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Phase I/II Trial of Cetuximab and Erlotinib in Patients with Lung Adenocarcinoma and Acquired Resistance to Erlotinib

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Abstract

Purpose: In patients with epidermal growth factor receptor (EGFR) mutant lung adenocarcinoma, treatment with erlotinib or gefitinib is associated with a 75% radiographic response rate and progression-free survival of approximately 12 months. The most common mechanism of acquired resistance to erlotinib is development of a secondary mutation in EGFR, suggesting that these tumors continue to depend on EGFR signaling. We hypothesized that combined EGFR blockade would overcome acquired resistance to erlotinib in patients with lung adenocarcinoma. To evaluate the toxicity and efficacy of cetuximab and erlotinib in patients with acquired resistance to erlotinib, we conducted this phase I/II clinical trial.

Experimental Design: Patients with lung adenocarcinoma and clinically defined acquired resistance to erlotinib were treated with erlotinib 100 mg daily, along with cetuximab every 2 weeks in three escalating dose cohorts (250 mg/m^2, 375 mg/m^2, and 500 mg/m^2). The recommended phase II dose was then evaluated in a two-stage trial, with a primary end point of objective response rate.

Results: A total of 19 patients were enrolled. The most common toxicities for the combination of cetuximab and erlotinib were rash, fatigue, and hypomagnesemia. The recommended phase II dose identified was cetuximab 500 mg/m^2 every 2 weeks and erlotinib 100 mg daily. At this dose and schedule, no radiographic responses were seen (0 of 13, 0%, 95% CI, 0–25).

Conclusions: Combined EGFR inhibition, with cetuximab 500 mg/m^2 every 2 weeks and erlotinib 100 mg daily, had no significant activity in patients with acquired resistance to erlotinib. *Clin Cancer Res; 17(8); 2521–7. ©2011 AACR.*

Introduction

Each year, nearly 20,000 people in the United States are diagnosed with lung adenocarcinomas that harbor epidermal growth factor receptor (*EGFR*) mutations. Most experience clinical and radiographic responses to treatment with the EGFR tyrosine kinase inhibitors (EGFR-TKI) gefitinib and erlotinib (1–3). Prospective trials have shown response rates of approximately 75% in patients with *EGFR* mutations (in exons 19 and 21) who are treated with erlotinib or gefitinib (4–7). In patients with *EGFR* mutations, single-agent erlotinib and erlotinib with chemotherapy have similar efficacy, but single-agent erlotinib is less toxic (8). Gefitinib showed a progression-free survival (PFS) advantage over chemotherapy as a first-line therapy in 3 randomized phase III trials in patients with *EGFR* mutant lung adenocarcinoma (9–11).

Despite initial response in patients with *EGFR* mutations, acquired resistance develops after a median of approximately 12 months. The consensus definition of acquired resistance includes patients who had previous treatment with a single-agent EGFR-TKI (e.g., gefitinib or erlotinib); either or both of the following: a tumor that harbors an *EGFR* mutation known to be associated with drug sensitivity (i.e., G719X, exon 19 deletion, L858R, L861Q) or objective clinical benefit from treatment with an EGFR-TKI; systemic progression of disease [Response Evaluation Criteria in Solid Tumors (RECIST) group criteria or World Health Organization (WHO)], while on continuous treatment with gefitinib or erlotinib within the last 30 days; and no intervening systemic therapy between cessation of gefitinib or erlotinib and initiation of new therapy (12). Some data suggest that patients who develop clinically defined acquired resistance to EGFR-TKI should continue to receive EGFR-TKI therapy (13). When erlotinib or

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Translational Relevance

Although epidermal growth factor receptor (*EGFR*) mutations are associated with dramatic sensitivity to EGFR tyrosine kinase inhibitors in patients with lung adenocarcinoma, all patients with benefit eventually develop acquired resistance to erlotinib or gefitinib. There is no targeted therapeutic strategy which has been shown to be beneficial at progression in this patient population. Laboratory and clinical data suggest that these tumors still depend on signaling through the EGFR pathway. This article reports the results of a trial combining erlotinib and cetuximab in patients with acquired resistance to erlotinib. These results show that, although combined EGFR inhibition is a viable strategy for patients with acquired resistance to erlotinib and gefitinib (with tolerable safety profile), the combination of erlotinib and cetuximab does not lead to significant radiographic regressions.

