Adding Erlotinib to Chemoradiation Improves Overall Survival but not Progression-Free Survival in Stage III Non-Small-Cell Lung Cancer

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Abstract

Background—Concurrent chemoradiotherapy is the standard of care for inoperable stage III non-small cell lung cancer (NSCLC) for patients who can tolerate it. We explored if adding erlotinib would increase the effectiveness of chemoradiotherapy without increasing toxicity in a single-arm prospective phase II trial.

Methods—Forty-eight patients with previously untreated NSCLC received intensity-modulated radiation therapy (63 Gy/35 fractions) on Monday–Friday, with chemotherapy (paclitaxel $45 \text{ mg/m}^2$, carboplatin $\text{AUC}=2$) on Mondays, for 7 weeks. All patients also received the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor erlotinib ($150 \text{ mg orally 1/day}$) on Tuesday–Sunday for 7 weeks followed by consolidation paclitaxel–carboplatin. The primary

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All remaining authors have declared no conflicts of interest.

Presented in part at the 54th annual meeting of the American Society for Radiation Oncology (ASTRO), October 28–31, 2012, Boston, MA.
endpoint was time to progression; secondary endpoints were overall survival (OS), toxicity, response, and disease control and whether any endpoint differed by EGFR mutation status.

**Results**—Of 46 patients evaluable for response, 40 were former or never-smokers and 41 were evaluable for EGFR mutations (37 wild-type [wt] and 4 mutated; all adenocarcinoma). Median time to progression was 14.0 months and did not differ by EGFR status. Toxicity was acceptable (no grade 5, one grade 4, eleven grade 3). Twelve patients (26%) had complete responses (10 wt, 2 mutated), 27 (59%) partial (21 wt, 2 mutated, 4 unknown), and 7 (15%) none (6 wt, 2 mutated, 1 unknown) ($P=0.610$). At 37.0 months’ follow-up (range 3.6–76.5 months) for all patients, median OS time was 36.5 months and 1-, 2-, and 5-year OS rates were 82.6%, 67.4%, and 35.9%; none differed by mutation status. Twelve patients had no progression and 34 had local and/or distant failure. Eleven of 27 distant failures were in the brain (7 wt, 3 mutated, 1 unknown).

**Conclusions**—Toxicity and OS were promising, but time to progression did not meet expectations. The prevalence of distant failures underscores the need for effective systemic therapy.

**Keywords**
epidermal growth factor receptor; tyrosine kinase inhibitor; Tarceva; prospective phase II trial; locally advanced non-small cell lung cancer; NCT00563784

**Introduction**

Despite significant treatment advances for locally advanced lung cancer (e.g., proton beam therapy, intensity-modulated radiation therapy (IMRT), and use of concurrent chemotherapy), the prognosis for patients with disease at this stage is unsatisfactory, in part because many tumors are resistant to radiation therapy. The molecular basis for radiation resistance is not fully understood, but resistance seems to involve increased capacity for DNA repair and suppressed apoptosis—both controlled in part by upstream signal transduction pathways triggered by activation of the epidermal growth factor receptor (EGFR) (reviewed in (1)).

EGFR is known to be constitutively activated in epithelial cancers, including non-small cell lung cancer (NSCLC) (2,3) and its activation leads to a radiation-resistant phenotype (4–6) and has been linked with poor prognosis (7,8). At least one-third of tumors exhibit EGFR dysregulation or overexpression, but whether expression of EGFR correlates with response to therapeutic EGFR inhibitors is unclear, with some investigations showing no correlation (9) and others a greater likelihood of response (10–14) or even a survival benefit (15) from EGFR inhibitors. However, many of the trials conducted to date have tested EGFR inhibitors either alone or with chemotherapy, and most have involved patients with disease that has recurred after prior therapy.

