Epidermal growth factor receptor tyrosine kinase inhibitor, erlotinib, and concurrent 5-fluorouracil, cisplatin and radiotherapy for patients with esophageal cancer: a phase I study

Michael C. Dobelbower, Suzanne M. Russo, Kevin P. Raisch, Leisa L. Seay, Lisa K. Clemons, Susan Suter, James Posey and James A. Bonner

This phase I trial investigates the safety of combining radiation, 5-fluorouracil (5-FU) and cisplatin with the epidermal growth factor receptor tyrosine kinase inhibitor, erlotinib, in patients with esophageal carcinoma. From April 2000 to January 2005, 11 patients with squamous or adenocarcinoma of the esophagus were enrolled. Patients received either 50, 100 or 150 mg oral erlotinib/day beginning on the first day of radiation (three patients in each dose cohort). Concurrent cisplatin (75 mg/m^2 i.v., days 8 and 36) and 5-FU (1000 mg/m^2 i.v., days 8–11 and 36–39) were also given with 50.4 Gy thoracic radiation, delivered at 180 cGy/day, 5 days/week. Toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria (version 3.0). Erlotinib with concurrent 5-FU, cisplatin and thoracic radiation was well-tolerated at 50, 100 and 150 mg/day. The major toxicities were diarrhea (grade 1 = 18%, grade 2 = 18%), skin rash (grade 4 = 54.5%), nausea (grade 1 = 18%, grade 2 = 54%, grade 3 = 9%) and dehydration (grade 3 = 27%). All patients experienced esophagitis during treatment (grade 1 = 55%, grade 2 = 32%, grade 3 = 9%, grade 4 = 9%). Two patients were discontinued from the study secondary to non-erlotinib-related toxicities. We conclude that the phase I study demonstrates the safety and tolerability of erlotinib delivered at 150 mg/day with concurrent 5-FU, cisplatin and thoracic radiation. The major toxicities encountered were grade 1–2 diarrhea, grade 1 skin rash, grade 1–3 nausea and grade 3 dehydration. A phase II study is planned. *Anti-Cancer Drugs* 17:95–102 © 2006 Lippincott Williams & Wilkins.

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University of Alabama at Birmingham, Birmingham, Alabama, USA.

Correspondence to S. Russo, Department of Radiation Oncology, 125 Wallace Tumor Institute, 619 19th St South, Birmingham, AL 35249-6832, USA.
Tel: +1 205 975 9704; fax: +1 205 975 0784;
e-mail: suzrusso@msn.com

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Introduction

There are approximately 13 100 new cases of esophageal cancer diagnosed in the US per year, resulting in 12 600 deaths per year [1]. Of the 40–60% of patients that present with clinically localized disease, the overall survival following surgery alone is approximately 20–25%. The use of adjuvant treatments remains controversial and has been the subject of many clinical trials, without proven benefit [2].

A number of chemotherapy agents have been evaluated for response in esophageal cancer; however, unfortunately, only 20% have an objective response to single-agent therapy. Improved response rates were observed for patients receiving combinations of cisplatin and 5-fluorouracil (5-FU), although duration of response was comparable with that observed with single-agent chemotherapy [3].

The use of concurrent chemoradiation has resulted in improved response rates. Three single-arm studies used pre-operative 5-FU with cisplatin and concurrent radiation with similar results of approximately 30% of resected specimens with no residual tumor present [4–6]. Subsequently, three trials have randomized patients to treatment with neoadjuvant chemoradiation following surgery compared to surgery alone in clinically resectable patients. These trials have demonstrated improvement in local control. Two of these trials, however, demonstrate no statistically significant improvement in survival [7–9].

The results of trimodality therapy, however, are promising for complete responders to neoadjuvant therapy. The 2-year survival rate approaches 30% for the 30% of patients obtaining a pathologic complete response to neoadjuvant chemoradiation [10]. These data are suggestive that trimodality therapy may be advantageous for certain patients, but identification of patients best suited for these regimens as well as the optimal regimen remains the subject of investigation.