gefitinib are stopped, tumors more rapidly enlarge and become more FDG-avid, a scenario analogous to that observed in individuals with gastrointestinal stromal tumors who acquire resistance to imatinib (14). Resumption of gefitinib or erlotinib slows tumor growth and decreases FDG uptake seen on PET in the majority of patients (13). No EGFR-directed treatment has been shown to induce a second radiographic response in patients with acquired resistance to erlotinib.

In addition to the primary *EGFR* mutations (associated with erlotinib and gefitinib sensitivity), approximately half of the patients with acquired EGFR-TKI resistance have a second *EGFR* mutation (T790M) in the ATP-binding pocket of the tyrosine kinase that may alter receptor affinity in favor of ATP (15–18). These second mutations enable the cancer cells to continue signaling via mutant EGFR, suggesting that in a proportion of patients with acquired resistance to EGFR-TKIs, tumor growth and proliferation remains dependent on EGFR.

Erlotinib inhibits EGFR tyrosine kinase activity by reversibly competing with ATP for binding in the kinase domain. Cetuximab, an EGFR monoclonal antibody, binds to the extracellular domain of EGFR and prevents ligand activation of the receptor. In EGFR-dependent human xenograft models of lung cancer, cetuximab led to significant tumor regression (19–21). *In vitro* and *in vivo*, cetuximab has been specifically shown to inhibit growth of lung adenocarcinoma harboring a drug sensitive L858R and drug resistant T790M mutation (22, 23). Two groups have shown tumor regression, synergistic effect, and regrowth delay in *EGFR*-mutant xenografts treated with an EGFR-TKI and cetuximab (20, 24). By binding the extracellular domain of EGFR, cetuximab may provide additional antitumor effect via activation of antibody-dependent cellular cytotoxicity and inhibition of the autocrine loop of cancer cell signaling (25, 26). Clinically, in patients with lung cancer treated with single agent cetuximab, few responses have been documented (27–30). Moreover, cetuximab, alone or with chemotherapy, has shown limited efficacy in EGFR-driven lung cancer (30, 31). Phase I studies have shown that various combinations of EGFR-TKI and EGFR monoclonal antibodies are safe and tolerable in patients with non–small cell lung carcinoma (32–36). However, combined *EGFR* inhibition has not been prospectively studied in patients with acquired resistance to EGFR-TKIs.

On the basis of the clinical data which suggested continued modest benefit of erlotinib despite acquired resistance and preclinical data which supported the use of cetuximab, we hypothesized that simultaneous inhibition of the EGFR signaling pathway using both erlotinib and cetuximab would overcome acquired resistance to erlotinib in patients with lung adenocarcinoma. To test this hypothesis, we carried out this clinical trial to evaluate the toxicity and efficacy of erlotinib and cetuximab in patients with acquired resistance to erlotinib.

Patients and Methods

Eligibility

Patients with metastatic lung adenocarcinoma with measurable indicator lesions not previously irradiated who had radiographic disease progression during treatment with erlotinib were candidates for this trial. Patients were eligible if they had treatment with erlotinib throughout the 1 month prior to enrollment with either or both of the following: a tumor that harbors an *EGFR* mutation in exon 19 or 21; previous treatment with a single-agent erlotinib for more than 3 months with a radiographic partial or complete response to treatment as defined by RECIST (patients may have received other treatments subsequently, including radiation or chemotherapy). There were no limits on prior cytotoxic chemotherapy. Other eligibility criteria included age 18 years or more; Karnofsky Performance Status 70% or more; adequate hepatic function [AST (aspartate amino transferase) and ALT (alanine amino transferase) levels $\leq 2.5 \times$ upper limit of normal and total bilirubin within normal limits]. Patients with grade 2 or more skin toxicity on erlotinib monotherapy were not eligible. The clinical trial protocol and informed consent were approved by the Memorial Sloan–Kettering Cancer Center Institutional Review Board. All patients provided written informed consent.

