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Protocol Page

A Phase II Study of TARCEVA (erlotinib) in Combination with Chemoradiation in Patients with Stage IIIA/B Non-Small Cell Lung Cancer (NSCLC)
2005-1023

Core Protocol Information

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Which Committee will review this protocol?

(●) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Background

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 172,570 new cases are estimated for 2005. It is the leading cause of cancer deaths in both men and women, with approximately 163,510 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] Tl-3 N2 MO, Stage IIIA) or contralateral mediastinal, hilar or ipsilateral or contralateral scalene or supraclavicular nodes (AJCC Tl-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 Epidermal Growth Factor Receptor Expression and Significance in Cancer

The control of cell growth is mediated by a complex network of signaling pathways responsive to external influences, such as growth factors, as well as to internal controls and checks. Epidermal growth factor (EGF) was one of the first growth factors to be described. It was shown to be mitogenic, an effect mediated by the binding of EGF (or other ligands) to the cell surface EGF receptor (EGFR), stimulating autophosphorylation of the intracellular tyrosine kinase domain of the receptor. Subsequent investigations revealed EGFR to be one of a family of closely related receptors that includes EGFR (HER1), HER2, HER3, and HER4.

EGFR and other HER family members are considered to be important in the development, progression, and aggressive behavior of human epithelial malignancies and to be relevant therapeutic targets. A number of human malignancies are associated with aberrant or over-expression of EGFR.[9] Stimulation of tumor cells via the EGFR is important for both tumor growth and tumor survival in vivo. Over-expression of EGFR in certain human tumors, including non–small cell lung carcinoma (NSCLC), has been correlated with both chemo-resistance and poor prognosis.[10-22] Inhibitors of EGFR tyrosine kinase activity have been in development for a number of years, and although earlier compounds lacked specificity and potency, newer compounds have proven active in nonclinical and clinical studies.

Erlotinib (previously known as OSI-774) is an orally active, potent, selective inhibitor of the EGFR tyrosine kinase. Early clinical data with Erlotinib indicate that the compound is generally safe and well tolerated at doses that provide the targeted effective concentration based on nonclinical experiments. A recently completed, randomized, double-blind, placebo-controlled trial has shown that Erlotinib as a single agent significantly improves the survival of patients with incurable Stage IIIb/IV NSCLC who have failed standard therapy for advanced or metastatic disease.[23]

1.2 Erlotinib as an EGFR Tyrosine Kinase Inhibitor

Erlotinib is an EGFR tyrosine kinase inhibitor that has been investigated in several Phase III studies. An overview of relevant nonclinical and clinical information is presented below; complete details are available in the Erlotinib Investigator Brochure.

1.2.1 Nonclinical Data

a. Pharmacology

Erlotinib, a quinazoline, directly and reversibly inhibits the human EGFR tyrosine kinase with an IC50 of 2 nM (0.79 ng/mL) in an in vitro enzyme assay and reduces EGFR autophosphorylation in intact tumor cells with an IC50 of 20 nM (7.9 ng/mL). This potent inhibition is selective for the EGFR tyrosine kinase both in assays assessing the effects of Erlotinib on a variety of other isolated tyrosine kinases and in cellular bioassays designed to isolate this functional pathway. Erlotinib is designed to inhibit EGF-dependent proliferation of cells at submicromolar concentrations and blocks cell cycle progression in the G1 phase.

Data on drug exposure and anti-tumor responses in human tumor xenograft models (HN5 and A431) were analyzed in order to estimate the plasma concentration of erlotinib associated with anti-tumor activity. Based on these efficacy models, the minimum steady-state plasma concentration targeted for clinical activity in humans is projected to be 500 ng/mL.

b. Toxicology

Toxicology studies have been performed in mice, rats (up to 6 months), dogs (up to 1 year), and monkeys (1 week). Treatment-related effects observed in at least one species or study included effects on the cornea (atrophy, ulceration), skin (follicular degeneration and inflammation, redness, and alopecia), ovary (atrophy), liver (necrosis), kidney (papillary necrosis and tubular dilatation), gastrointestinal tract (delayed gastric emptying and diarrhea), and embryo-fetal toxicity. Red blood cell parameters were decreased, and white blood cells (primarily neutrophils) were increased. There were treatment-related increases in ALT, AST and bilirubin; increases in bilirubin were likely caused by a treatment-related impairment of bilirubin metabolism.

1.2.2 Clinical Experience with Erlotinib

As of April 2004, Erlotinib has been studied clinically in more than 4000 healthy subjects and patients (excluding patients exposed to placebo) in a number of Phase I, II, and III studies.

a. Dose Selection for Single-Agent Trials of Erlotinib

Phase I trials of Erlotinib explored both schedule and dose to evaluate the safety, tolerability, and pharmacokinetic profile of the compound given as a single agent. A number of pharmacokinetic trials in healthy subjects have been conducted, along with three classic Phase I trials in patients with advanced cancer. The single-agent maximum tolerated dose (MTD) was estimated to be 150 mg administered once daily.

The primary toxicities of single-agent Erlotinib consisted of rash (dermatosis), diarrhea, nausea, fatigue, stomatitis, vomiting, and headache. When given daily, dose-limiting toxicity (diarrhea) was observed at 200 mg/day. At 150 mg/day, diarrhea was manageable with the addition of loperamide therapy; this dose was considered the maximal tolerated dose.

Rash (variously referred to as dermatitis, acneiform rash, or maculopapular rash) has been variable in onset, duration, and severity, but typically appears on the face, neck, scalp, chest, and back starting after ~1 week of treatment. The mechanistic basis of the rash remains uncertain; histopathologic examination of biopsies of the rash demonstrated inflammatory cell infiltrate and mild epidermal hyperproliferation. In some cases, the rash gradually improved despite continued dosing and, in general, resolved without sequelae following Erlotinib discontinuation. The rash did not result in study discontinuation in patients with cancer in the Phase I trials.

Laboratory abnormalities observed infrequently with single-agent Erlotinib involved primarily liver function tests, including elevation of ALT, AST, and/or bilirubin.

Selection of the 150 mg/day dose of Erlotinib for subsequent single-agent studies was based on pharmacokinetic parameters, as well as the safety and tolerability profile of this dose in Phase I trials in heavily pretreated patients with advanced cancer. Drug levels seen in patients with cancer receiving the 150 mg/day dose were consistently above the average plasma concentration of 500 ng/mL targeted for clinical efficacy.

b. Pharmacokinetics

Oral Erlotinib is well absorbed and has an extended absorption phase, with mean peak plasma levels occurring at 3 hours after oral dosing of 150 mg/dL at steady state. A study in healthy subjects provided an estimate of bioavailability of 59% (95% CI: 55%, 63%). The time to reach steady-state plasma concentration was ~5 days. The accumulation ratio with daily dosing of Erlotinib was estimated to be 2.0. From a population pharmacokinetic analysis of 708 patients, the median trough concentration (Cmin) 24 hours following the previous dose was 1041 (697) ng/mL. Median AUC achieved during the dosing interval at steady state was 19,801 ng hr/mL. Exposure after an oral dose is increased by food.

There is extensive binding of Erlotinib and metabolites to both serum albumin and AAG (alpha-1-acid glycoprotein), with total plasma protein binding for

Erlotinib and OSI-420 of ~95% and 91%, respectively. Erlotinib is extensively metabolized in the liver by the hepatic cytochromes in humans–primarily by CYP3A4 and to a lesser extent by CYP1A2. The primary metabolite of Erlotinib, OSI-420, has potency comparable to that of erlotinib, but is present at levels that are 10% of erlotinib levels. Erlotinib is excreted predominantly via the feces (90%). The elimination half-life after a 150-mg oral dose is ~30 hours. In population-based data analyses, no relationships were identified between predicted steady-state trough concentration and patient age, body weight, sex, ethnicity, or creatinine clearance.

d. Phase II and III Trials in Patients with Advanced Cancer

Multiple Phase II trials evaluating the safety, tolerability, and antitumor activity of Erlotinib have been conducted in patients with advanced, refractory malignancies including cancer of the head and neck, lung, aerodigestive tract, ovary, breast, central nervous system (glioma), and others. Erlotinib has been evaluated both as a single agent and administered concurrently with conventional chemotherapy agents using various doses and schedules.