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Erlotinib

Erlotinib hydrochloride (Tarceva; OSI Pharmaceuticals/Genentech/Roche), a member of a class of targeted anticancer drugs that inhibit the activity of the epidermal growth factor receptor (EGFR), was approved by the US FDA in November 2004 for the treatment of advanced non-small cell lung cancer after failure of at least one prior chemotherapy regimen. It is the first such drug to demonstrate an increase in survival in phase III trials in patients with advanced non-small cell lung cancer, and is currently being investigated in combination with radiation, chemotherapy and targeted therapies for efficacy in a number of malignancies.

It is an orally available quinazoline derivative which inhibits EGFR tyrosine kinase *in vitro* and its analogs have been shown to be direct-acting, reversible, ATP-competitive inhibitors of tyrosine phosphorylation [11]. Erlotinib also inhibits autophosphorylation of EGFR in a variety of EGFR-overexpressing tumor cells, and produces inhibition of tumor growth inhibition, mitogenesis, cell division and G_1 cell cycle arrest [11]. The maximum tolerated dose (MTD) of erlotinib has been demonstrated to be 150 mg orally/day in phase I and pharmacogenetic studies as a single agent in solid tumors; however, the MTD of erlotinib differs when used in different regimens for different indications [11].

Preclinical data

EGFR is overexpressed in approximately 80% of esophageal cancers [12]. Studies have also shown overexpression of EGFR in up to 88% of lymph node metastases [13] and have correlated overexpression of EGFR with poor prognosis in esophageal cancer patients [14–16]. The radiosensitizing potential of erlotinib has been demonstrated in a variety of human tumor cell lines and xenografts [17]. Preclinical studies investigating specific mechanisms of erlotinib-induced radiosensitization show enhance radiation response at several levels, including cell cycle arrest, apoptosis induction, accelerated cellular repopulation and DNA damage repair. Specifically, erlotinib combined with radiation results in an increase in the reduction in the S-phase fraction following radiation alone. Erlotinib also enhances the induction of radiation-induced apoptosis, and inhibits EGFR autophosphorylation and Rad51 expression following radiation exposure, resulting in increased radiosensitivity. Tumor xenograft studies confirm that radiation combined with systemic erlotinib results in substantial tumor growth inhibition. Microarray analyses have confirmed specific genes that may influence radiosensitization by erlotinib including Egr-1, CXCL1 and interleukin-1β, suggesting that additional mechanisms underlying the complex interaction between EGFR signaling and radiation response exist [17].

Preclinical studies performed at the University of Alabama at Birmingham have investigated the potential of erlotinib as a radiation sensitizer specifically for human esophageal cancer cell lines [18–20]. Five cell lines (three adenocarcinomas and two squamous cell carcinomas) were analyzed for EGFR expression; only one squamous cell line did not express detectable EGFR protein or mRNA. All cell lines, independent of EGFR expression levels, however, demonstrated dose-dependent erlotinib-induced growth inhibition following exposure to various concentrations of erlotinib. Two of the five cell lines (one adenocarcinoma and one squamous cell carcinoma) also demonstrated erlotinib-induced radiosensitization utilizing the colony formation assay. In addition, an erlotinib dose-dependent inhibition of EGF-activated EGFR phosphorylation and downstream signal transduction markers, mitogen-activated protein kinase (MAPK; ERK1/ERK2) and AKT was observed in three of the EGFR overexpressing cell lines. The *in vitro* data indicates that the erlotinib not only inhibits activation of EGFR, but also inhibits EGFR by preventing activation of downstream signal transduction pathway markers [19,20].

These data suggest that the erlotinib/radiation combination represents a strategy worthy of further examination in clinical trials. Therefore, it was of interest to evaluate erlotinib as a potential component of a treatment strategy including radiotherapy for esophageal cancer. The specific aim of this phase I study was to establish the MTD of erlotinib given concurrently with 5-FU, cisplatin and thoracic radiation in patients with esophageal cancer. Subsequent studies using the MTD of erlotinib identified in the study will investigate the efficacy of this treatment.

Methods

The study was conducted according to the principles of the Declaration of Helsinki as amended in Somerset West in 1996 and to Good Clinical Practice guidelines. Approval was gained from the University of Alabama institutional review board and each patient gave written informed consent before being recruited onto the trial.

