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 mg/m^2, carboplatin AUC=2) on Mondays, for 7 weeks. All patients also received the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor erlotinib (150 mg orally 1/day) on Tuesday–Sunday for 7 weeks followed by consolidation paclitaxel–carboplatin. The primary

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.

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/m^2 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/m^2 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 EFGR 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

References

1. Seiwert TY, Salama JK, Vokes EE. The concurrent chemoradiation paradigm—general principles. Nat Clin Pract Oncol. 2007; 4:86–100. [PubMed: 17259930]

2. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med. 2004; 350:2129–2139. [PubMed: 15118073]

3. Neal JW. The SATURN trials: the value of maintenance erlotinib in patients with non-small call lung cancer. Future Oncol. 2010; 6:1827–1832. [PubMed: 21142856]

4. Akimoto T, Hunter NR, Buchmiller L, Mason K, Ang KK, Milas L. Inverse relationship between epidermal growth factor receptor expression and radiocurability of murine carcinomas. Clin Cancer Res. 1999; 5:2884–2890. [PubMed: 10537357]

5. Chinnaiyan P, Huang S, Vallabhaneni G, et al. Mechanisms of enhanced radiation response following epidermal growth factor receptor signaling inhibition by erlotinib (Tarceva). Cancer Res. 2005; 65:3328–3335. [PubMed: 15833866]

6. Chen DJ, Nirodi CS. The epidermal growth factor receptor: a role in repair of radiation-induced DNA damage. Clin Cancer Res. 2007; 13:6555–6560. [PubMed: 18006754]

7. Araújo A, Ribeiro R, Azevedo I, et al. Genetic polymorphisms of the epidermal growth factor and related receptor in non-small cell lung cancer--a review of the literature. Oncologist. 2007; 12:201–210. [PubMed: 17296816]

8. Toschi L, Cappuzzo F. Understanding the new genetics of responsiveness to epidermal growth factor receptor tyrosine kinase inhibitors. Oncologist. 2007; 12:211–220. [PubMed: 17296817]

9. Mendelsohn J. The epidermal growth factor receptor as a target for cancer therapy. Endocr Relat Cancer. 2001; 8:3–9. [PubMed: 11350723]

10. Tsao MS, Sakurada A, Cutz JC, et al. Erlotinib in lung cancer - molecular and clinical predictors of outcome. N Engl J Med. 2005; 353:133–144. [PubMed: 16014883]

11. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009; 361:947–957. [PubMed: 19692680]

12. Xu C, Zhou Q, Wu YL. Can EGFR-TKIs be used in first line treatment for advanced non-small cell lung cancer based on selection according to clinical factors? A literature-based meta-analysis. J Hematol Oncol. 2012; 5:62. [PubMed: 23050865]

13. Petrelli F, Borgonovo K, Cabiddu M, Barni S. Efficacy of EGFR tyrosine kinase inhibitors in patients with EGFR-mutated non-small-cell lung cancer: a meta-analysis of 13 randomized trials. Clin Lung Cancer. 2012; 13:107–114. [PubMed: 22056888]

14. Dahabreh IJ, Linardou H, Siannis F, Kosmidis P, Bafaloukos D, Murray S. Somatic EGFR mutation and gene copy gain as predictive biomarkers for response to tyrosine kinase inhibitors in non-small cell lung cancer. Clin Cancer Res. 2010; 16:291–303. [PubMed: 20028749]

15. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. for the National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med. 2005; 353:123–132. [PubMed: 16014882]

16. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006; 354:567–578. [PubMed: 16467544]

17. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol. 2010; 11:21–28. [PubMed: 19897418]

18. Wang J, Xia TY, Wang YJ, et al. Prospective study of epidermal growth factor receptor tyrosine kinase inhibitors concurrent with individualized radiotherapy for patients with locally advanced or metastatic non-small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2011; 81:e59–e65. [PubMed: 21345607]