Evidence of activity has been observed in squamous cell carcinoma of the head and neck, ovarian, breast and pancreatic carcinoma, non–small cell lung cancer (NSCLC), and glioblastoma multiforme (GBM). Patients received 150 mg/day of Erlotinib in all of these studies except the GBM study where dose escalation was allowed until limited by rash and where a higher starting dose was tested in subjects receiving concomitant enzyme inducing anti-epileptic drugs. Dose reduction was allowed in all studies in the case of intolerance. Diarrhea was treated with loperamide therapy and/or dose reduction. Rash was treated with a variety of agents, including oral and topical antibiotics, corticosteroids, and other agents.

Patients receiving Erlotinib in combination with various chemotherapy agents have generally experienced the same type of adverse events (AEs) as with either agent alone.

The first randomized placebo controlled trial to demonstrate a survival advantage for an EGFR inhibitor was the Phase III study, BR21. This international trial, conducted by the National Cancer Institute of Canada Clinical Trial Group (NCIC CTG), included 731 patients with incurable Stage IIIb/IV NSCLC who have failed standard therapy for advanced or metastatic disease. Patients randomized in a 2:1 ratio to single-agent Erlotinib 150 mg/day obtained a 42.5% improvement in median survival over placebo, from 4.7 to 6.7 months. The one-year survival increased significantly (from 22% to 31%) as did the median and 6 month PFS, response rate, and the time to deterioration of tumor related symptoms of pain, cough, and dyspnea.[23]

In BR-21, of the 727 patients evaluable for safety (485 Erlotinib, 242 placebo), the most common AEs in the Erlotinib arm were rash (75% Erlotinib, 17% placebo), diarrhea (54% Erlotinib, 18% placebo) and stomatitis (17% Erlotinib, 18% placebo) events. The majority of these events were mild to moderate in severity. The incidence of interstitial lung disease (ILD) reported was the same

in the placebo and Erlotinib groups at 0.8% in each arm.

Two large, Phase III, randomized studies in first-line NSCLC patients evaluated Erlotinib in combination with platinum-based two-drug combination chemotherapy. A total of 1079 previously untreated patients received carboplatin/paclitaxel with either Erlotinib or placebo in the TRIBUTE trial (OSI2298g) conducted in the United States. An additional 1172 patients received cisplatin/gemcitabine plus either Erlotinib or placebo in the TALENT trial (BO16411) conducted in 27 countries in Europe and other ex-U.S. locations. Neither study met its primary endpoint of improved overall survival or a secondary endpoint of improved time to disease progression or overall response rate. Overall, the number of adverse events and serious adverse events were well balanced between the two arms of each study, with two exceptions. As expected, rash and diarrhea occurred more frequently in the Erlotinib arms. In the TRIBUTE study, more serious adverse events resulting in death were seen in the Erlotinib arm compared with the placebo arm (53 vs. 27). Most of the apparent imbalance was due to events reported as pneumonia or progression of underlying cancer.[24]

e. Patients with Hepatic or Renal impairment

The influence of hepatic metastases and/or hepatic dysfunction on the pharmacokinetics of Erlotinib is not yet known. However, Erlotinib is cleared predominately by the liver, and caution should be used when administering Erlotinib to patients with hepatic dysfunction. Erlotinib is also a strong inhibitor of the UDP-glucuronosyltransferase UGT1A1 enzyme responsible for the glucuronidation of bilirubin. Hyperbilirubinemia appears most often to be a side effect related to genetic polymorphisms of UGT1A1.

No clinical studies have been conducted in patients with compromised renal function since Erlotinib and its metabolites are not significantly excreted by the kidneys.

1.3 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.[25] 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.[26] 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.[27] 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.[28] 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, ZD1839, were reported.[29-31] Two of the trials, designated IDEAL 1 37 (n=210) and IDEAL 2 37 (n=216), evaluated the activity of oral, single agent ZD1839 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 ZD1839 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.[31]

In regard to the maintenance EGFR inhibitor, the gefitinib maintenance in pateint with inoperable stage III NSCLC treated with concurrent chemoradiotherapy did not improve the outcome compared to placebo maintenance according to the SWOG trial 0023.[34] Therefore we are not using erlotinib maintenance.

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.[32]

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 ZD1839, and it is a logical step to evaluate the activity of erlotinib in this disease. Baselga et al. have reported on three phase I erlotinib studies in which a total of eight patients with NSCLC were given erlotinib, two as single agent therapy and six in combination with cisplatin.[33] Although results were not reported by disease state, patients in all three studies experienced disease stabilization and erlotinib-associated toxicity was minimal.

2.0 Objectives

2.1 Primary Objective

Determine the efficacy of concurrent erlotinib and chemoradiation as measured by time to progression.

2.2 Secondary Objectives

2.2.1 Safety as measured by the rate of grade 3 or worse non-hematological toxicities (dose limiting toxicity or DLT) occurring prior to the beginning of consolidation therapy (including all toxicities attributed to chemoradiation occurring within 90 days of the start of radiation therapy) .

2.2.2 Compliance defined to be completion of concurrent chemoradiation plus erlotinib with no more than minor variations as defined (See Section 6.10).

2.2.3 Response rate (complete and partial response rates)

2.2.4 Overall survival rates (one and two year rates, median survival).

2.2.5 Disease local control rate

2.2.6 Association between EFGR expression and toxicity, response, overall survival, and progression (exploratory analysis)

2.2.7 Association between EGFR expression and response correlated with imaging study.

3.0 Study Design

This is a phase II study of Erlotinib (erlotinib) in combination with chemoradiation in patients with stage IIIA/B non-small cell lung cancer (NSCLC). 48 patients will be treated with concurrent chemoradiation and Erlotinib followed by consolidation therapy of chemotherapy.

SCHEMA

NOTE: Erlotinib is not to be taken on the days of chemotherapy administration.

Concurrent Chemoradiation and Erlotinib

Weeks 1-7:
Erlotinib, 150 mg p.o. daily throughout the radiation, except for chemotherapy day

+

Paclitaxel, 45mg/m², and Carboplatin, AUC=2, weekly, **throughout the radiation, for up to 7 treatments**.

+

RT: 63 Gy/35 fractions/7weeks (+/- 5 days)

(1.8 Gy/ fraction, a total dose of 63.0 Gy in 35 fractions over 7 weeks)

Concurrent Chemoradiation should be completed within 9 weeks

Consolidation therapy:

Weeks 11-17
Paclitaxel, 200 mg/m², and
Carboplatin, AUC=6, every 3 weeks for two cycles

3.2 Rationale for Study Design

At the 2003 ASCO annual meeting, the results of several phase II studies were reported regarding the combination of C225 with chemotherapy.[34] In a phase I/II study in untreated metastatic NSCLC combining C225 with paclitaxel and carboplatin (C225 loading dose of 400 mg/m^2 then weekly 250 mg/m^2 maintenance; paclitaxel 225 mg/m^2 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.[35] 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.

NCI Canada clinical trials group conducted a study of Erlotinib in previously treated NSCLC. They conducted a randomized, placebo-controlled, double-blind trial to determine whether the epidermal growth factor receptor inhibitor erlotinib prolongs survival in non-small-cell lung cancer after the failure of first-line or second-line chemotherapy. Patients had stage IIIB or IV non-small-cell lung cancer, with performance status from 0 to 3, were eligible if they had received one or two prior chemotherapy regimens. The patients were stratified according to center, performance status, response to prior chemotherapy, number of prior regimens, and prior platinum-based therapy and were randomly assigned in a 2:1 ratio to receive oral erlotinib, at a dose of 150 mg daily, or placebo. The median age of the 731 patients who underwent randomization was 61.4 years; 49 percent had received two prior chemotherapy regimens, and 93 percent had received platinum-based chemotherapy. The response rate was 8.9 percent in the erlotinib group and less than 1 percent in the placebo group (P<0.001); the median duration of the response was 7.9 months and 3.7 months, respectively. Progression-free survival was 2.2 months and 1.8 months, respectively (hazard ratio, 0.61, adjusted for stratification categories; P<0.001). Overall survival was 6.7 months and 4.7 months, respectively (hazard ratio, 0.70; P<0.001), in favor of erlotinib. Five percent of patients discontinued erlotinib because of toxic effects. They concluded that Erlotinib can prolong survival in patients with non-small-cell lung cancer after first-line or second-line chemotherapy.[36]

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 which is based upon Arm 3 of the LAMP study and the SWOG 9504 study. The addition of biologic therapy with erlotinib to the regimen hopefully will result in even better efficacy without increasing toxicity.