Eligibility criteria

Male or female patients 19 years of age or older with ECOG performance status (PS) 0–2 and histologically confirmed esophageal squamous cell or adenocarcinoma were eligible for this study. Demonstration of EGFR overexpression by the tumor was not required for participation in this study. Exclusion criteria included previous chemotherapy, radiotherapy or chemoradiotherapy for esophageal cancer, patients with a previous malignancy who were not disease free for at least 5 years, or patients with a tracheo-esophageal fistula.

Objective

The primary objective of the study was to determine the MTD of oral erlotinib administered continuously daily in combination with 5-FU, cisplatin and standard thoracic radiotherapy in patients with esophageal cancer, using a standard dose-escalation design for erlotinib.

Study design and treatment

Erlotinib therapy

Erlotinib was administered at planned escalating doses of 50, 100 and 150 mg/day for the duration of radiotherapy. Three evaluable patients were accrued to each cohort. The number of patients at each dose level was increased to six patients if one dose-limiting toxicity (DLT) was observed in any cohort at a given dose level. The DLTs for erlotinib were defined per National Cancer Institute Common Toxicity Criteria (NCI CTC; version 3.0) as grade 3 or above skin toxicity, grade 3 or above diarrhea and grade 4–5 unusual toxicities. Safety evaluations were performed weekly throughout the duration of the therapy and at time of follow-up. Dose modification guidelines were provided for erlotinib for all DLTs as described. Erlotinib therapy was delay for up to 1 week with no change in dose level, while symptoms were treated with best supportive care. Erlotinib therapy was resumed at the assigned dose when toxicity resolved to grade 2 or less. With the second and third occurrences of grade 3 toxicity, erlotinib therapy was to be delayed again for up to 1 week with concomitant dose reductions to the previously tolerated dose level. Erlotinib treatment was discontinued if there were more than three subsequent occurrences of grade 3 toxicity. Erlotinib therapy was not withheld for toxicities clearly related to chemotherapy or radiation. Patients were terminated from the study if erlotinib therapy was discontinued.

Erlotinib doses were not escalated until all patients in a cohort had been followed for at least 3 months. The MTD was based upon the experiences of all patients who completed therapy or discontinued treatment due to DLT while on study. Patients who dropped out of the study before completion of radiation (for reasons other than toxicity) were not included in the analysis of MTD.

Radiotherapy

Computer tomography (CT) image-based three-dimensional treatment planning was utilized to optimize radiation treatment planning by facilitating identification of the target volume and surrounding normal structures. Plans were designed to minimize dose to the normal structures while ensuring adequate dose to the target volume. Dose-limiting normal structures were contoured for dose–volume histogram analysis. The maximum extent of the tumor and involved nodal areas, and areas at risk for residual microscopic disease were also defined by CT.

External beam radiation therapy was delivered from high-energy linear accelerators with 6 or 15 MV photon beams beginning on the first day of week 1 of the study. Patients received 1.8 Gy/day, 5 days/week, for 23–25 fractions, limiting the spinal cord dose to 45 Gy. A subsequent radiation boost using radiation fields designed to avoid the spinal cord was continued at 1.8 cGy/day to a total dose of 50.4 Gy (28 fractions total).

Radiation treatment break guidelines were provided for radiation-induced toxicities. Weekly toxicity evaluations were performed. Radiation-induced esophagitis was treated with best supportive care and radiation was interrupted for grade 3 or above dysphagia or odynophagia with dehydration and weight loss (above 15% from pretreatment baseline) requiring nasogastric feeding or hyperalimentation. Radiation resumed when toxicity resolved to grade 2. Radiation was also interrupted for up to 1 week for clinical or radiological evidence of acute pneumonitis. Pneumonitis was treated with steroid therapy. Patients were terminated from the study if radiation was discontinued permanently.

Chemotherapy

Cisplatin (75 mg/m^2) was delivered by i.v. bolus on the first day of weeks 1 and 5 of treatment. 5-FU was delivered i.v. at 1000 mg/m^2/24 h on days 1–4 weeks 1 and 5 of treatment. Dose modification guidelines were also provided for chemotherapy-related toxicities. Clinical evaluation and hematologic and renal toxicity were assessed at weekly intervals. Dose modifications were neutropenia, renal toxicity, grade 3 neurotoxicity and grade 3 hand–foot syndrome or stomatitis. Patients were terminated from study if chemotherapy was discontinued permanently.