19. Okamoto I, Takahashi T, Okamoto H, et al. Single-agent gefitinib with concurrent radiotherapy for locally advanced non-small cell lung cancer harboring mutations of the epidermal growth factor receptor. Lung Cancer. 2011; 72:199–204. [PubMed: 20828860]

20. Chang CC, Chi KH, Kao SJ, et al. Upfront gefitinib/erlotinib treatment followed by concomitant radiotherapy for advanced lung cancer: a mono-institutional experience. Lung Cancer. 2011; 73:189–194. [PubMed: 21247653]

21. Baumann M, Krause M, Dikomey E, et al. EGFR-targeted anticancer drugs in radiotherapy: preclinical evaluation of mechanisms. Radiat Oncol. 2007; 83:238–248.

22. Tortora G, Gelardi T, Ciardiello F, Bianco R. The rationale for the combination of selective EGFR inhibitors with cytotoxic drugs and radiotherapy. Int J Biol Markers. 2007; 22:S47–S52. [PubMed: 17520581]

23. Nyati MK, Morgan MA, Feng FY, Lawrence TS. Integration of EGFR inhibitors with radiochemotherapy. Nat Rev Cancer. 2006; 6:876–885. [PubMed: 17036041]

24. Tanaka T, Munshi A, Brooks C, Liu J, Hobbs ML, Meyn RE. Gefitinib radiosensitizes non-small cell lung cancer cells by suppressing cellular DNA repair capacity. Clin Cancer Res. 2008; 14:1266–1273. [PubMed: 18281562]

25. Kim JC, Ali MA, Nandi A, et al. Correlation of HER1/EGFR expression and degree of radiosensitizing effect of the HER1/EGFR-tyrosine kinase inhibitor erlotinib. Indian J Biochem Biophys. 2005; 42:358–365. [PubMed: 16955736]

26. Wang M, Morsbach F, Sander D, et al. EGF receptor inhibition radiosensitizes NSCLC cells by inducing senescence in cells sustaining DNA double-strand breaks. Cancer Res. 2011; 71:6261–6269. [PubMed: 21852385]

27. Wang M, Kern AM, Hülskötter M, et al. EGFR-mediated chromatin condensation protects KRAS-mutant cancer cells against ionizing radiation. Cancer Res. 2014; 74:2825–2834. [PubMed: 24648348]

28. Liu XQ, Qiao TK. Radiosensitizing effect of erlotinib on human lung adenocarcinoma cell line A549. Zhonghua Zhong Liu Za Zhi. 2013; 35:819–823. [article in Chinese]. [PubMed: 24447478]

29. Blumenschein GR Jr, Paulus R, Curran WJ, et al. Phase II study of cetuximab in combination with chemoradiation in patients with stage IIIA/B non-small-cell lung cancer: RTOG 0324. J Clin Oncol. 2011; 29:2312–2318. [PubMed: 21555682]

30. Liu HH, Balter P, Tutt T, et al. Assessing respiration-induced tumor motion and internal target volume using four-dimensional computed tomography for radiotherapy of lung cancer. Int J Radiat Oncol Biol Phys. 2007; 68(2):531–540. [PubMed: 17398035]

31. Socinski MA, Blackstock AW, Bogart JA, et al. Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. J Clin Oncol. 2008; 26:2457–2463. [PubMed: 18487565]

32. Rothschild S, Bucher SE, Bernier J, et al. Gefitinib in combination with irradiation with or without cisplatin in patients with inoperable stage III non-small cell lung cancer: a phase I trial. Int J Radiat Oncol Biol Phys. 2011; 80:126–132. [PubMed: 20646869]

33. Nakagawa M, Nishimura T, Teramukai S, et al. Interstitial lung disease in gefitinib-treated Japanese patients with non-small cell lung cancer - a retrospective analysis: JMTO LC03-02. BMC Res Notes. 2009; 2:157. [PubMed: 19656374]

34. Kudoh S, Kato H, Nishiwaki Y, et al. Interstitial lung disease in Japanese patients with lung cancer: a cohort and nested case-control study. Am J Respir Crit Care Med. 2008; 177:1348–1357. [PubMed: 18337594]

35. Bradley J, Paulus R, Komaki R, et al. A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy with or without cetuximab for stage III non-small cell lung cancer: Results on radiation dose in RTOG 0617. Presented at the 2013 meeting of the American Society of Clinical Oncology. J Clin Oncol. 2013; 31(suppl) abstr 7501.