Clearly this study is a logical next step in the attempt to find the optimal regimen for the treatment of advanced NSCLC.

3.3 Safety Plan

3.3.1 Adverse Events Using Erlotinib

To date, at least 4000 cancer patients have received Erlotinib at a dose of 150 mg/day in previous clinical trials.

Common adverse events associated with Erlotinib administration include rash and diarrhea. Other common adverse events include nausea/vomiting, stomatitis, headache, and fatigue.

A rash occurred in 75% of Erlotinib-treated NSCLC patients enrolled in BR.21. A papular, pustular rash manifesting most often on the face and upper trunk was common across all studies, but rash was rarely the cause of study drug discontinuation. The rash may be associated with erythema, pain, pruritus, dryness, and less commonly, stomatitis, keratitis and nailbed changes. Wearing of contact lenses while receiving Erlotinib therapy is not recommended. The incidence of diarrhea in BR.21 was 54% of Erlotinib-treated NSCLC patients. The median time to onset of skin rash was 8 days and median time to occurrence of first diarrheal symptom was 9 days.

There have been infrequent reports of serious (including fatal) interstitial lung disease (ILD) in patients receiving Erlotinib for treatment of NSCLC or other advanced solid tumors. In Study BR.21, the incidence of ILD (0.8%) was the same in the placebo and Erlotinib groups. The overall incidence in Erlotinib-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6%. Included in this rate of ILD are reported diagnoses of pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome, and lung infiltration, irrespective of investigator assessed causality. Most of the cases were associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, preexisting parenchymal lung disease, metastatic lung disease, or pulmonary infections.

Reversible renal impairment has been reported in association with dehydration associated with nausea, vomiting, and diarrhea. There have been rare reports of renal failure in patients receiving Erlotinib in combination with platinum-containing chemotherapy regimens. Febrile neutropenia has been reported in patients receiving concomitant chemotherapy.

Erlotinib is both protein bound (92%–95%) and metabolized by hepatic cytochromes CYP3A4 and CYP3A5 and pulmonary cytochrome CYP1A1. Therefore, a potential for drug–drug interaction exists when Erlotinib is co-administered with drugs that are highly protein bound or that are CYP3A4 inhibitors/inducers.

Co-administration of Erlotinib with an inhibitor of CYP3A4 metabolism (ketoconazole,

200 mg po BID for 5 days) resulted in increased exposure to Erlotinib as measured by an 86% increase in median Erlotinib AUC and a 69% increase Cmax, compared with administration of Erlotinib alone.

Induction of CYP3A4 metabolism by a known enzyme inducer (rifampin, 600 mg po QD for 7 days) resulted in a 69% decrease in the median Erlotinib AUC, compared with administration of Erlotinib alone. However, the effect of rifampin on Cmax was negligible.

International normalized ratio (INR) elevations and/or bleeding events have been reported in some cancer patients taking warfarin while on Erlotinib.

3.3.2 General Plan to Manage Safety Concerns

A number of measures will be taken to ensure the safety of patients participating in this trial, addressed through exclusion criteria and routine monitoring. Patients will be evaluated for adverse events at each study visit for the duration of their participation in the study and for 30 days after the discontinuation of Erlotinib.

Skin toxicities will be monitored by routine physical examination and managed symptomatically. Because secondary bacterial infections are common and can lead to more serious complications, topical or systemic antibiotics may be considered. Anecdotally, topical or a short course of systemic corticosteroids can be helpful. See Section 4.3.3 and Table 2 for management guidelines, including Erlotinib dose reduction/interruption.

Diarrhea will be monitored and managed symptomatically. Guidelines for management include administration of loperamide and Erlotinib dose reduction/interruption as described in Section 4.3.3 and Table 2.

Although quite rare, ILD can be life threatening. Therefore, patients should be monitored closely for symptoms consistent with ILD, such as new onset dyspnea without an obvious cause. In the event that ILD is suspected, Erlotinib treatment should be discontinued and the patient should receive appropriate medical management. Although there is no proven therapy, systemic corticosteroids are often provided. Erlotinib should not be restarted in those patients suspected of having drug-related ILD. See Section 4.3.3 and Table 2 for management guidelines, including Erlotinib dose interruption.

Women of childbearing potential should have a negative pregnancy test prior to starting therapy with Erlotinib and should use adequate contraceptive methods during and for at least 4 weeks after Erlotinib therapy. If a patient becomes pregnant despite precautions, she should be apprised of the potential risk of fetal morbidity or loss.

3.4 Administrative Structure

This is a sponsored trial performed with the support of Genentech, Inc. and OSI Pharmaceuticals. Ritsuko Komaki, MD will be the Principle Investigator. Patients will be

seen and enrolled at the University of Texas M. D. Anderson Cancer Center, Houston, TX. The University of Texas M.D. Anderson Cancer Center IND office will monitor the study investigators to assure satisfactory enrollment rate, data recording, and protocol adherence.

4.0 Materials and Methods

4.1 Patients

4.1.1 Inclusion Criteria

4.1.1.1 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 Tl 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 4.5.2 for RECIST definitions of measurable disease.

4.1.1.2 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.

4.1.1.3 Patients must be $\geq$18 years of age;

4.1.1.4 Patients with Zubrod performance status 0-1 (See Appendix E);

4.1.1.5 Adequate hematologic function defined as: ANC $\geq$ 1,500/mm^3, platelets $\geq$ 100,000/mm^3, and hemoglobin $\geq$ 9 g/dL (prior to transfusions); adequate hepatic unction defined as: total bilirubin $\leq$ 1.5 mg/dl, SGOT or SGPT $\leq$ 3 x ULN, adequate renal function defined as a serum creatinine level $\leq$ 2.0 mg/dl, alkaline phosphatase $\leq$ 2.5 x ULN, glucose $\leq$ 2 x ULN;

4.1.1.6 FEV1 with $\geq$ 1000 cc;

4.1.1.7 Patients with weight loss $\leq$ 10% over the past 3 months;

4.1.1.8 Patients with a pleural effusion that is a transudate, cytologically negative and nonbloody are eligible if the radiation oncologists feel the tumor can still be encompassed within a reasonable field of radiotherapy. 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.

4.1.1.9 If patients had exploratory thoracotomy, they must have recovered from the procedure. Exploratory Thoracotomy and beginning of treatment should be within one month.

4.1.1.10 Women of childbearing potential (A woman of child-bearing potential is a sexually mature woman who has not undergone a hysterectomy or who has not been naturally postmenopausal for at least 24 consecutive months [i.e., who has had menses at any time in the preceding 24 consecutive months])

and male participants must practice effective contraception (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) throughout the study and for four weeks after completion of treatment.

4.1.1.11 For women of childbearing potential, a urine or blood pregnancy test must be performed within 48 hours prior to the start of protocol treatment;

4.1.1.12 Medical Oncology and Radiation Oncology consults and approval.

4.1.1.13 Patients must sign a study-specific consent form prior to study entry.

4.2 Exclusion Criteria

4.2.1 Prior systemic chemotherapy and/or thoracic radiotherapy for any reason and/or surgical resection of present cancer;

4.2.2 Exudative, bloody, or cytologically malignant effusion or effusion that are exudative and/or bloody and are suggestive or malignant involvement.

4.2.3 Prior therapy with any other drug that targets the EGFR pathway,

4.2.4 Active pulmonary infection not responsive to conventional antibiotics;

4.2.5 History of interstitial lung disease;

4.2.6 History of severe COPD requiring $\geq$ 3 hospitalizations over the past year;

4.2.7 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 (50-70%) on a baseline multiple gated acquisition (MUGA) scan or echocardiogram.

4.2.8 Patients with > grade 1 neuropathy;

4.2.9 Evidence of malignancy in the past 3 years except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other in situ cancers;

4.2.10 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;

4.2.11 Women of childbearing potential and male participants who are unwilling or unable to use an acceptable method of contraception (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) throughout the study and for four weeks after completion of treatment or those who are using a prohibited contraceptive method (methods with unknown efficacy).

4.2.12 Patients who currently are participating in other clinical trials and/or who have participated in other clinical trials in the previous 30 days. Clinical trials involving administration of investigational agents or interfering with the safe conduct of this trial. All clinical trials would exclude observational trials which would not interfere with the endpoints of our study.