Statistics

A standard phase I dose escalation trial was performed with cohorts of three patients planned for each dose level. If no DLT was observed in the cohort of three patients, no additional patients were enrolled in the cohort. The number of patients at each dose level was increased to six patients if one DLT was observed in any cohort at a given dose level. The probabilities of stopping at a particular dose if the true probability of a DLT are given in Table 1. For example, if 50% of the patients experienced a DLT at a particular dose, say 100 mg erlotinib, then the probability of stopping at that dose and declaring 50 mg erlotinib the MTD was 77%.

Results

A total of 11 patients were accrued onto the study at University of Alabama at Birmingham between April 2003 and January 2005. The safety analysis included all 11 patients who received at least one dose of erlotinib. All adverse events were monitored continuously during

Table 1 Probability of stopping for given probabilities of DLTs

Probability of DLT	0.1	0.2	0.3	0.4	0.5	0.6	0.7
Probability of stopping (%)	9	29	51	69	83	92	97

Table 2 Patient characteristics

Characteristics	No. patients
Patients enrolled	
evaluable	9
non-evaluable	2
Patients enrolled	11
Men	10
Women	1
Age (years) [median (range)]	58 (26–69)
Race	
Caucasian	9
African-American	2
Stage	
I	0
II	1
III	2
IV	8
Histology	
adenocarcinoma	8
squamous cell	3
ECOG PS	
0	6
1	4
2	1

treatment and for 12 weeks after the end of treatment. Four patients (three evaluable) were recruited to the 50 mg dose level, four patients (three evaluable) to the 100 mg dose level and three patients to the 150 mg dose level.

The patient characteristics are listed in Table 2. All patients had newly diagnosed disease, three were deemed medically inoperable by a surgical oncologist and eight had evidence of metastatic disease at the time of diagnosis. Three patients were diagnosed with squamous cell carcinomas and eight had adenocarcinomas of the esophagus. Six patients had ECOG PS 0, four patients had ECOG PS 1 and one patient had ECOG PS 2. There were no major deviations from the protocol, but two patients were taken off the study due to reasons unrelated to erlotinib toxicity.

Dose escalation and DLTs

Patient dose cohorts and DLTs are summarized in Table 3. Two of the three patients treated with erlotinib 150 mg/day experienced grade 2 diarrhea, which responded to a low-fiber diet and anti-diarrheal agents. Six patients (two at 50, three at 100 and one at 150 mg/day) developed skin rash, all grade 1, which resolved spontaneously within 1 week of completion of erlotinib therapy. There were no erlotinib dose reductions and no treatment delays or interruptions were required. Since no DLTs were observed at any of the erlotinib dose levels in this study, the erlotinib dose escalation was stopped at

Table 3 Patients enrolled at each dose level and DLT

Dose level (mg/day)	Patients enrolled	Evaluable[a]	No. patients with DLTs[b]
50	4	3	0
100	4	3	0
150	3	3	0

[a]Two patients were taken off study due to non-erlotinib-related toxicities. All patients are included in toxicity reporting.
[b]DLT for erlotinib: defined as grade 3 or greater skin rash, diarrhea, or any grade 4 or greater unusual toxicity.

150 mg/day based on pharmacokinetic profiles and data from other phase I studies. Therefore, 150 mg p.o. daily with concomitant 5-FU, cisplatin and thoracic radiation is the recommended dosage for subsequent trials.

Hematologic toxicity

Hematological toxicities are summarized in Table 4. Grade 1–2 anemia was seen during all erlotinib dose levels, with one grade 3 anemia seen at the 100 mg dose level. Grade 1–4 leukocytopenia was observed in this study, and the nadir usually occurred 7–10 days following 5-FU and cisplatin treatments. Grade 1 and 3 thrombocytopenia was also observed approximately 7–10 days following 5-FU and cisplatin infusions, with no trend toward cumulative toxicity. Cases of grade 3 or 4 anemia, neutropenia and thrombocytopenia resolved to grade 2 or less prior to the subsequent dose of chemotherapy, and therefore no cisplatin or 5-FU dose reductions, treatment interruptions or delays were required for hematologic toxicity.