Drug administration

Erlotinib 100 mg daily was administered on a continuous schedule with cetuximab given intravenously (IV) every 2 weeks. This cetuximab dosing regimen has antitumor activity and safety similar to those reported for the weekly dosing regimen (37, 38). For the phase I component of this study, 3 dose levels were evaluated: cetuximab 250 mg/m^2 IV every 2 weeks and erlotinib 100 mg daily; cetuximab 375 mg/m^2 IV every 2 weeks and erlotinib 100 mg daily; cetuximab 500 mg/m^2 IV every 2 weeks and erlotinib 100 mg daily (Fig. 1). Cetuximab dose

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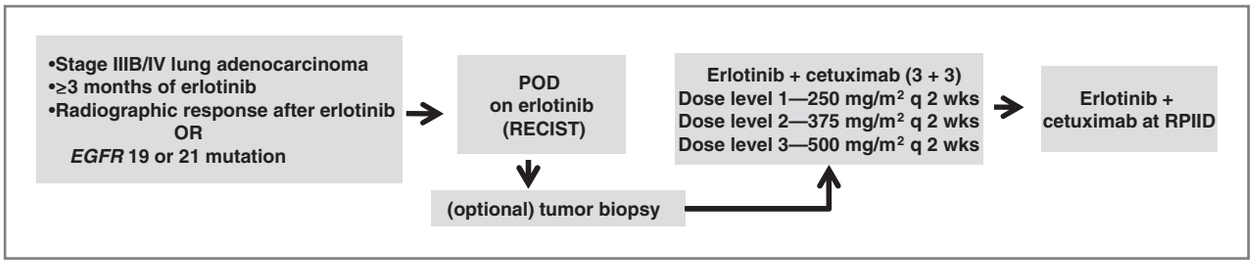

Figure 1. Schema for the phase I portion of the trial. POD, progression of disease. RPIID, recommended phase II dose.

reductions were permitted up to 2 times per patient. Patients received cetuximab and erlotinib until they developed evidence of progressive disease or unacceptable toxicity attributed to therapy.

Dose-limiting toxicities (DLT) were defined as the following adverse events considered at least possibly related to the study-drug combination occurring during the first 4 weeks therapy: grade 3 diarrhea lasting longer than 48 hours (despite intensive loperamide therapy), grade 4 diarrhea, grade 3 rash (or rash requiring dose delay lasting greater than 2 weeks), grade 3 fatigue lasting greater than 1 week, or any other nonhematologic treatment-related grade 3/4 toxicity (except nausea and vomiting). The recommended phase II dose was defined as the highest dose level, in which no more than 1 of 6 patients experienced DLT.

Pretreatment and follow-up evaluations

A medical history, physical examination, complete blood count, serum comprehensive chemistry panel with magnesium level were measured within 2 weeks prior to study entry, at week 1, and then every 2 weeks throughout the study. Patients were assessed for toxicity on the basis of the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0 (NCI CTCAE V3.0). Objective tumor responses were determined by cross-sectional imaging of all known sites of disease, less than 2 weeks prior to initiation of treatment, after 4 weeks of study therapy, and every 8 weeks thereafter using RECIST (39).

Statistical analysis and sample size determination

For the phase I portion of the study, 3 patients were enrolled per dose level. If no DLT were observed, ensuing patients were enrolled at the next dose level. If 1 DLT was observed in 3 patients, 3 additional patients were enrolled at that dose level. If 0 to 1 DLT occurred in 6 patients, then additional patients were treated at the next dose level. The recommended phase II dose was defined as the highest dose level in which no more than 1 of 6 patients experienced DLT.

For the phase II component, response rate was set for sufficient and insufficient drug activity at 5% and 25%, respectively, with $\alpha = 0.10$ and $\beta = 0.10$ (40). In the first stage, 13 patients assessable for response were enrolled. This group included the patients treated at the recommended phase II dose in the phase I portion. If 1 or more objective responses were observed, accrual would proceed to the second stage and the phase II portion would expand to include 7 additional patients. Given the homogeneity of the patient population, the combination of erlotinib and cetuximab would be considered worthy of further study if at least 3 objective responses were observed in 20 patients included in the phase II portion of the study.