4.3 Study Treatment

4.3.1 Formulation

Erlotinib oral tablets are conventional, immediate-release tablets containing erlotinib as the hydrochloride salt. In addition to the active ingredient, Erlotinib contains lactose (hydrous), microcrystalline cellulose, sodium starch glycolate, sodium lauryl

sulfate, and magnesium stearate.

Tablets containing 25 mg, 100 mg, and 150 mg of Erlotinib are available. Each bottle will contain 30 tablets, a quantity sufficient for 4 consecutive weeks of dosing, with overage.

For further details, see the Erlotinib Investigator's Brochure

4.3.2 Dosage, Administration and Storage

Erlotinib will be self-administered in an open-label, unblinded manner to all patients enrolled in the study. During the treatment period, patients will receive single-agent Erlotinib, 150 mg/day. Tablets should be taken at the same time each day with 200 mL of water at least 1 hour before or 2 hours after a meal. Patients who are unable to swallow tablets may dissolve the tablets in distilled water for administration.

Dose reductions for adverse events will be permitted (see Section 4.3.3). Treatment is continued daily until disease progression or other reason for termination of study therapy (see Section 4.6).

Erlotinib tablets will be supplied for clinical trials in white, high-density polyethylene (HDPE) bottles with child-resistant closures and should be stored at temperatures between 15°C and 30°C (59°F and 86°F).

Erlotinib is being provided from investigational supply and may have unknown differences from the commercial stock.

4.4 Concomitant and excluded Therapies

Use of anti-neoplastic or anti-tumor agents not part of the study therapy, including chemotherapy, radiation therapy, immunotherapy, and hormonal anticancer therapy, is not permitted while participating in this study.

Use of concurrent investigational agents is not permitted.

There are potential interactions between Erlotinib and CYP3A4 inhibitors and CYP3A4 promoters. Although caution and careful monitoring are recommended when use of these compounds is necessary, use of these compounds does not exclude patients from participating in this trial (see Appendix F for a list of CYP3A4 inhibitors).

Patients taking warfarin or other warfarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.

4.5 Study Assessments

Procedure	Pre-Treatment	During Therapy	One month after end of Consolidation Therapy	Post Treatment Follow-up[n]
Medical History	X[a]		X	X
Physical Examination, Zubrod	X[a]	X[d]	X	X
RT and Med Onc consultation	X[i]			
Vital Signs	X[a,b]	X[b]		
Height and Weight and BSA	X[a]	X[d,e]	X[e]	
PFT (FEV1)	X[c]		X	X[j]
EKG	X[c]		X	
Toxicity Assessment/Adverse Events		X	X	X
CBC with differential and platelet count, serum creatinine	X[a]	X[d]	X	X[f]
Electrolytes, Mg++	X	X[d]		
Bilirubin, SGOT or SGPT, alk. Phos., glucose	X[a]		X	X[f]
Pregnancy Test (urine or serum)	X[h]			
CT Scan of the chest/upper abdomen	X[c]		X	X[g]
Bone Scan[k]	X[c]			X[f]
MRI of Brain or CT	X[c]			X[f]
PET Scan	X[c]		X	X[l]
SPECT (Tc99m MAA)	X[c]			
MUGA (if indicated)	X[l]			
Coagulation Profile (PT, PTT, INR)	X[m]	X[m]	X[m]	X[m]
Additional Biopsy (optional)	X[o]			
Blood Sample (optional)	X	X		X[p]

a. Within 2 weeks prior to study treatment;
b. Pre Chemotherapy, per standard of care for this chemo regimen.
c. Within 4 weeks +/- 5 days prior to start of study treatment; perform CT scan of the

chest/upper abdomen at less than 1 cm slice thickness to include the lung apices through the adrenals. It is recommended that a consistent evaluation (CT scan of the chest/upper abdomen) 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 48 hours prior to start of protocol treatment;
i. Approval to proceed must be received prior to initiation of study treatment.
j. At 6 months after completion of consolidation therapy, then at 1 year
k. A pretreatment PET scan, rather than a bone scan, is permitted to rule out bone metastases.
l. If indicated
m. Weekly, if receiving anticoagulant agents (until Erlotinib completed)
n. patient will return one month after treatment, once a month until recovery from treatment related toxicities, then every 3 months for 2 years, then every 4 months for 2 years (total of 4 years)
o. Specimen will be stored for analysis immunochemical staining to analyze EGFR status.
p. Optional blood samples will be obtained for evaluation the last week of concurrent treatment, at the start of consolidation therapy, at the first post- treatment follow-up visit, and every three months up to 12 months in coordination with the follow up visits. Serum or plasma samples will be assessed using in-house assays or in collaboration with outside institutions/vendors. All samples will be de-identified and will not be re-identified except through unique codes tied into clinical information for statistical analysis. All statistical analysis will be done at MD Anderson on a password protected clinical database.
q. PET scan will be performed 1 month after completion of consolidation chemotherapy.

4.5.1 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 (total of 4 years). Patients will be off study at the time of death or 4 years after treatment

4.5.2 Response Assessment (RECIST Criteria)

4.5.2.1 Measurement of Response :Response will be evaluated in this study using RECIST Version1.1 for all patients with measurable disease at baseline and completing at least two weeks of concurrent chemoradiation. (Please refer to the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009] under Appendix M).

4.6 Patient Discontinuation

Patients may discontinue study treatment at any time. Any patient who discontinues treatment will be encouraged to return to the study center to undergo treatment discontinuation assessments. The primary reason for discontinuation should be recorded. Reasons for discontinuation of a patient by the investigator include, but are not limited to, the following:

- Documented disease progression
- Clinically significant deterioration of the patient's condition prior to treatment discontinuation
- Patient noncompliance
- Persistent (3 weeks) NCI-CTCAE version 3.0 Grade 3 or Grade 4 adverse event or any significant adverse event that compromises the patient's ability to participate in the study
- Investigator determination that it is not in the patient's best interest to continue participation
- Pregnancy

4.7 Statistical Methods

4.7.1 Statistical Considerations

The primary objectives for this phase II study is to evaluate the efficacy of the combination therapy by adding erlotinib to the standard chemoradiation therapy for patients with stage IIIA/B NSCLC. In addition, we have built in a Bayesian toxicity monitoring plan to ensure the safety of the study regimen. If the toxicity exceeds the pre-specified boundaries, the trial will be stopped. The maximum sample size for this study is 48.

4.8 Study Endpoints

4.8.1 Primary Endpoints: Efficacy of concurrent erlotinib and chemoradiation as measured by time to progression.

4.8.2 Secondary Endpoints:

4.8.2.1 Safety as measured by the rate of grade 3 or worse non-hematological toxicities (dose limiting toxicity or DLT) occurring prior to the beginning of consolidation therapy (including all toxicities attributed to chemoradiation occurring within 90 days of the start of radiation therapy)

4.8.2.2 Compliance defined to be completion of concurrent chemoradiation plus erlotinib with no more than minor variations as defined (See Section 6.10).

4.8.2.3 Response rate (complete and partial response rates)

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

4.8.2.5 One and two year disease progression rates

4.8.2.6 Disease local control rate

4.8.2.7 Association between EFGR expression and toxicity, response, overall survival, and progression (exploratory analysis)

4.9 Sample Size

We assume that the primary endpoint for the phase II study, time-to-progression, follows an exponential distribution. We hypothesize that the combination of erlotinib and chemoradiation can increase the median time to progression from 15 months to 25 months (a 67% increase). Using a logrank test, a total of 48 patients will yield 80% power with 10% one-sided type I error rate. The sample size calculation assumes the accrual rate is 3 patients per month with an additional 12 months of follow-up after the last patient is enrolled. We also factor in a 10% inevaluable rate due to drop-out or loss-to-follow up, etc. The total study duration is estimated to be 28 months (16 months of accrual plus 12 months of follow up) Socinski et al., JCO 2008: median survival: 24.3 months; median time to progression is 14.9 months.

A 95% exact confidence interval will be computed to estimate the compliance rate under the assumption of a binomial distribution. With 65 evaluable patients, we will have a maximum confidence interval width of 25.3%. BMSO/ACR 427 had a compliance rate of 84% for patients receiving at least 6 cycles. If the compliance rate is the similar as in BMSO/ACR 427 (i.e. 55 compliant cases out of the 65 analyzable, 85.0%) the width of the confidence interval will be 18.8%. If the observed compliance rate is at or no better than 34 cases out of 65 (52.3% with an exact 95% confidence interval of [39.5%, 64.85%]) – where the upper bound of the confidence interval is less than 65% – the regimen will be considered unfeasible.

