survival time (MST) from 17 months to 24 months will be calculated. An increase in MST to 24 months is justified by the results of the SWOG S9504³³, which showed an MST of 26 months in a similar patient population. With accrual of 5 patients per month, 12 months of follow-up, and an alpha of 0.10, a one-sided test⁴⁵ on 80 patients has 81% statistical power.

Because the primary endpoint is supported by the larger sample size required to detect a meaningful increase in MST, the sample size for this study will be 80 patients. Adjusting the number of accrued cases by 5% to allow for patient ineligibility, the targeted sample size is **84 cases**.

Compliance is defined to be completion of concurrent chemoradiation plus cetuximab with no more than minor variations as defined (See Section 6.10). BMSO/ACR 427 had a compliance rate of 84% for patients receiving at least 6 cycles. Using a 95% exact confidence interval around a binomial proportion of compliant patients, with 80 analyzable patients we will have a maximum confidence interval width of 22.8%. If the compliance rate is the same as in BMSO/ACR 427 (i.e. 71 compliant cases out of the 80 analyzable, 85.0%) the width of the confidence interval will be 16.7%. If the observed compliance rate is at or no better than 46 cases out of 80 (53.75% with an exact 95% confidence interval of [42.2%, 64.97%]) – where the upper bound of the confidence interval is less than 65% – the regimen will be considered unfeasible.

13.3 Patient Accrual

We expect to see accrual of 5 patients per month. This trial should complete accrual in approximately eighteen months. If the monthly accrual is less than 3 cases per month (excluding the first three months of the study to allow institutions to get IRB approval of the study), the study will be re-evaluated to determine if it is reasonable to continue.

13.4 Analysis and Reporting Plans

13.4.1 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.

13.4.2 Interim Treatment Analyses for Early Stopping Due to Severe or Excessive Non-hematologic Toxicities

Accrual to this study will be suspended if any patient experiences a fatal treatment-related toxicity. In the event that a patient has a fatal treatment-related toxicity at any time, the study chairs, the RTOG Lung Committee Chair, and the RTOG Executive and Research Strategy Committees will be asked to review the data and patient information to make appropriate recommendations about continuing the study.

There will be five reviews of the rate of grade 3 or worse non-hematological toxicities within 90 days of the first day of radiation therapy. They will occur after the 10th, 20th, 30th, 60th, and 80th patients have been treated and followed for at least 90 days from the end of radiation therapy. According to Fleming’s method, with Type I error of 0.15018 and Type II error of 0.14247, the rules are as follows:

Number of patients	Reject H_0 ($\geq 75\%$ toxicity) if number of patients with grade 3 or worse non hematological toxicities is \leq	Reject H_A ($\leq 60\%$ toxicity) if number of patients with grade 3 or worse non hematological toxicities is \geq
10	2 (20%)	N/A
20	9 (45%)	20 (100%)
40	24 (60%)	32 (80%)
60	40 (67%)	44 (73%)
80	55 (69%)	56 (70%)

However, even if a boundary for rejecting H_0 is reached at some point in the study, the study chairs may choose not to close the study so as to get better estimates of the endpoints (compliance, toxicity, response rate, survival rate, time to progression rate).

13.4.3 Interim Analyses of Accrual and Toxicity Data

Interim reports will be prepared every 6 months until the initial manuscript reporting the treatment results has been submitted. The usual components of this report are:

- a) The patient accrual rate with a projected completion date for the accrual phase;
- b) Accrual by institution;
- c) The distribution of pretreatment characteristics;
- d) The quality of submitted data with respect to timeliness, completeness, and accuracy;
- e) The frequency and severity of the toxicities.

The statistician will report any problems identified to the RTOG lung cancer committee, and if appropriate, to the RTOG Executive Committee.

13.4.4 Analysis for Reporting Initial Treatment Results

This analysis will be done when all the patients accrued to the study have been potentially followed for a minimum of 12 months. It will include:

- a) Tabulation of all cases entered into the trial; exclusions with reasons;
- b) Institutional accrual;
- c) Distribution of important prognostic baseline variables;
- d) Observed results for the endpoints listed in Section 13.1.

Overall survival will be plotted using Kaplan-Meier estimates and the MST tested using the methods of Lawless⁴⁵ in a one-sided test against the null value of 17 months MST.

Estimates of overall survival (calculated using the Kaplan-Meier method⁴⁶) and time to progression (calculated using the method of cumulative incidence⁴⁷) at one and two years will be calculated along with their associated 95% confidence intervals.