All patients that received 1 complete dose of cetuximab were considered to be assessable for safety and toxicity. Patients with cetuximab infusion reactions were removed from the study and replaced. Survival time was defined as the time from first treatment with cetuximab to death. Time to event distributions were estimated using the Kaplan–Meier method.

Results

Between August 2008 and July 2009, 21 patients were enrolled in this single-institution study. Two patients treated at dose level 2 (375 mg/m^2) who had hypersensitivity reactions during the first infusion of cetuximab were removed from the study and replaced. The pretreatment characteristics, including results of *EGFR* T790M analysis after acquired resistance (if available), are summarized in Table 1.

Table 1. Patient characteristics ($n = 19$)

Age, y, median (range)	61 (50–78)
Sex, *n*	
Women	12
Men	7
Months from beginning erlotinib/gefitinib, median (range)	22 (5–72)
EGFR mutation, *n*	
Exon 19 deletion	12
Exon 21 L858R mutation	4
Negative	1
Unknown	2
EGFR T790M acquired mutation, *n*	
Yes	9
No	3
Unknown	7

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Table 2. Toxicities (all cycles)

	Cetuximab 500 mg/m^2 (n = 13)			Cetuximab 375 mg/m^2 (n = 3)			Cetuximab 250mg/m^2 (n = 3)			Total
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4	
Anemia	1				1		1			3
AST/ALT, elevated	2	1						1		4
Bilirubin, elevated	1	1		1			2			5
Conjunctivitis				2						2
Creatinine, high	1			1	1					3
Edema					1					1
Fatigue	8			1	1		2			12
Hyperglycemia	1	1								2
Hyperkalemia	1		1			1				2
Hypernatremia		1								1
Hypokalemia		2								2
Hypomagnesemia	5	4	1	1	1	1	1			14
Hyponatremia		1								1
Hypophosphatemia			1							1
Leukopenia	1	3								4
Mucositis	3			1						4
Nausea	1									1
Paronychia	1			1	1		1			4
PTT, elevated		1								1
Rash	5	3		1	2		1	1		13
Thrombocytopenia		1								1

Abbreviation: PTT, partial thromboplastin time.

Safety

During the phase I component of this trial, 3 assessable patients were treated at the 250 mg/m^2 and 375 mg/m^2 dose levels of cetuximab in combination with erlotinib 100 mg. DLT were not encountered in these dose levels. Observed toxicities are described in Table 2. During the first 4 weeks of treatment, 5 patients experienced grade 1 fatigue, 2 patients had grade 1 AST/ALT elevation, and 3 patients had grade 1 rash. Grade 2 rash, grade 2 hypomagnesemia, and grade 2 AST/ALT elevation were experienced by 1 patient each. One of 3 patients treated with cetuximab 500 mg/m^2 in combination with erlotinib 100 mg had grade 3 AST and ALT elevation; therefore, this dose level was expanded to include 3 additional patients. No further DLTs were encountered at this dose level. Cetuximab 500 mg/m^2 was determined to be the recommended phase II dose.

During the phase II portion of the trial, 13 patients were treated with cetuximab 500 mg/m^2, including 6 patients who received treatment during the phase I component. All grade 2, 3, and 4 adverse events considered possibly, probably, or definitely related to study therapy for all dose levels are listed in Table 2. The most common grade 2, 3, and 4 toxicities were rash, fatigue, and hypomagnesemia experienced by 13 (68%), 12 (63%), and 14 (74%) patients, respectively. Median number of cetuximab doses, dose delays, and reductions are outlined in Table 3. Therapy was discontinued due to progression of

Table 3. Treatment delivery and efficacy

	500 mg/m^2 (n = 13)	375 mg/m^2 (n = 3)	250 mg/m^2 (n = 3)
Doses of cetuximab, median (range)	4 (2–15)	5 (4–6)	6 (4–6)
Patients requiring dose reductions, n (%)	4 (31)	3 (100)	0
Patients requiring dose delay, n (%)	4 (31)	3 (100)	1 (33)
Best response (RECIST)			
Partial response	0	0	0
Stable disease	11	3	3
Progression of disease	2	0	0