4.10 Patient Accrual
We expect to see accrual of 3 patients per month.

4.11 Bayesian Toxicity Monitoring Plan
Our prior experience shows that 30% to 50% of the patients may experience DLT with the standard chemoradiation therapy. A DLT rate of greater than 60% is considered unacceptable. A Bayesian toxicity monitoring plan is constructed such that if the probability of unacceptable toxicity (Prob(DLT) > 50%) is high ($\geq$ 80%), the trial will be stopped early. With a prior distribution of beta(0.9, 2.1), the posterior distribution of the probability of unacceptable toxicity can be computed using the relationship between the beta and binomial distributions. Based on these criteria, the trial will be stopped due to excessive toxicity when 8 in 10, 13 in 20, 18 in 30, 24 in 40, and 29 in 50 patients experience DLT.

The following table lists the operating characteristics for the design based on 1,000 simulation runs. As it can be seen, when the probability of true toxicity rate increases, the probability of early stopping also increases and the average sample size decreases. The percent of patients experiencing DLT is close to the true toxicity rate but is slightly higher because early stopping due to excessive toxicity can cause the estimator to have an upward bias.

Our assumptions are based on the premise that a 30% to 50% of DLT are acceptable due to the fact that the most DLT's are expected and manageable and the disease has a grave consequence. The operating characteristics show that when the true toxicity rate is 40%, only 4% of the time the trial will be stopped early and when the true toxicity rate is 50%, 32% of the time the trial will be stopped early. The corresponding average sample sizes are 68.0 and 57.5, respectively. When excessive toxicity is shown (i.e., DLT rate is 0.60), the probability of early stopping is 86% with an average sample size of

34.2.

True Toxicity (DLT) Rate	Probability of Early Stopping due to toxicity	Average Sample Size	Percent of Patients Experiencing DLT
0.40	0.04	68.0	0.41
0.45	0.13	64.4	0.47
0.50	0.32	57.7	0.53
0.55	0.62	45.6	0.60
0.60	0.86	34.2	0.66

4.12 Analysis and Reporting Plans

4.12.1 Interim Analyses for Early Stopping Due to Severe or Excessive Nonhematologic 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 PI, will review the data and patient information to make appropriate recommendations about continuing the study.

The rate of grade 3 or worse non-hematological toxicities within 90 days of the first day of radiation therapy will be closely monitored with the stopping boundaries listed in Section 4.11

4.12.2 Interim Analyses for Efficacy

There will be no interim analysis for efficacy. We consider the early stopping due to futility is unnecessary because the chemoradiation therapy is the standard therapy for this patient population and adding erlotinib is not expected to decrease its efficacy. Early stopping due to efficacy is also not recommended in this phase II evaluation.

4.13 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) The distribution of pretreatment characteristics;
c) The frequency and severity of the toxicities.

The statistician will report any problems identified to the IRB.

4.14 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) Distribution of important prognostic baseline variables;
d) Observed results for the endpoints listed in Section 4.8.1

All the time-to-event endpoints will be plotted using Kaplan-Meier estimate and the logrank test with a one-sided test against the null hypothesis.

Estimates of overall survival and time to progression 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 $\geq$ 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.

4.15 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.

5.0 Specification of Safety Variables

ASSESSMENT OF SAFETY

5.1 Specification of Safety Variables

Drug toxicities will be evaluated according to CTC version 3 (Appendix B). Reporting of adverse events will be according to M.D. Anderson Guidelines for AE Reporting (Appendix A).

Serious adverse events will be delivered to ORERM and will be submitted to the FDA by the regulatory compliance coordinator according to 21CR 312.32.

Unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and all subject deaths should be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil), or by facsimile (301-619-7803) to the U.S. Army Medical Research and Materiel Command, Human Subjects Research Review Board (HSRRB). A complete written report should follow the initial notification. In addition to the methods above, the complete report can be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-QH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

5.1.1 Communication Between Principal Investigator and Genentech

The investigators will submit written reports of all SAEs, regardless of attribution, to

Genentech within 48 hours of learning of the events to the following:

Genentech's Drug Safety Department at:

(650) 225-4682

or

(650) 225-5288

6.0 Sponsor and Investigator Requirements

Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

6.1 Informed Consent

All study participants must sign and date an informed consent form prior to study participation. The investigator will be responsible for designing the consent form using appropriate National or Regional Guidelines (equivalent to the American Federal Guidelines Federal Register July 27, 1981, or 21 CRF Part 50, or International Committee on Harmonization-Good Clinical Practice).

The informed consent form must be approved by the IRB or Ethics Committee and USAMRMC HSRRB. State and local laws, and/or institutional requirements may require the disclosure of additional information on the informed consent form.

Participants will be consented by the treating physician and the research nurse. Witnesses will be clinic nurses or other members present during the informed consent interview process. Participants may request information and decide to enroll at a later date. Follow-up will occur through the research nurse.

Once consent has been obtained, a copy of the informed consent form will be given to the participant. The investigator will keep each participant's signed informed consent form on file for inspection by a regulatory authority at any time.

For a detailed description of the informed consent process see Appendix G.

6.2 Institutional Review Board Approval

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. In addition, any advertising materials must be approved by the IRB. The study will be conducted in accordance with U.S. FDA, applicable national and local health authority, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case the IRB must be updated at least once a year for annual review. Copies of the annual review and final study report will also be submitted to the HSRRB and/or USAMRMC, Human Research Protection Office. The Principal Investigator must also keep the IRB informed of any significant adverse events.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Investigator Brochure and that are considered possibly or probably related to the study drug by the investigator. Some IRBs may have other specific adverse event requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Genentech (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

6.3 Study Monitoring Requirements

The University of Texas M.D. Anderson Cancer Center IND office will monitor the study investigators to assure satisfactory enrollment rate, data recording, and protocol adherence. The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. M.D. Anderson Cancer Center will monitor and/or audit the other participating sites to assure satisfactory protocol adherence and enrollment.

6.4 Data Collection

The investigator and other appropriate study staff will be responsible for maintaining all documentation relevant to the study. Such documentation includes:

- Copies of all Serious AE reporting forms faxed to the USAMRMC, Human Research Protection Office.
- Participant Files—should substantiate the data entered in PDMS with regard to laboratory data, participant histories, treatment regimens, etc.
- Participant Exclusion Log—should record the reason any participant was screened for the study and found to be ineligible.
- Drug Dispensing Log—should record the total amount of study drug received and returned to sponsor, and the amount distributed and returned or destroyed. This information must agree with the information entered in PDMS.
- Informed Consent Forms—completed consent forms from each participant must be available and verified for proper documentation.
- Informed Consent Log—must identify all participants who signed an Informed

Consent Form so that the participants can be identified by audit.

The Investigator must keep on file protocols, amendments, IRB approvals, all copies of Form FDA 1572, all correspondence, and any other documents pertaining to the conduct of the study for a minimum of two (2) years.

6.5 Study Medication Accountability

For the drug supplied for this study, an accountability ledger containing current and accurate inventory records covering receipt, dispensing, and the return of study drug supplies must be maintained. Drug supplies must be kept in a secure, limited-access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the accountability ledger: the identification code of the subject to whom drug is dispensed, the date(s) and quantity of drug dispensed to the subject, and the date(s) and quantity of drug returned by the subject. Patients should return empty containers to the investigator, with the return noted on the ledger. These Accountability Forms must be readily available for inspection and are open to FDA inspection at any time.

All study drug required for completion of this study will be provided by OSI-Pharmaceutical (manufacturer), in partnership with Genentech (*unless otherwise noted*). The recipient will acknowledge receipt of the drug by returning the drug receipt form indicating shipment content and condition. Damaged supplies will be replaced.

Study drug accountability records should be maintained by the site in accordance with the regulations.

The original drug supply request of Erlotinib will be submitted to Genentech along with the form “Approval for Drug Re-Supply”, indicating which personnel will be able to submit drug re-supply requests.

All subsequent drug re-supply requests will be directly submitted to OSI-Pharmaceuticals from the site.

At the time of study closure, the unused, used and expired study drug will be destroyed at the site per Institutional SOPs, or returned to the OSI-Pharmaceutical Drug Depot.

6.6 Disclosure of Data

Data will be reviewed by the collaborating biostatistician prior to publication. HSRRB and/or USAMRMC, Human Research Protection Office will have 30 days to review all definitive publications, such as manuscripts and book chapters, and a minimum of 10-15 days to review all abstracts.