Non-hematologic toxicity

Adverse events according to maximum CTC version 3.0 are presented for the whole patient group (Table 5). Figure 1 presents the frequency and grade of adverse events by body/organ system. Gastrointestinal toxicities were common, as they occurred in more than half of all patients, consisting primarily of grade 1–3 nausea (grade 1 in two, grade 2 in six and grade 3 in one) and vomiting (grade 1 in three and grade 2 in one). Most patients with nausea and vomiting responded to anti-emetic therapy; however, grade 3 dehydration resulted in three patients, who responded to i.v. administration of anti-emetics and fluids. Diarrhea occurred in four patients (grade 1 in two and grade 2 in two; the latter being observed at the highest dose level), and was treated with a low-fiber diet and anti-diarrhea agents. Fatigue was also a common toxicity. No chemotherapy dose reductions, treatment delays or interruptions were required for nausea, vomiting, dehydration, diarrhea or fatigue.

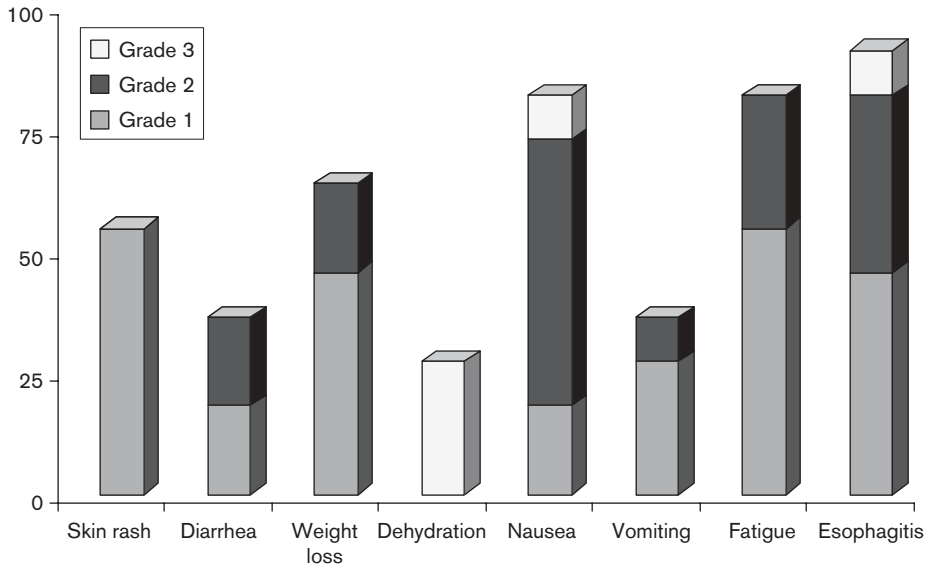
Table 4 Hematological toxicities (grade)

Dose level (mg/day)	WBC				Hemoglobin				Platelet				ANC			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
50	–	2	–	1	–	4	–	–	–	–	1	–	1	1	–	1
100	–	–	3	–	2	1	1	–	4	–	–	–	–	2	1	–
150	–	3	–	–	–	2	–	–	2	–	–	–	2	1	–	–

Table 5 Non-hematological toxicities (grade)

Dose level (mg/day)	Skin rash ($n=6$)		Diarrhea ($n=4$)			Weight loss ($n=7$)			Dehydration ($n=3$)				Nausea ($n=9$)				Vomiting ($n=4$)			Fatigue ($n=9$)			Esophagitis ($n=11$)			
	1	2	1	2	3	1	2	3	1	2	3	4	1	2	3	4	1	2	3	1	2	3	1	2	3	4
50	2	–	1	–	–	2	1	–	–	–	1	–	–	3	1	–	2	1	–	3	1	–	2	2	–	1
100	3	–	–	–	–	1	1	–	–	–	1	–	1	1	–	–	–	–	–	2	1	–	2	1	–	–
150	1	–	1	2	–	2	–	–	–	–	1	–	1	2	–	–	1	–	–	1	1	–	1	1	1	–

Fig. 1



Frequency and grade of non-hematological toxicities.