36. Socinski MA, Stinchcombe TE, Moore DT, et al. Incorporating bevacizumab and erlotinib in the combined-modality treatment of stage III non-small-cell lung cancer: results of a phase I/II trial. J Clin Oncol. 2012; 30:3953–3959. [PubMed: 23045594]

37. D'Angelo SP, Janjigian YY, Ahye N, et al. Distinct clinical course of EGFR-mutant resected lung cancers: results of testing of 1118 surgical specimens and effects of adjuvant gefitinib and erlotinib. J Thorac Oncol. 2012; 7:1815–1822. [PubMed: 23154553]

38. Welsh JW, Komaki R, Amini A, et al. Phase II trial of erlotinib plus concurrent whole-brain radiation therapy for patients with brain metastases from non-small cell lung cancer. J Clin Oncol. 2013; 31(7):895–902. [PubMed: 23341526]

39. Casal Rubio J, Firvida-Perez JL, Lazaro-Quintela M, et al. A phase II trial of erlotinib as maintenance treatment after soncurrent chemoradiotherapy in stage III non-small-cell lung cancer: A Galician Lung Cancer Group study. Cancer Chemother Pharmacol. 2014; 73:451–457. [PubMed: 24352251]

40. Kelly K, Chansky K, Gaspar LE, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. J Clin Oncol. 2008; 26:2450–2456. [PubMed: 18378568]

41. Bhutani M, Pathak AK, Mao L. SWOG S0023: what meets the eye may be only half the truth. J Clin Oncol. 2008; 26:4848–4849. author reply 4850-851. [PubMed: 18779597]