Other trials have tested EGFR inhibitors with radiation therapy for head and neck squamous cell carcinoma and NSCLC. In one pivotal phase III trial, adding the monoclonal anti-EGFR antibody cetuximab (Erbitux) to radiation improved local control of locally advanced head and neck squamous cell cancer and overall survival (OS) (16,17). EGFR tyrosine kinase inhibitors (TKIs) such as gefitinib (Iressa) and erlotinib (Tarceva) have been evaluated in
combination with radiation for several types of cancer, including lung (18–20). This combination seems to have a strong biological rationale, as gefitinib and erlotinib disrupt cell growth pathways and enhance the sensitivity of cells to the effects of radiation (5,21–24). Conversely, radiation may enhance the effectiveness of erlotinib via tumor cytoreduction (1,22). The mechanisms by which erlotinib leads to radiosensitization are unclear but may involve inhibition of DNA repair, with consequent senescence or apoptosis (25–28). Hypothesizing that the response of NSCLC to the current standard of care can be improved through the addition of anti-EGFR-targeted therapy, we undertook a single-arm, single-institution prospective phase II trial to test if adding the EGFR-TKI erlotinib to concurrent chemoradiotherapy for previously untreated, locally advanced, inoperable NSCLC would improve survival and disease control without increasing toxicity.

Methods

All patients provided written informed consent to participate in this study (MDA 2005-1023; ClinicalTrials.gov Identifier NCT00563784), which was approved by the appropriate institutional review board. Eligible patients had confirmed stage IIIA or IIIB NSCLC that was inoperable because of tumor location or coexisting medical conditions according to a thoracic multidisciplinary review board; other inclusion criteria were having good performance status (Karnofsky score 80–100), weight loss ≤5% over the previous 3 months, forced expiratory volume in 1 second (FEV1) ≥1.0 L, and adequate hematologic, hepatic, and renal function. Exclusion criteria were prior chemotherapy or thoracic radiation or surgical resection of NSCLC; severe chronic obstructive pulmonary disease (requiring >3 hospitalizations over the past year); history of cardiac disease; and prior use of drugs targeting the EGFR pathway. Disease was staged in all cases, and response evaluated in most, with positron emission tomography/computed tomography (PET/CT) scanning.

Treatment

Chemoradiation—During weeks 1–7, patients were given reduced-dose chemotherapy (paclitaxel 45 mg/m² and carboplatin AUC=2) on Mondays, and radiation (IMRT; given to 63 Gy in 35 fractions of 1.8 Gy) was given on Monday through Friday. Erlotinib (150 mg p.o./day) was given on Tuesday through Sunday. Hence chemoradiation was given every Monday followed by erlotinib with radiation on Tuesday through Friday and erlotinib alone over the weekend. After a 4-week break during which no treatment was given (weeks 8–11), patients began two cycles of consolidation chemotherapy (paclitaxel 200 mg/m² and carboplatin AUC=6), which lasted from weeks 12 through 17. These doses and schedules were chosen to facilitate direct comparison of the findings with those of Radiation Therapy Oncology Group (RTOG) 0324 (29), which examined the addition of cetuximab to the same chemoradiation protocol. Because our radiation dose is biologically equivalent to 60 Gy in 30 fractions, we gave consolidation chemotherapy at systemic doses in an attempt to control microscopic disease.

Radiotherapy—All patients received radiation planned and delivered as IMRT. Four-dimensional computed tomography (4D CT) was used to track tumor motion during treatment planning (30) and to develop internal gross tumor volume (iGTV) and
corresponding internal clinical target volume (iCTV). If the tumor moved more than 1.5 cm with respiration, consideration was given to gating or breath hold. Gross tumor volume (GTV), CTV, planning target volume (PTV), and normal tissue constraints were defined as in RTOG 0324 and RTOG 0617. Briefly, the GTV included the primary tumor and nodes considered positive by CT (>1 cm), PET (standardized uptake value >5), endobronchial ultrasonography, or mediastinoscopy. Because the ITV approach was used in all cases, the CTV was the ITV plus a 0.5-cm to 1-cm margin. Elective nodal treatment was not used. Treatment plans were to cover 95% of the PTV with the prescription dose, and the minimum PTV dose was to be no less than 95% of the prescription dose. Normal tissues constraints were as follows: $V_{20}$ for both lungs (less the CTV) <37% or mean lung dose ≤20 Gy.; maximum dose to the spinal cord, <45 Gy; maximum dose to 100% of the heart <45 Gy, and that to 50% of the heart, <50 Gy; and maximum dose to 50% of the esophagus <60 Gy, and that to 5 cm of esophagus, <66 Gy. PET with fluorodeoxyglucose uptake was used to delineate tumors during treatment planning and also to assess response.