Response (determined two months after completion of consolidation chemotherapy) is taken to be complete response (CR) or partial response (PR) using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3): 205-216, 2000]. Point and interval estimates of the proportion of patients with either PR or CR, using an exact 95% confidence interval, will be calculated.

The exploratory analysis of EGFR expression and toxicity, response, and progression will be a chi-squared test for association after dichotomizing EGFR expression for each patient. The maximum reported toxicity for each patient will be dichotomized to < Grade 3 or ≥ Grade 3; response will be categorized to CR, PR, or other than CR/PR; and progression will be dichotomized to yes/no. Patients will be grouped according to their dichotomized EGFR expression level and survival in the two groups will be compared.

13.4.5 Analysis for Reporting Long-Term Results

This analysis, if necessary, will be done when all the patients accrued to the study have been potentially followed for a minimum of 30 months or when all patients are dead. It will include all items found in section 13.4.4.

13.5 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.⁴⁸⁻⁴⁹ In conformance with the National Institute of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, the projected gender and minority accruals are shown below. Given the small number of cases on the trial, no analyses of treatment efficacy will be performed on any gender or racial subset.

Planned Gender and Minority Inclusion

Ethnic Category	Females	Gender		Total
		Males		
Hispanic or Latino	3	3		6
Not Hispanic or Latino	33	45		78
Ethnic Category: Total of all subjects*	36	48		84

Racial Category	Females	Gender		Total
		Males		
American Indian or Alaskan Native	1	2		3
Asian	2	1		3
Black or African American	2	3		5
Native Hawaiian or other Pacific Islander	0	0		0
White	31	42		73
Racial Category: Total of all subjects*	36	48		84

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APPENDIX IA

RTOG 0324

SAMPLE CONSENT FOR RESEARCH STUDY

STUDY TITLE

A PHASE II STUDY OF CETUXIMAB (C225) IN COMBINATION WITH CHEMORADIATION IN PATIENTS WITH STAGE IIIA/B NON-SMALL CELL LUNG CANCER (NSCLC)

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

You are being asked to take part in this study because you have lung cancer.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to test the safety of cetuximab (C225), an investigational drug, given with chemotherapy and radiation therapy and see what effects (good and bad) cetuximab, chemotherapy, and radiation therapy have on you and your lung cancer.

C225 has been designed to block certain chemical pathways that lead to tumor cell growth. In prior studies with lung cancer patients, C225 has delayed tumor growth and provided relief of symptoms in some patients.

This research is being done because we need to test the safety and effectiveness of C225 when given with chemotherapy and radiation therapy.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 84 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

If you take part in this study, before your first dose of C225, you will be given some medications through your vein to prevent an allergic reaction to C225. Then you will be given the first dose of C225 through your vein for approximately 1½ hours. You will not receive chemotherapy or radiation therapy on the day you receive the first dose of C225.

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

If you tolerate the first dose of C225 well, the following week you will begin receiving C225 and chemotherapy once a week for 7 weeks while you are receiving radiation therapy once a day. You will receive C225 through your vein before receiving chemotherapy through your vein and radiation therapy. Receiving C225 and then chemotherapy will take about 6 hours.

You then will receive C225 once a week for 3 weeks without chemotherapy or radiation therapy. Receiving C225 will take about 3 hours. Finally, you will receive C225 through your vein once a week for 6 weeks. During the 6 weeks, you also will receive chemotherapy through your vein (after C225 is given) once every 3 weeks (2 doses). Receiving C225 and then chemotherapy will take about 6 hours.

Bristol-Myers Squibb will provide C225 free of charge for the patients on this study.

If you take part in this study, you also will have the following tests and procedures: **(11/23/04)**

- A physical exam before beginning treatment, weekly during the first 7 weeks of treatment, at the end of the 7 weeks of treatment, at the end of all treatment, one month after treatment and once a month as long as your doctor feels is necessary to monitor your recovery from treatment. Once your side effects have lessened, you will be seen in follow-up visits every 3 months for 2 years, then every 4 months for 2 years.

- Blood tests before beginning treatment, weekly during the first 7 weeks of treatment, at the end of the 7 weeks of treatment, at the end of all treatment, and then as advised by your doctor
- For women who are able to have children, a test before beginning treatment to see that they are not pregnant
- An EKG (a test to measure the electrical activity of the heart) before beginning treatment and at the end of all treatment
- Tests of your lung function before beginning treatment, at the end of all treatment, and at 6 months and one year after the end of all treatment
- A CT scan or MRI of your chest before beginning treatment, at the end of all treatment, every 6 months for two years, and then yearly
- A CT scan or MRI of your head and a bone scan (or a PET scan, if advised by your doctor) before beginning treatment and then as advised by your doctor
- A PET scan, if advised by your doctor, before beginning treatment and 4 weeks following the end of 7 weeks of treatment

HOW LONG WILL I BE IN THE STUDY?