Patient medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the patient’s permission, medical information may be given to his or her personal

physician or other appropriate medical personnel responsible for his or her welfare. This medical information must be made available to Genentech and authorized representatives of Genentech, upon request, for source verification of study documentation.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, local health authorities, M. D. Anderson Cancer Center, Genentech, Inc, OSI Pharmaceuticals and their authorized representative(s), collaborators and licensees, and the IRB for each study site, if appropriate.

6.7 Retention of Records

HSRRB and/or USAMRMC, Human Research Protection Office, M.D. Anderson or their representatives may have access to subject records.

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

6.8 Medical Monitoring

The medical monitor will review all serious and unexpected adverse events associated with this protocol and provide an unbiased written report of the event within ten (10) calendar days of the initial report. At a minimum, the medical monitor will comment on the outcomes of the adverse event (AE) and relationship of the AE to the study. The medical monitor will also indicate whether he/she concurs with the details of the report provided by the study investigator. This individual should be a qualified physician, other than the principal investigator, not associated with the protocol, able to provide medical care for research volunteers for conditions that may arise during the conduct of the study, and who will monitor the volunteers during the conduct of the study. The medical monitor is required to review all serious and unexpected adverse events (per ICH definitions) associated with the protocol and provide an unbiased written report of the initial report. At a minimum the medical monitor should comment on the outcomes of the adverse event (AE) and relationship of the AE to the test article. The medical monitor should also indicate whether he/she concurs with the details of the report provided by the study investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death should be promptly forwarded to the HSRRB.

The medical monitor for this study will be James Welsh, MD:

James Welsh, M.D.
University of Texas M.D. Anderson Cancer Center
Department of Radiation Oncology
1515 Holcombe Blvd. - 97
Houston, Texas 77030 USA
Phone: 713/563-2300

Fax: 713/563-5331
Email: Jwelsh@mdanderson.org

The medical monitor will forward reports to the U.S. Army Research and Material Command, ATTN: MCMR-RCQ, 504 Scott Street, Fort Detrick, Maryland, 21702-5012.

6.9 Termination of Study

The HSRRB and/or USAMRMC, Human Research Protection Office and M. D. Anderson will retain the right to terminate the study and remove all study materials from the study site at any time. Specific instances that may precipitate such termination are as follows:

- Unsatisfactory participant enrollment with regard to quality or quantity
- Inaccurate and/or incomplete data recording on a recurrent basis
- The incidence and/or severity of adverse drug events in this or other studies indicating a potential health hazard caused by the treatment

6.10 Study Amendments

The investigator will only alter the protocol to eliminate apparent immediate hazards to the participant. If preliminary or interim statistical analysis indicated that the experimental design, dosages parameters, or selection of participants should be modified, these changes will be described in an amendment to be approved by the institution's and other appropriate review committees after consultation with the statistician and Study Chairman. Any amendments cannot be enacted unless approved by the HSRRB and/or USAMRMC, Human Research Protection Office. All revisions made to protocols previously approved by the IRB will be submitted to the IRB for approval prior to implementation of the revision. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing. No changes to the protocol will be initiated unless also approved by the Human Subjects Research Review Board.

6.11 Protocol Violations

In the event of a protocol violation, the principal investigator will notify M.D. Anderson and the study Medical Monitor. This notification will occur as soon as the violation is identified and will be included in the annual review and final study report. Any violation that affects the safety or rights of the subject and/or integrity of the study data will also be reported promptly to the United States Army Medical Research and Materiel Command, Office of Research Protections, Human Research Protection Office (USAMRMC ORP HRPO)

6.12 Annual Review and Final Study Reports

The investigator must submit an annual review and final study report to the IRB or Ethics Committee for review and approval. Copies of the annual review and final study report must also be submitted to the HSRRB.

6.13 Ethical and Legal Considerations

This study will undergo full approval in accordance with the human surveillance

requirements of each institution. Blood samples will be obtained for the evaluations as described in the protocol. Tissue samples obtained at the time of prior surgeries will be reviewed before participant enrollment to confirm the participant's diagnosis. Measures will be taken to ensure confidentiality of participant information. Tissue samples will be collected prospectively during the trial. Data collected on paper forms will be stored in locked file cabinets with restricted access. Data collected on electronic media will be stored in computer files with restricted password access. All staff members in the study will be informed prior to employment and at regular intervals of the necessity for keeping all data confidential. Computers will not be accessible to the public and will be located in locked offices. Subjects will be assigned a separate study number to protect subject identification. No patient identifiers will be used in any publications of this research. Data will be maintained indefinitely. When the time comes to dispose of the data, all database files will be deleted, patient identifiers will be removed from all paper forms and documents will be shredded.

6.14 Risks/Benefits

Venipuncture may cause pain, bleeding, clotting, bruising at the injection site, and rarely infection.

Erlotinib may cause rash, diarrhea, fatigue, nausea, vomiting, abdominal pain, headache, stomatitis, anorexia, alopecia, pruritis, myalgias, bone pain, cough dyspnea, elevated liver enzymes, interstitial lung dz, ocular changes.

- Renal impairment in combination with N/V/D or platinum containing chemotherapy regimens, febrile neutropenia with concomitant chemotherapy.
- Warfarin drug interactions. Drug interactions with CYP3A4 inhibitors/inducers
- Caution advised in combination with NSAIDS due to risk of GI bleed
- Containdicated in subjects with hypersensitivity to components/drug or class
- Unanticipated risks
- Unknown risks

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

Carboplatin may cause Myelosuppression; Nausea and vomiting; hepatic toxicity; electrolyte imbalance; hypomagnesemia; hypercalcemia; Peripheral neuropathy, ocular changes; Ototoxicity, myalgia, fatigue, allergic reaction

Radiation Therapy may cause Mucositis, stomatitis, erythema, desquamation, alopecia, bone marrow toxicity, skin pigmentation and esophagitis; Radiation pneumonitis and subsequent fibrosis of the lung; radiation-induced myocarditis or transverse myelitis (rarely occur at doses lower than 50 Gy)

Participants will not be financially responsible for any study-related tests outside of accepted standard of care follow-up.

Treatment on this study may help to control the disease. Future patients may benefit from what is learned. There may be no benefits for you in this study.

6.15 Gender and Minority Inclusion

Women and minorities will be actively recruited to participate in the trial. However, since only 42% of lung cancer participants and 22% of laryngeal cancer participants are female, we expect to have more male than female subjects on the study. We expect that the ethnic distribution of the enrolled participants will reflect the local ethnic mixture of each institution's surrounding community.

6.16 Roles and Responsibilities of Key Study Personnel

Dr. Ritsuko Komaki will serve as the Study Chairman for this protocol at M. D. Anderson Cancer Center. She will assume primary responsibility for the study.

Dr. Ray Meyn will serve as Study Co-Chairman of this protocol.

Dr. George Blumenschein will serve as Study Co-Chairman of this protocol.

Research Nurses will identify eligible patients, schedule patients for collection of tissue and/or blood samples, coordinate the activities of oncologists/technicians, and be responsible for follow-up of patients.

OSI/Genentech Pharmaceuticals will supply investigational study agent, erlotinib.

6.17 Recruitment Process

MD Anderson Cancer Center (MDACC): Representatives from Thoracic/Head & Neck Medical Oncology (i.e., the principal investigator, the co-principal investigator, sub-investigators, and the research nurse) will screen and evaluate patients seen in the M.D. Anderson Thoracic Center to identify potential subjects. If a patient is outside of the institution, he/she may be directly referred by a physician and/or contact the research nurse directly by phone numbers provided by the MDACC website.

7.0 Radiation Therapy

Intensity Modulated RT (IMRT) is allowed.

7.1 Doses

Total dose of radiation will be as follows:
A total radiation dose of 63Gy at 1.8 Gy per fraction once a day .
All doses are to be prescribed and calculated assuming a homogeneous patient.

7.1.1 At the center of the target area on the central ray for a single beam.
7.1.2 At mid-separation on the central ray for two opposed coaxial equally weighted beams.
7.1.3 At the center of the target area on the central ray for two opposed coaxial unequally weighted beams.

7.1.4 At the point of intersection of the central rays for two or more intersecting beams which are not coaxial.

7.1.5 At the center of the rotation in the plane of rotation containing the central axis for rotation or arc therapy.

7.1.6 At the center of the target area for complex treatment arrangements which are not covered above.

7.1.7 At the depth of the 90% isodose line for single electron beams. Select an electron beam energy which provides at least 90% dose at 3 cm depth.