**Treatment Evaluations**

Posttreatment evaluations took place at 1 month after treatment and then at 3-month intervals for 2 years; at 6-month intervals in years 3 and 4; and annually thereafter. CT scans were obtained at each visit unless PET/CT scanning had been done. Interval history and physical exams, biochemical surveys and hematologic studies were obtained at each visit; PET scanning or magnetic resonance images of the brain were obtained as indicated. Particular attention was paid at each visit to any adverse treatment effects, and toxicity was scored according to the NCI Common Terminology Criteria for Adverse Events version 3.

**Response**

Clinical response was measured according to the RECIST criteria (v1.1) on CT scans obtained 1–3 months after completion of chemoradiation. If recurrent disease was suspected, PET/CT scans were obtained and areas suspected of harboring disease were biopsied. OS was measured from the date of enrollment to the date of death.

**EGFR Mutation Analyses**

The presence of EGFR mutations was analyzed in formalin-fixed and paraffin-embedded tumor tissue specimens obtained for diagnosis before treatment; all analyses were done in a single laboratory. Specimens that contained malignant cells and sufficient tissue for biomarker testing were microdissected and their DNA extracted. Polymerase chain reaction (PCR) amplification was then used to evaluate EGFR exons 18–21 by using HotStarTaq Master Mix (Qiagen). PCR products were directly sequenced using the Applied Biosystems PRISM dye terminator cycle sequencing method (Perkin-Elmer Corporation).

**Statistical Analyses**

The primary endpoint of this trial was originally safety and feasibility, with safety defined as rate of grade ≥3 non-hematologic toxicities occurring before the beginning of consolidation therapy, including all toxicities attributed to chemoradiation occurring within 90 days of the start of radiation therapy. Secondary endpoints were overall survival (OS), time to
progression, response rates, and local and distant disease control, and exploratory analyses were planned to test for associations between EGFR mutation status and secondary endpoints. Indeed, the first 5 patients enrolled and treated showed no evidence of toxicity and no difficulties with compliance. However, ongoing difficulties with patient recruitment and accrual led the study principal investigator, in consultation with the lead statistician, to amend the protocol by changing the primary endpoint to progression-free survival (PFS) and reducing the number of patients from 72 to 48 as described below. These changes were documented in the ClinicalTrials.gov archive.

The maximum sample size for the phase II study, 48, was chosen based on the assumption that time to progression follows an exponential distribution. We hypothesized that combining erlotinib and chemoradiation would increase the median time to progression from 15 months (31) to 25 months (a 67% increase). According to log-rank tests, a total of 48 patients would yield 80% power with a one-sided type I error rate of 10%.

Fisher’s exact tests were used to compare categorical patient-, disease-, and treatment-related characteristics according to EGFR status; Kaplan-Meier estimates with log-rank tests were used to compare OS and time to progression between EGFR-status groups. All statistical analyses were done with Stata/MP 13.1 for Windows (StataCorp LP, CollegeStation, TX).