You will receive 17 weeks of treatment. You will be seen in follow-up visits at the end of all treatment, one month after treatment, and once a month as long as your doctor feels is necessary to monitor your recovery from treatment. Once your side effects have lessened, you will be seen in follow-up visits every 3 months for 2 years, then every 4 months for 2 years, for a total of 4 years.

Your doctor may decide to take you off this study if side effects become very severe, if new scientific developments occur that indicate the treatment is not in your best interest, if funding for this study is stopped, if the drug supply is insufficient, or your condition worsens.

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

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict.

Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the C225, chemotherapy, and radiation therapy are stopped, but in some cases, side effects can be serious or long lasting or permanent.

Risks Associated with Cetuximab (C225)

Very Likely

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

Less Likely

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

Less Likely, But Serious

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

Rare

- Inflammation of the lining of the brain

Cetuximab also may cause allergic reactions such as hives, itching, and/or skin rash. Some patients have had allergic reactions with the first dose of cetuximab, but some patients have had reactions with later doses. The allergic reactions also can be severe, involving shortness of breath, wheezing, difficulty swallowing, lightheadedness, very low blood pressure, and rarely, heart attack and/or death.

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

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

Risks Associated with Paclitaxel

Very Likely

- Slow pulse
- Hair loss
- Tingling, numbness, burning pain in hands and feet
- Lower blood counts during treatment, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
- Inflammation of the lining of the mouth
- Skin redness or rash

Less Likely

- Nausea and/or vomiting
- Mouth sores
- Diarrhea
- Inflammation of the lining of the throat and/or intestines
- Tiredness
- Blurred vision and/or the feeling of seeing flashing lights
- Flushing
- Lightheadedness
- Tenderness, hardness, or itching of the skin; rarely, blistering of the skin
- Pain in muscles and joints
- Mood swings

Less Likely, But Serious

- Areas of decreased vision or visual awareness
- Reaction to paclitaxel, resulting in injury to the skin, lung, and/or lining of the digestive tract in the chest area that has received radiation
- Cardiovascular changes, such as low or high blood pressure, speeding up or slowing of heartbeat, a blockage of blood flow to the heart, and/or heart attack
- Seizures
- Allergic reactions, which could involve sweating, difficulty breathing, lightheadedness, and/or rapid heartbeat
- Severe inflammation of the small and large intestines
- Severe rash called Stevens-Johnson Syndrome, which can cause fever and red sores in your mouth and eyes

- Changes in liver enzymes in the blood, which may mean damage to the liver that could lead to being hospitalized, or rarely, to death

Risks Associated with Carboplatin

Very Likely

- Tingling, numbness, burning pain in hands and feet
- Lower blood counts during treatment, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
- Nausea and/or vomiting
- Tiredness

Less Likely

- Muscle pain

Less Likely, But Serious

- Allergic reactions, which could involve sweating, difficulty breathing, lightheadedness, and/or rapid heartbeat
- Changes in liver enzymes in the blood, which may mean damage to the liver that could lead to being hospitalized, or rarely, to death
- Blurred vision
- Hearing loss

Risks from Radiation Therapy

Radiation therapy to the chest

Very Likely

- Difficulty, pain, or burning sensation when swallowing, which is temporary; the use of chemotherapy with radiation may increase this risk. You should avoid acidic or spicy foods and alcoholic beverages.
- Fatigue (tiredness) for no apparent reason, which is temporary
- The skin in the treatment area may become reddened and/or dry, and chest hair may not grow back.
- Decrease in blood counts while undergoing treatment, which could lead to an increased risk of infection, weakness, and/or in bleeding and bruising easily
- Cough
- Some difficulty breathing, due to lung damage, as described below

Less Likely, But Serious

- Irritation of the lining around the heart, which can cause chest pain, shortness of breath, and irregular or rapid heart beat; rarely, this can require surgery to correct.
- Irritation and/or damage to the muscle of the heart;

rarely, this can cause a heart attack, heart failure, and/or death.

- Irritation and/or damage to the spinal cord (the major nerve within the spine), which can lead to weakness, tingling or numbness of the lower body and legs; very rarely, this can lead to inability to move or control the lower half of the body.
- Narrowing of the esophagus (tube to the stomach)

Chest radiotherapy can cause changes in normal lungs. These changes can be as unimportant as small amounts of "scarring" seen on x-rays that does not cause symptoms. Sometimes chest radiotherapy can cause lung damage that leads to symptoms such as shortness of breath, cough, or fever. Rarely, these symptoms can be severe or life threatening. The combined use of chemotherapy and radiotherapy, as in this study, may increase the risk of developing symptoms due to lung damage.