Two different target volumes shall be considered, the initial large field target volume consisting of the primary tumor and mediastinum and the boost target volume consisting of the primary tumor only.

In treating the initial fields, various sets of fields may be used, which may be coplanar but not coaxial or may not even be coplanar.

7.2 Irradiation Portals:

The irradiated target volume must be defined by the individually shaped ports with secondary lead blocking or tailor-made blocks.

7.2.1 Target volume of primary tumor:

a) Includes complete extent of visible primary or as defined radiographically with a minimum of 1.5 cm and a maximum of 2.0 cm around the mass.

b) Entire lung may be included for extensive lesions if complicated by atelectasis or pneumonitis, which will be modified depending on FEV1 and/or other pulmonary function tests. One endobronchial brachytherapy is allowed to open up total atelectasis before definitive radiation therapy plus chemotherapy.

7.2.2. Target volume of lymph nodes:

The following nodes must be included:

a) PTV :Take 3 mm beyond CTV .

b) CTV :Take 5 mm margin beyond GTV (Node)

c) GTV (In the mediastinal, hilar or supraclavicular node(s): PET positive node (SUV>5) ,positive node(s) according to MDACC diagnostic Radiologist's intererpretation , largest diameter of the lymph node larger than 1.0 cm on CT of the chest if the PET negative or EBUS or medistenoscopy revealed pathologically positive node.

7.3 Technical Factors

7.3.1 Electron Beam Energy. Megavoltage equipment is required with effective photon energies higher than 1 MeV. Electrons with at least 90% dose at 3 cm depth may be used to boost supraclavicular lymph nodes.

7.3.2 Treatment Distance. Minimal treatment distance to skin should be 80 cm for SSD technique and minimum isocenter distance should be 80 cm for SAD techniques.

7.3.3 Blocking:

a) 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 volumes of tissues that are not to be irradiated.

b) With Cobalt 60, however, beam trimmers or secondary blocking must be used all the way around the ports.

7.3.4 Compensating Filters or Wedges:
In the case of a large sloping contour, such as that 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, field size must be reduced appropriately to avoid excessive irradiation to critical structures.

7.3.5 Fractionation:
a) Each field is to be treated every day.
b) Adherence to the fractionation schemes is required, although slight deviations in the daily dose fraction are allowed (± 5%).

7.3.6 Therapy Interruptions:
a) If interruptions of therapy up to two weeks become necessary, irradiation should be completed to the prescribed doses. Total number of fractions and elapsed days should be carefully reported.
b) If more than two weeks, interruption is required, resumption of the treatment is at the discretion of the radiation oncologist. The patient will be considered a major protocol deviation although follow-up will be continued.
c) If patients experience Grade 3 esophogitis radiation treatment should be continued without interruption.
d) Interruption is required for Grade 4 in-field toxicities.

7.3.7 Treatment Planning:
a) Treatment planning should be performed in accordance with the prescribing doses to each target volume, together with restrictions in dose to normal tissues as given in Section 7.1
b) One set should be calculated without lung correction while the other should be calculated with lung correction. Sagittal dose distributions are encouraged. The lung correction reporting form must be completed, which requires both uncorrected and corrected calculations of the dose to the center of the target volume. The lung correction can be calculated by any method which the institution prefers.
c) In addition to the isodose distributions, the following specific points of dose calculations, should be observed:
    1) Spinal Cord Dose:. Maximal spinal cord dose should not exceed 45 Gy at any level for patients .
    2) Subcarinal Nodes: Are assumed to be at mid-plane.
    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 borders of the initial treatment fields in the ipsilateral lung.
    4) Contralateral Normal Lung Dose: This is to be calculated at the level of the central rays of the boost field at the point of maximum dose in the lung which lies at least 2 cm outside of the projected border of the initial treatment fields in the contralateral lung.
    5) Maximum Normal Tissue Dose: This is to be calculated at the level of the central rays of boost fields as the maximum total dose at least 2 cm outside of the target volume.

7.3.8 Localization Films:
Localization films taken on simulators and/or on the treatment machine will be necessary in all cases.

7.4 Anticipated Side Effects or Toxic Effects:

7.4.1 Suggested Maximum Uncorrected Doses to Critically Sensitive Normal Structures

The following maximum doses to normal structures are suggested:

Organ	Dose Schedules
Normal	
Ipsilateral	25 Gy
Contralateral (only if necessary)	20 Gy
Spinal Cord (Maximum Dose)	45 Gy
Heart	
Entire Organ	45 Gy
Less than 50%	50 Gy
Esophagus	
50%	60 Gy
5 cm	66 Gy

7.4.2 The uncorrected dose to the spinal cord must be limited to 45 Gy . A posterior spinal cord shield will not be an acceptable technique. Patient must be treated with an oblique or lateral field.

7.4.3 Reversible alopecia, bone marrow toxicity, skin pigmentation and esophagitis are expected side effects of radiation therapy, while radiation-induced myocarditis or transverse myelitis rarely occur at doses lower than 50 Gy. Radiation pneumonitis and subsequent fibrosis of the lung will occur in 100% of all patients receiving 40 Gy to the lung, usually within the first six months after initiation of treatment, so it is essential to spare all normal lung possible.

8.0 Drug Therapy

8.2 Paclitaxel

8.2.1 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.

8.2.2 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.

8.2.3 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 antiallergy premedication approximately 30 minutes prior to paclitaxel administration as follows:

<u>During Weeks 1-7 (Concurrent Chemoradiation)</u>
Ondansetron 8 mg PO
Dexamethasone: 10 mg IV in 50ml NS IVPB
Diphenhydramine: 25 mg IV in 50ml NS IVPB
Cimetidine: 300 mg in 50 mL NS IVPB

<u>During Weeks 11-17 (Consolidation Therapy)</u>
Ondanesetron 8 mg IV
Dexamethasone: 20 mg IV
Cimetidine: 300 mg IV
Diphenhydramine: 50 mg IV

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

8.2.4 Storage

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

8.2.5 Adverse Effects:

- Hematologic: Myelosuppression
- Gastrointestinal: Nausea and vomiting; diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis, increased liver function tests (SGOT, SGPT, bilirubin, alkaline phosphatase); hepatic failure, hepatic necrosis
- Heart: Arrhythmias, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia, hypotension, hypertension, lightheadedness

- Neurological: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights; blurred vision, scintillating scotoma
- Allergy: Anaphylactoid and urticarial reactions (acute); Stevens-Johnson Syndrome; flushing, rash, pruritus
- Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration); radiation recall reaction.

8.2.6 Supply

Paclitaxel is commercially available.

8.3 Carboplatin

8.3.1 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.

8.3.2 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:

Vial Strength	Diluent Volume
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.

8.3.3 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:
AUC dose = Target AUC* x (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 Cockroft-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:

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

8.3.4 Storage

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

8.3.5 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

8.3.6 Supply

Carboplatin is commercially available.

8.4 Dose Modifications

8.4.1 Paclitaxel and carboplatin infusions will not be concurrently withheld if erlotinib is withheld. Likewise, if paclitaxel, carboplatin, or RT are delayed or withheld, erlotinib will not be concurrently delayed or withheld.

8.4.2 Dose Levels

Patients will be treated at the following dose levels:

Dose Levels of Paclitaxel, Carboplatin, and Erlotinib

	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

[a] For concurrent therapy, paclitaxel and carboplatin doses wil not be adjusted.
[b] For consolidation therapy, dose reduction of paclitaxel and carboplatin below the –1 dose level will not be allowed. Dose reductions for erlotinib will not be allowed below the –2 dose level.

8.4.3 Erlotinib Dose Modifications

As stated in Section 8.4.2, erlotinib dose reductions below the –2 dose level will not be allowed. All dose reductions are permanent; that is, there will not be any reescalation of erlotinib dose. If erlotinib is omitted for more than seven consecutive doses for toxicity due to erlotinib or for an intercurrent illness (e.g., infection) requiring interruption of therapy, the patient should be discontinued from further erlotinib therapy. If toxicities prevent the administration of erlotinib, the patient may continue to receive paclitaxel, carboplatin, and RT without erlotinib.