Results

Patient- and treatment-related characteristics are shown in Table 1. Of the 48 patients with stage III NSCLC prospectively enrolled in the phase II trial from November 2007 through June 2010, 46 completed the treatment and were evaluable for response (96% compliance rate). Two patients were taken off protocol, one for diarrhea unrelated to treatment and the other for chemotherapy-induced chest pain. Of the 46 evaluable patients, 17 (37%) were female, 23 (50%) had adenocarcinoma, and 40 (87%) were former or never-smokers. None of the 46 evaluable patients required interruption of chemotherapy; one required suspension of erlotinib for 3 days because of diarrhea. EGFR mutation status was known for 41 patients: 37 had wild-type (wt, unmutated) EGFR and 4 had EGFR mutations (three with a CTG858CGG change in exon 21 and one with a 15-base-pair deletion in exon 19). All four patients with EGFR mutations had adenocarcinoma. All patients received the full 63 Gy with no treatment interruptions. Seven patients did not complete the second cycle of consolidation chemotherapy (five for hematologic toxicity, one pneumonia/pneumonitis, and one neuropathy). Survival curves are shown in Figure 1.

Toxicity

No patient experienced grade 5 toxicity; one patient had grade 4 toxicity (pneumonitis); and 11 patients had grade 3 toxicity (six skin, two pneumonitis, one esophagitis, and two acneiform rash) (Table 2). Toxicity incidence and severity were no different for those with wt versus mutated EGFR.
**Time to Progression**

The median time to progression was 14.0 months (95% confidence interval [CI] 9.0–18.6 months), which did not meet our hypothesized increase to 25 months. Time to progression also was no different by EGFR status (14.9 months wt 10.2 months mutated, $P=0.38$ by log-rank test). The 1-, 2-, and 5-year probabilities of freedom from progression were 56.2%, 30.4%, and 25.8% (59.2%, 32.6%, and 29.7% for wt; 25%, 25%, and 0% for mutated).

**Overall Survival**

At a median follow-up interval of 37.0 months for all 46 patients (range, 3.6–76.5 months), 31 had died (23 wt, 4 mutated EGFR, and 4 unknown) and 15 were alive (14 wt and 1 unknown). The median OS time for all patients was 36.5 months (95% CI 25.5–47.5 [34.1 months for wt EGFR and 41.1 months for mutated EGFR]; median OS time for patients alive at last follow-up was 61.0 months (range 46.2–76.5 months). The 1-, 2-, and 5-year OS rates were 82.6%, 67.4%, and 35.9% and were not different for patients with wt or mutated EGFR (wt 81.1%, 62.2%, 37.3%; mutated 100%, 100% and 50%; log-rank $P=0.87$).

**Response**

Complete responses were noted in 12 patients (26%; 10 wt and 2 mutated EGFR), partial in 27 (59%; 21 wt, 2 mutated, and 4 unknown EGFR), and none in 7 (15%; 6 wt, 2 mutated, and 1 unknown EGFR) ($P=0.610$ for EGFR wt vs. mutation groups by Fisher’s exact test). None of the 4 patients with EGFR mutations experienced local-regional failure; however, all had distant metastases.

**Disease Control and Patterns of Failure**

Thirty-four patients (73.9%) experienced failure, which was local-only in 7 patients, distant-only in 16, and both local and distant in 11 (12 had no failure). Of the 27 distant failures, the location was known for 26 patients: 15 were outside the brain (12 wt, 1 mutation, 2 unknown) and 11 were within the brain (7 wt, 3 mutation, 1 unknown). Patterns of failure among those with EGFR mutations are shown in Table 3.

**Discussion**

This prospective phase II study was one of the first to evaluate the combination of erlotinib with concurrent thoracic radiation plus carboplatin and paclitaxel chemotherapy for previously untreated stage III NSCLC, and it was the first to evaluate this combination in light of EGFR mutation status. We found that erlotinib, given at 150 mg/day for 6 days/week, produced excellent OS (median 36.5 months) compared with trials such as RTOG 0324 and RTOG 0617. The incidence and severity of toxicity were also low, with no grade 5 events, only one grade 4 event (pneumonitis), and 11 grade 3 events, all of which were effectively managed with supportive care. Although only 4 of 41 patients evaluable for EGFR mutation status were found to have mutations (10%), all 4 of those patients had adenocarcinoma and all 4 experienced distant failure. Although these numbers were small, more patients with EGFR mutations had brain metastases (75%) than did patients with EGFR wt tumors (19%). On the other hand, our primary endpoint (improvement in time to progression to 25 months) was not met, and disease control was disappointingly low,
underscoring the ongoing need for more effective systemic therapy for inoperable locally advanced NSCLC.