Reproductive Risks

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

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

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

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

The benefit of C225, chemotherapy, and radiation therapy to patients with lung cancer is unknown. This treatment may keep your lung cancer from growing, and this may provide relief from

symptoms and improve your quality of life. This treatment may improve control of your lung cancer. However, none of these benefits is guaranteed, and the effects of a combination of C225, chemotherapy, and radiation therapy may be no different or worse than chemotherapy or radiation therapy alone.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) radiation therapy; (2) chemotherapy; (3) a combination of radiation therapy and chemotherapy or (4) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. C225 is an investigational drug and is not available unless you are participating in a research study.

Your doctor can tell you more about your condition and the possible benefits of the different available treatments. Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

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

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include the Radiation Therapy Oncology Group (RTOG) and groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI) or its authorized representatives, and qualified representatives of Bristol-Myers Squibb.

WHAT ARE THE COSTS? (7/26/04)

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

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

You or your insurance company will be charged for continuing medical care and/or hospitalization. Medicare should be considered a health insurance provider.

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

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. If you choose to stop participating in the study, you should first discuss this with your doctor. In order to provide important information that may add to the analysis of the study, he/she may ask your permission to submit follow-up data as it relates to the study. You may accept or refuse this request. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

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

A group of experts in lung cancer from the RTOG Lung Committee, the study chairs, and the RTOG study statistician will be reviewing the data periodically throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

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

_____ Name

_____ Telephone Number

For information about this study, you may contact:

Name

Telephone Number

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

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

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

Visit the NCI's Web sites for comprehensive clinical trials information at **www.cancer.gov/clinicaltrials** or for accurate cancer information including PDQ (Physician Data Query) visit **www.cancer.gov/cancerinfo/pdq**

SIGNATURE

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

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

Patient's Name

Signature

Date

Name of Person Obtaining Consent

Signature

Date

APPENDIX IB

SAMPLE CONSENT FORM FOR USE OF TISSUE FOR RESEARCH

RTOG 0324

A PHASE II STUDY OF CETUXIMAB (C225) IN COMBINATION WITH CHEMORADIATION IN PATIENTS WITH STAGE IIIA/B NON-SMALL CELL LUNG CANCER (NSCLC)

ABOUT USING TISSUE FOR RESEARCH

You have had or you will have a biopsy (or surgery) to see if you have cancer. Your doctor has removed or will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that remains for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Your tissue may be helpful for research whether you do or do not have cancer.

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

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

THINGS TO THINK ABOUT

The choice to let us keep the left over tissue for future research is up to you. **No matter what you decide to do, it will not affect your care.** If you decide not to let us keep the left over tissue, you can still take part in this study.

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue and then any tissue that remains will no longer be used for research; or, you may request that your tissue, if any remains, be returned to you or your designee.

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

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

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

BENEFITS

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

RISKS

Physical Risks

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

Social-Economic risks

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

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

MAKING YOUR CHOICE

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

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

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

Yes

No

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

Yes No

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

Yes No

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

Yes No

WHOM DO I CALL IF I HAVE QUESTIONS?

(This section must be completed)

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

Name

Telephone Number

For information about research-related questions, you may contact:

Name

Telephone Number

Participant statement:

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

Patient’s Name

Signature

Date

Witness statement:

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

Name of Person Obtaining Consent

Signature

Date

Appendix II

KARNOFSKY PERFORMANCE SCALE

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

ZUBROD PERFORMANCE STATUS

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

APPENDIX III

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 III (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 IV (7/26/04)

C225 (Cetuximab) CLINICAL SUPPLY SHIPMENT REQUEST TO INVESTIGATIONAL SITE

Cetuximab will be shipped only to institutions that have identified a single individual for receipt of shipment. For the initial shipment, U.S. and Canadian institutions must email the shipment form for this study to RTOG_BMS@phila.acr.org as soon as the individual responsible for the study agent has been identified and prior to registration of the institution's first case. (Fax 215-574-0300 if unable to email) Allow adequate processing time (7-10 days) before calling to randomize your first patient.

For Resupply Requests, email the shipment form for this study to cetuximab.drug@bms.com. (Fax to 866-227-7229 if unable to email). For questions, call 800-743-9224.

NOTE: THE SHIPMENT FORM FOR THIS STUDY IS AVAILABLE AT
<http://www.rtog.org/members/protocols/0324/0324shipmentform.doc>