No patients developed hand–foot syndrome or mucositis. One patient at the 150 mg erlotinib dose level developed a grade 2 ototoxicity related to cisplatin and remained on study, resulting in a 50% cisplatin dose reduction. Another patient at the 50 mg erlotinib dose level developed symptomatic renal failure with elevated creatinine at 3.6 due to cisplatin toxicity, resulting in discontinuation of cisplatin termination from the study. A second patient at the 100 mg dose level was terminated from the study after developing prolonged respiratory compromise secondary to oversedation and therapy was discontinued.

As expected from previous experience using chemoradiation to treat esophageal cancer, weight loss and esophagitis occurred frequently in this study. All patients experienced esophagitis during treatment (grade 1 = 55%, grade 2 = 32%, grade 3 = 9%, grade 4 = 9%), which developed 2–5 weeks after initiation of chemoradiation and resolved 2–3 weeks after completion of therapy. Radiation treatment was interrupted in two patients and resumed after 3 days when esophagitis improved to grade 2 or less. Seven patients (64%) lost weight during treatment (grade 1 = 46%, grade 2 = 18%).

Discussion

The current phase I study was undertaken to identify whether this radiosensitizer could be integrated in a tolerable fashion with chemoradiation for treatment of esophageal cancer. In fact, this study demonstrates the safety and tolerability of erlotinib delivered at 150 mg/day with concurrent 5-FU, cisplatin and thoracic radiation. The major toxicities encountered were diarrhea, skin rash, nausea and dehydration, and no DLTs were encountered.

The incidence of toxicities encountered in this study was similar to those encountered in other studies using similar treatment regimens without erlotinib. The Southwest Oncology Group (SWOG) [5] and Radiation therapy Oncology Group (RTOG) [6] performed phase II trials utilizing concurrent 5-FU and thoracic radiation as preoperative treatment for esophageal cancer, based on pilot data from Wayne State University [21]. Toxicity included gastrointestinal symptoms, mucositis and myelosuppression in both studies. In the SWOG study, nausea and vomiting occurred in most patients and was severe in 7%, severe mucositis occurred in 6%, and severe leukopenia was encountered in 7% and was life threatening in an additional 3%. Neurotoxicity preventing a full second course of chemotherapy was reported in one patient. Five percent of patients demonstrated a rise in serum creatinine of 2 mg per dose level or above. Esophagitis was experienced by most, but was graded as moderate in three patients. There were no treatment-related deaths reported in the SWOG trial [5] and 5% patients did not complete therapy due to mortality caused by treatment-related complications in the RTOG study [6].

In the current study, similar doses and schedules of chemotherapy were delivered with a higher dose of radiation and erlotinib. Despite the more vigorous treatment regimen, there were no treatment-related deaths. Similar to the previous studies, nausea and vomiting was experienced by most (63 and 36%, respectively). Mucositis did not occur nor did life-threatening leukopenia, although most patients (82%) demonstrated some leukopenia, including 36% grade 3–4. Grade 1 and 2 diarrhea was encountered in this study, which was not reported in the previous studies. In addition, grade 1 skin rashes were seen in 11 patients, also not reported in the aforementioned studies. Both of these toxicities could be attributed to the addition of the erlotinib therapy.

Erlotinib is currently being combined with chemotherapy and/or radiation for the treatment of other solid tumors. In a randomized phase III National Cancer Institute of Canada Clinical Trials Group study for patients with advanced pancreatic adenocarcinoma, patients received either gemcitabine (1000 mg/m^2 i.v. weekly for 7 of 8 weeks, then weekly for 3 of 4 weeks) with placebo or erlotinib 100 mg/day. No radiotherapy was given in this trial. An increase in grade 1 and 2 skin rash, diarrhea and hematological toxicity was encountered in the erlotinib arm. In addition, there was a slight improvement in the overall and progression-free survival for this group of patients [22]. Currently, studies are evaluating the use of this regimen with concurrent radiation. Similar trials are also being pursued for other solid tumors.