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.
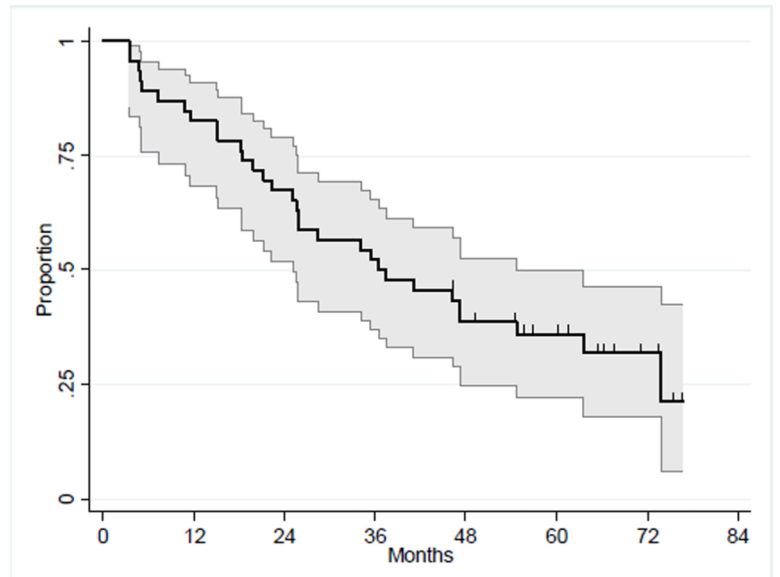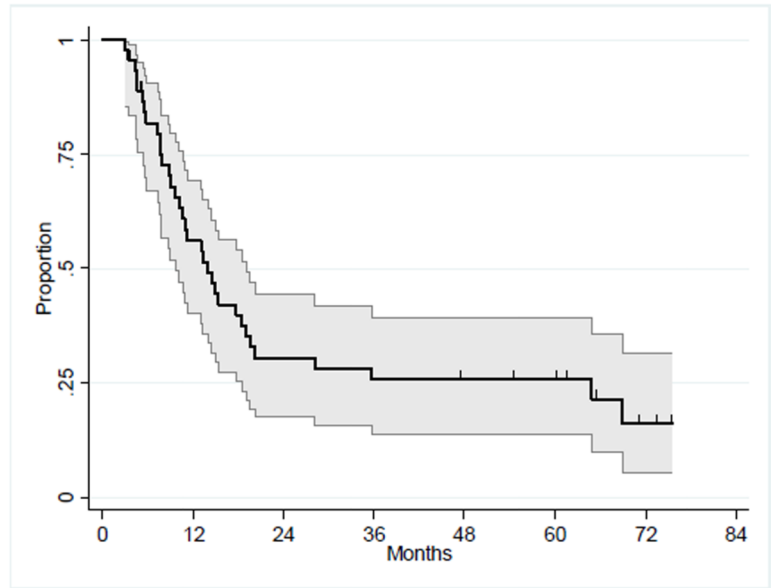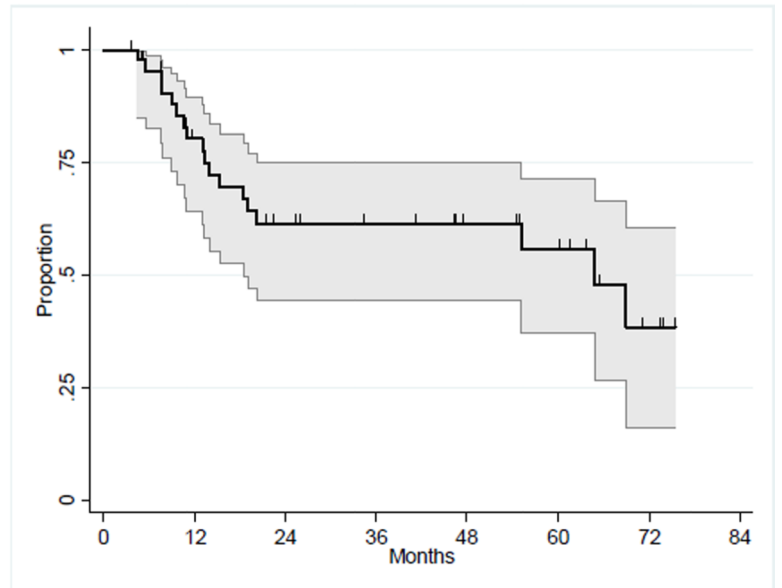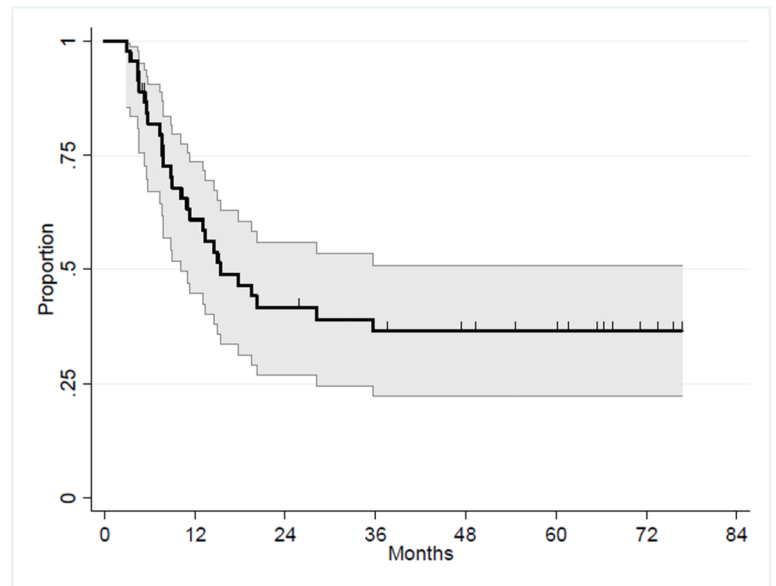
A

B

C

D

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