Our findings did suggest that erlotinib can be safely added to chemoradiation, with the caveat that we did not give erlotinib on the same days as chemotherapy because of concerns regarding severe toxicity from combining EGFR-TKIs with cisplatin (32). Indeed, concern has been expressed that the addition of gefitinib, another EGFR-TKI, to chemotherapy or radiation led to higher rates of severe and occasionally fatal interstitial pneumonitis (33,34). However, patients in those studies were most often Asian, male, heavy smokers, and had squamous cell carcinomas. In our study, only 3 of the 46 patients in our study experienced severe pneumonitis (two grade 3 and one grade 4).

The total radiation dose and dose per week in this study were lower than in some recent studies; however, the results of RTOG 0617 (35) suggest that a total dose of 60 Gy in 30 fractions given in 6 weeks is a reasonable standard, and the current study’s dose/fractionation regimen is not substantially different from this standard. As noted previously, the chemotherapy doses and schedule were chosen to facilitate comparison with RTOG 0324 (29).

The reason for the discordance between median OS and PFS intervals (OS 36.5 months and PFS 14.0 months) is not clear, although the criteria for progression are clearly less certain than for death. Our OS rates (82.6% at 1 year, 67.4% at 2 years, and 35.9% at 5 years) are better than most reports in the literature (Supplementary Table S1). The incidence and severity of toxicity were low, with no grade 5 events, only one grade 4 event (pneumonitis), and 11 grade 3 events, all of which were effectively managed with supportive care. The incidence of grade 3 esophageal toxicity (only 1 patient, or 2%) is among the lowest reported to date and could reflect our use of erlotinib, IMRT, or both.

To date, two other phase I/II studies have been published on EGFR-TKIs with chemoradiation for stage III lung cancer (32,36), but both found the regimens tested to be quite toxic. In a phase I/II study of erlotinib with concurrent carboplatin-paclitaxel chemotherapy and thoracic conformal radiation therapy (to 74 Gy) after induction therapy with bevacizumab plus carboplatin-paclitaxel, substantially greater esophageal toxicity was observed (29% grade 3 or 4 esophagitis [vs. our 2% grade 3]) (36). This toxicity, plus a relative lack of efficacy in terms of OS time and time to progression (18.4 and 10.2 months) led the investigators to not recommend bevacizumab or erlotinib as administered in that study. Similarly, another phase I study of gefitinib and either radiation or radiation+cisplatin (32) found that giving gefitinib with radiation was feasible but that the addition of cisplatin led to enhanced toxicity, with 2 of 9 patients tested experiencing dose-limiting toxicity (one neutropenic pneumonia and the other elevated liver enzymes). The differences between the findings in these two studies and the current study may reflect differences in design and dose; the phase I/II trial (36) included induction chemotherapy, which ours did not, and a higher radiation dose (74 Gy vs. 63 Gy in the current study). Although patients in the phase I study (32) received the same 63-Gy radiation dose as did patients in the current study, most (93%) had had prior chemotherapy, which was not allowed in the current study; other differences were the use of gefitinib rather than erlotinib and cisplatin rather than
carboplatin and paclitaxel. Another study involving high-dose radiation, RTOG 0617, involved giving 74 Gy in 37 fractions with concurrent weekly paclitaxel and carboplatin with or without the EGFR monoclonal antibody cetuximab; the higher dose did not improve survival over 60 Gy given in 30 fractions with same chemotherapy and cetuximab (35).

Our OS times and rates for those given erlotinib with concurrent chemoradiotherapy also compare favorably with our experience with patients treated with IMRT for similar-stage disease, in particular because patients in the latter group tended to receive higher radiation doses. Indeed, the median survival times and 1- and 2-year OS rates in this study are superior to those obtained in six other large studies (Supplementary Table S1), suggesting that erlotinib enhances the effectiveness of chemoradiation therapy. Unfortunately the disease control rates were no better in the current study than in our historical experience with patients treated with IMRT, underscoring the need for more effective systemic therapy.