Dose reduction or interruption of Erlotinib for toxicity may take place at any time during the study. Toxicity grading is based on NCI-CTCAE, v 3.0. Dose level reductions are presented in Table 1. If patients do not tolerate the second dose reduction, Erlotinib is to be discontinued.

Table 1
Erlotinib Dose Level Reductions

Starting Dose	First Reduction	Second Reduction
150 mg/day	100 mg/day	50 mg/day

Dose modification guidelines are summarized in Table 2.

Management of a tolerable Grade 2 or 3 rash should include continuation of Erlotinib at the current dose and symptomatic management. If skin rash is intolerable, dose reduction according to Table 2 should be considered. When skin toxicity improves by at least one grade level, the dose may be re-escalated as tolerated. In Phase II trials, this approach enabled dose re-escalation for the majority of patients requiring dose reduction for skin toxicity. Patients

experiencing Grade 4 skin toxicity should be discontinued from study treatment.

For Grade 1 or 2 diarrhea, early intervention should include continuation of Erlotinib at the current dose and initiation of loperamide therapy as described in Table 2. Grade 2 diarrhea that persists over 48–72 hours, despite optimal medical management, should be managed by dose reduction according to Table 2. Patients experiencing Grade 3 diarrhea should interrupt Erlotinib until resolution to Grade 1 and re-start at a reduced dose according to Table 2. Patients should be maintained at the reduced dose without attempt at dose re-escalation. Patients experiencing Grade 4 diarrhea should be discontinued from study treatment.

Erlotinib should not be restarted in those suspected of having drug-related ILD.

Table 2
Dosage Modification Criteria and Guidelines for Management
of Erlotinib-Related Toxicities

NCI-CTCAE (v 3.0) Grade	Erlotinib Dose Modification	Guideline for Managment
Diarrhea		
Grade 1	None	Consider loperamide (4 mg at first onset, followed by 2 mg q 2-4 hours until free of diarrhea for 12 hours)
Grade 2	None (Dose reduction of Erlotinib is necessary if diarrhea persists over 48-72 hours despite optimal medical management	Loperamide (4 mg at first onset, followed by 2 mg q 2-4 hours until diarrhea free for 12 hours)
Grade 3	Interrupt then dose reduce Erlotinib. Erlotinib should not be re-escalated	Interrupt Erlotinib until resolution to Grade $\leq$ 1, and restart at next reduced dose
Grade 4	Discontinue study treatment.	
Pulmonary Events if possibly ILD		
All Grades	Temporarily interrupt Erlotinib pending the diagnostic evaluation. If the pulmonary adverse event is assesses as related to Erlotinib, discontinue the patient from treatment study	Unexplained dyspnea, either new or progressive, should be aggressively evaluated
Rash		
Tolerable Rash	None	Any of the following: minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course) at discretion of investigator
Intolerable Rash	Consider interruption and or dose reduction if unresponsive to symptomatic management. Re-escalation is allowed.	Manage as described above
Grade 4	Discontinue study treatment	Manage as described above

8.4.3.1 Retreatment with Erlotinib Following Allergic/Hypersensitivity or Cytokine Release Reactions

Once a erlotinib dose has been decreased due to an allergic/hypersensitivity or cytokine release reaction, it will remain decreased for all subsequent doses. If the patient has a second allergic/hypersensitivity or cytokine release reaction with the slower dose, the drug should be stopped, and the patient should receive no further erlotinib 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 erlotinib 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 subsequent dosing should be 50% of the previous rate. If fever recurs following dose 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 erlotinib therapy.

8.4.4 Dose Modifications During Concurrent Therapy

8.4.4.1 Paclitaxel/Carboplatin/Erlotinib Dose Modifications for Hematologic Toxicity

Toxicity NCI CTCAE Grade (CTCAE v3.0	Paclitaxel Dose At Start of Subsequent Cycles of Therapy	Carboplatin Dose at Start of Subsequent Cycles of Therapy[3]	Erlotinib Dose at Start of Subsequent Cycles of Therapy[3]
Neutropenia 1(1500-199/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 leucopenia are based on NCI CTCAE and are the same as recommended for neutropenia above.		

[a]Dose levels are relative to the staring dose in the previous cycle. Dose reductions of erlotinib below the –2 dose level will not be allowed. For concurrent therapy, paclitaxel and carobplatin doses will not be adjusted.
[b]repeat lab work weekly and resume chemotherapy based on this table.

8.4.4.2 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.

8.4.4.3 Paclitaxel/Carboplatin/erlotinib 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]	Erlotinib 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 ≤ 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. For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.

c With the exception of allergic/hypersensitivity or cytokine release reaction (see Section 8.4.3.1), acne-like rash (rash/desquamation), anorexia, and viral infections. See Table 2 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 8.4.4.5 for further neuropathy details.

8.4.4.4 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.

8.4.4.5 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.

8.4.4.6 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.

8.4.4.7 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	CTAE Toxicity Grade	XRT	Paclitaxel	Carboplatin	Erlotinib
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 6.5.3.3
Skin	3	No change	No change	No change	Follow guidelines in Section 6.5.3.3

8.4.4.8 For Grade 4 infield esophagitis, radiotherapy and chemotherapy should be interrupted as detailed in the table above. Re-evaluate patient weekly.

8.4.4.9 For Grade >/= 3 esophagitis/pharyngitis, dermatitis, or other in-field radiotherapyrelated 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 erlotinib skin toxicity management, follow the guidelines in Table 2.

8.4.4.10 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.

8.4.4.11 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.

8.5. Paclitaxel/Carboplatin 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]
Nail Changes (paronychia) Grade 2	Maintain dose level	Maintain dose level
Neuropathy		
≤ Grade 1	Maintain dose level	Maintain dose level
Grade 2	Hold therapy until Grade ≤ 1; restart at Full dose [e]	Maintain dose level
Grade 3	Discontinue therapy	Maintain dose level
Other non-hematologic Toxicities[c] Grade 3	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. For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.

[c] With the exception of allergic/hypersensitivity reaction (see Section 8.4.3.1), acne-like rash (rash/desquamation), anorexia, and viral infections. Table 2 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.

[e] See Section 8.4.4.5 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.

8.6 Paclitaxel/Carboplatin Dose Modifications for Hematologic Toxicity During Consolidation Therapy

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]
Neutropenia		
1 (1500- 1999/mm^3)	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 ≥ 1,500 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3
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 ≥ 1,500 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3
4 (<500/mm^3)	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3
Neutropenic fever	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3
Thrombocytopenia		
1 (≥75,000/mm^3)	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 ≥ 7,500 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 7,500 mm^3
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 ≥ 7,500 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 7,500 mm^3
4 (< 25,000/mm^3)	Hold therapy[b] and decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 75,000 mm^3
Other Hematologic toxicities (d)	Dose modifications for leukopenia are based on CTCAE, v3.0 and are the same as recommended for neutropenia above.	

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

[b] Repeat lab work weekly and resume chemotherapy based on this table

[c] Dose delays greater than 2 weeks will warrant discontinuation of chemotherapy for the consolidation cycles.

[d]With the exception of allergic/hypersensitivity reaction (see Section 8.4.3.1), acne-like rash (rash/desquamation), anorexia, and viral infections. Table 2 treatment modifications for in-field GI and skin toxicity management.

8.7 Duration of Treatment

8.7.1 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.

8.7.2 This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for grading of all treatment related adverse events.

8.8 Reporting Requirements

AE's should be reported in accordance with UTMDACC's policy (see appendix A)

9.0 Pathology

All patients need to have biopsy specimen and/or unstained histological slides available for review by Dr. Wistuba at UTMDACC for EGFR expression. If original biopsy for EGFR is adequate a second biopsy is not necessary. However if the biopsy specimen is to small for EGFR status then a second optional biopsy is encouraged. 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.

Strict patient confidentiality will be maintained. Patient confidentiality will be respected at all times. Patient's name and medical record number will be removed from any stored data. Only the collaborators and the research team of this study will have access to patient information, and only information relevant to this protocol will be examined. All protected health information will be de-identified prior to releasing outcomes of the study outside the research team. Patient identifiers will be destroyed after data is analyzed. Until then, the database will be password protected on a limited access computer.

If you choose to stop participating in the study and would like to also remove your donated samples, you should tell the study chair or research nurse at the time of your request to leave the study. The study chair or research nurse will request to dispose of all of your samples that have not already been used in research testing.

10.0 Investigational Centers

Patients will be seen and enrolled at the University of Texas M. D. Anderson Cancer Center, Houston, TX.

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