Similarly, other EGFR inhibitors have been utilized in combined treatment regimens utilizing radiation for various malignancies. Gefitinib (ZD1839, Iressa) is another small-molecule EGFR-specific tyrosine kinase inhibitor (TKI), which has been used in combination with chemotherapy and/or radiation in clinical trials. In one phase I study, ZD1839 was combined with carboplatin and paclitaxel in chemotherapy-naive patients with advanced non-small cell carcinoma of the lung without new or increased toxicity observed over carboplatin/paclitaxel chemotherapy alone [23]. Another phase I study investigated the use of ZD1839 in combination with cisplatin and gemcitabine in chemotherapy-naive patients with a variety of advanced solid tumors. Once again, there was no significant increase in toxicity with the addition of ZD1830 to this regimen [23]. Two phase III trials (the Iressa NSCLC Trial Assessing Combination Treatments-INTACT 1 and 2) combined either gemcitabine and cisplatin (INTACT 1) or carboplatin and paclitaxel (INTACT 2) with placebo, ZD1839 250 mg/day or ZD1839 500 mg/day. Although there were no improvements in survival demonstrated in these trials, the toxicity profile was similar to chemotherapy alone [23]. Ongoing studies combining ZD1839 with other agents include SWOG-0023 (a phase II trial of cisplatin, etoposide and radiotherapy with consolidation docetaxel followed by maintenance therapy with ZD1839 or placebo in patients with inoperable locally advanced stage III non-small cell lung cancer), Cancer and Leukemia Group B (CALGB) 30106 (a phase II study of ZD1939 with induction paclitaxel and carboplatin followed by either radiation or concurrent radiation with weekly paclitaxel and carboplatin for stage III non-small cell lung cancer), a phase I/II study of pre-operative ZD1839 in combination with chemoradiation using cisplatin and etoposide in patients with stage III non-small cell lung cancer, and a phase I/II biological, pharmacodynamic and response study of ZD1839 with external beam radiation and chemotherapy with untreated, locally advanced, non-metastatic non-small cell lung cancer [23]. Combination therapy using ZD1839 is also being evaluated for other solid tumors in addition to non-small cell lung cancer.

Erbitux (IMC-C225) is a human/mouse chimerized Ig grade 4 = antibody with high affinity to the EGFR [24,25]. In both *in vitro* and *in vivo* preclinical studies,

IMC-C225 was shown to enhance the anti-tumor effects of several chemotherapeutic agents [24,26–29]. The most notable clinical experience to date combining IMC-C225 with radiation evaluated 424 patients with locally advanced squamous cell carcinoma of the head and neck randomized to receive either radiation alone or radiation with weekly IMC-C225 in an international phase III trial. The median survival was 28 months for the radiation alone treatment cohort versus 54 months for the cohort receiving IMC-C225. Three-year overall survival was also significantly improved by the addition of IMC-C225 (44 versus 57%, respectively). The treatment was well tolerated with minimal enhancement in the toxicity profile associated with curative radiotherapy [30]. In addition, a multicenter phase II study combining IMC-C225 with carboplatin, paclitaxel and thoracic radiation in patients with stage III/IV non-small cell carcinoma of the lung is underway [23].

In each of the previously mentioned trials, combination therapy using EGFR inhibitors, erlotinib, ZD1839 or IMC-C225, was shown to be safe and tolerable, with minimal or no increase in toxicity over the treatment regimen without the inhibitor. The safety of combining radiation, 5-FU and cisplatin with the EGFR TKI, erlotinib, in patients with esophageal carcinoma was demonstrated in this phase I study.

Based on promising preclinical results utilizing erlotinib as a radiosensitizer [17–20], further work is warranted to determine whether erlotinib may enhance the effects of standard chemoradiotherapy treatment approaches for esophageal cancer. A phase II trial using concurrent erlotinib, at the dose level identified in this study, with concurrent 5-FU, cisplatin and thoracic radiation is planned for patients with resectable squamous cell or adenocarcinomas of the esophagus. This regimen will be delivered in a pre-operative approach. The primary objective of the phase II study is to determine the pathologic response rate for patients with squamous cell or adenocarcinomas of the esophagus. Secondary objectives include assessment of toxicities associated with treatment, time to progression or recurrence, 2-year disease-free and overall survival. In addition, we will explore the potential interaction between erlotinib and radiation *in vivo* with laboratory-correlative studies. These laboratory correlatives will assess the prognostic significance of various proteins associated with EGFR signaling. Additionally, the prognostic significance of EGFR mutations has been the subject of recent investigations [31–33]. It will be important to determine the prognostic significance of these mutations relative to combined modality treatment.

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