This study had several strengths; the phase II trial was the first prospective clinical trial to suggest that an EGFR-TKI could lead to radiosensitization of NSCLC without causing higher normal tissue toxicity, especially pneumonitis. Further, to the best of our knowledge we are the first to show that giving an EGFR-TKI with chemoradiation led to excellent local-regional control.

We do acknowledge several limitations. The number of patients in this prospective phase II trial was relatively small. Although we were able to test EGFR mutation status in tumor samples from 41 of the 48 patients in the phase II trial, only 4 of those patients were found to have EGFR mutations, preventing us from considering the effects of mutation status on the efficacy of erlotinib in terms of survival or disease control. However, the response rates achieved that erlotinib does have some activity in stage III NSCLC regardless of EGFR mutation status.

Our findings, albeit preliminary, suggest several avenues for future study. First, it would be interesting to compare the relative effectiveness of erlotinib according to EGFR mutation status. Investigations underway at Memorial Sloan Kettering indicate that patients with resected lung cancers and EGFR mutation derived benefit from adjuvant erlotinib or gefitinib in terms of lower risk of recurrence or death and perhaps improved OS (37). Indirect support for this approach comes from another study of erlotinib with whole-brain radiation therapy, the findings of which suggest that erlotinib may have had a radiosensitizing effect in patients with EGFR mutations (38). The recently opened RTOG 1306/Alliance 31101 trial is expected to clarify this issue further by testing whether the addition of erlotinib as induction therapy improves PFS in patients with previously untreated stage III non-squamous NCLSC treated with chemoradiation to 60 Gy. Another avenue to explore would be the use of erlotinib as maintenance therapy after definitive therapy for stage III NSCLC; the Galician Lung Cancer Group (39) found this approach to have tolerable toxicity, although at 22.7 months’ median follow-up time, their median OS time (24 months) and time to progression (9.9 months) were shorter than in the current study. However, trial S0023 by the Southwest Oncology Group showed that maintenance gefitinib (the mechanism of action of which is similar to that of erlotinib) after chemoradiation led to significantly poorer OS (40), although whether this result was influenced by the molecular
subtype of the patients in that study has been questioned (41). Another possibility would be to include EGFR-TKI agents during radiation therapy for chest consolidation or for palliation of metastases to the brain, bone, or other distant sites. Mechanistic studies are also needed to clarify the interactions between response to EGFR-TKIs, the epithelial-mesenchymal transition (EMT) status, and c-Met and ALK signaling; such studies are currently underway.

In conclusion, we found that the addition of erlotinib to standard chemoradiotherapy for inoperable stage III NSCLC did not improve time to progression or disease control but did lead to improved survival and lesser normal-tissue toxicity than chemoradiotherapy alone in RTOG 0324 and 0617. Also, the prevalence of distant failures underscores the need for more effective systemic therapy. By analyzing potential associations between EGFR mutation status, EMT, c-Met, and ALK status, and patterns of failure, we hope to be able to develop more effective and more personalized treatment approaches in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors are indebted to the members of the MD Anderson Thoracic Center and to the patients who participated in this study. We appreciate the generosity of Zhongxing Liao, MD, in sharing information on the historical control subjects. We are also deeply grateful to Christine F Wogan, MS, ELS, of MD Anderson’s Division of Radiation Oncology for developing this report.

This work was supported in part by OSI/Genentech Pharmaceuticals; the Department of Defense Lung Cancer Research Program (NCI-2012-01761); and National Institutes of Health Cancer Center Support (Core) Grant CA016772 to The University of Texas MD Anderson Cancer Center. Dr. Blumenschein has received research funding for other projects from Genentech;

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SUMMARY

In this prospective single-arm phase II trial, we found that adding erlotinib to chemoradiation for previously untreated stage III non-small cell lung cancer produced excellent overall survival and low toxicity, but the primary endpoint (progression-free survival time) was not met. The low rates of disease control, especially distant metastases, underscore the need for more effective systemic therapy.
Fig. 1.
Survival curves, with 95% confidence intervals, for patients who received erlotinib with chemoradiation for inoperable stage III non-small cell lung cancer. A, overall survival; B, disease-free survival; C, local-regional failure-free survival; and D distant metastasis-free survival.
### Table 1

Characteristics of the 46 Evaluable Patients

| Characteristic                  | No. of Patients |
|--------------------------------|-----------------|
| **Sex**                        |                 |
| Female                         | 17              |
| Male                           | 29              |
| **Age, years**                 |                 |
| Median                         | 63              |
| Mean                           | 63.2            |
| Range                          | 46–81           |
| **Ethnicity**                  |                 |
| White                          | 40              |
| Non-white                      | 6               |
| **Disease Stage**              |                 |
| IIIA                           | 20              |
| IIIB                           | 26              |
| **Tumor Histology**            |                 |
| Adenocarcinoma                 | 23              |
| Squamous cell carcinoma        | 15              |
| NSCLC unspecified              | 8               |
| **Karnofsky Performance Score**|                 |
| 100                            | 3               |
| 90                             | 31              |
| 80                             | 12              |
| **Smoking History**            |                 |
| Former                         | 34              |
| Current                        | 6               |
| Never                          | 6               |
| **EGFR Status**                |                 |
| Wild-type                      | 37              |
| Mutated or deleted             | 4               |
| Unknown                        | 5               |
Table 2

Toxicity for all 46 Patients Who Completed Treatment *

| Toxicity                  | Grade |                  |                  |                  |                  |                  |
|---------------------------|-------|------------------|------------------|------------------|------------------|------------------|
|                           | 0     | 1                | 2                | 3                | 4                | 5                | Unknown          |
| Esophagitis               | 27 (22 wt, 2 mut) | 5 (3 wt, 1 mut) | 13 (11 wt, 1 mut) | 1 (1) | 0 (0) | 0 (0) | 0 (0) |
| Pneumonitis               | 26 (20 wt, 2 mut) | 2 (2) | 5 (4) | 2 (1 wt, 1 mut) | 1 (1) | 0 (0) | 10 (9 wt, 1 mut) |
| Skin Toxicity, any        | 30 (24 wt, 3 mut) | 4 (3) | 6 (5 wt, 1 mut) | 6 (5) | 0 (0) | 0 (0) | 0 (0) |
| Acneiform Rash            | 16 (15 wt, 1 mut) | 4 (1 wt, 1 mut) | 24 (19 wt, 2 mut) | 2 (2) | 0 (0) | 0 (0) | 0 (0) |
| Fatigue                   | 43 (35 wt, 3 mut) | 0 (0) | 3 (1 wt, 2 mut) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

* Numbers in parentheses refer to the 41 patients with known EGFR status.

No differences in toxicity were found between all 46 patients and the 41 patients with known EGFR status; similarly, no differences in toxicity were found between the 37 patients with wt EGFR and the 4 patients with mutated EGFR.
Table 3

Patterns of Failure among Patients with *EGFR* Mutations

| Patient No. | Tumor Histology | Site of Failure* | Failure Date | Current Status | EGFR Mutation Site | Effect |
|-------------|-----------------|-----------------|--------------|----------------|-------------------|--------|
| 1           | Adenocarcinoma  | Brain           | 26 Aug 2010  | Dead of disease | exon 21           | CTG858CGG |
| 2           | Adenocarcinoma  | Bone, Brain     | 14 Jul 2009  | Dead of disease | exon 21           | CTG858CGG |
| 3           | Adenocarcinoma  | Brain           | 1 Aug 2011   | Dead of disease | exon 21           | CTG858CGG |
| 4           | Adenocarcinoma  | DM Lung         | 30 Oct 2009  | Dead of disease | exon 19           | 15-base-pair deletion |

*All 4 patients died with local control

*Abbreviation: DM, distant metastasis