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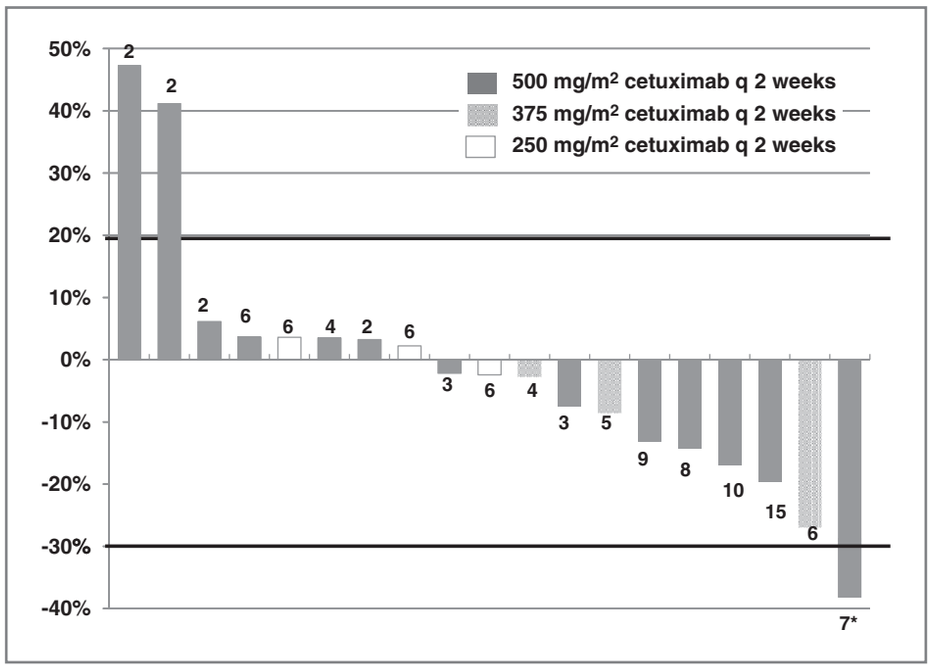

Figure 2. Best response of indicator lesions (RECIST). Numbers indicate number of doses of cetuximab given. A single patient (*) had greater than 30% tumor shrinkage but was found to have progression of extrathoracic disease prior to confirmatory scan.

disease in 13 of 19 patients (68%). Six of 19 (31%) patients discontinue treatment due to intolerable rash (of these 6 patients, 3 had evidence of progressive disease at off-study evaluation).

Efficacy

None of the 13 patients (0%; 95% CI, 0–25) had a radiographic partial response; 11 (85%; 95% CI, 0–25) had disease stabilization. Individual patient best radiographic responses are summarized in Figure 2. Median PFS and overall survival were 3 months and not reached (>6 months), respectively.

Discussion

EGFR tyrosine kinase mutations in exons 19 and 21 impart dramatic sensitivity to erlotinib and gefitinib. Despite the high frequency of radiographic response, patients develop progressive disease after a median of 12 months. Other than conventional cytotoxic chemotherapy, there are no proven therapeutic strategies for patients with acquired resistance to erlotinib or gefitinib. Laboratory and clinical data support that these tumors still depend on signaling through the EGFR pathway.

This is the first prospective study to evaluate combined EGFR targeted therapy using an EGFR monoclonal antibody together with erlotinib in patients with clinically defined acquired resistance to erlotinib. The safety profile for the combination was consistent with the individual safety profile of each drug and no unexpected toxicities occurred. The recommended phase II dose identified was the highest dose evaluated, cetuximab 500 mg/m^2 every 2 weeks and erlotinib 100 mg daily. Because the development of hypomagnesemia, rash, and fatigue at the recommended phase II dose did not occur during the initial treatment cycle, these events were not DLTs according to protocol. However, the relatively high incidence of these adverse events highlights the potential toxicities of combined EGFR inhibition. One third of the patients discontinued study therapy due to intolerable rash.

Combined treatment with cetuximab and erlotinib led to no confirmed radiographic partial responses in patients with acquired resistance to erlotinib. The addition of cetuximab to erlotinib is insufficient to overcome erlotinib resistance in *EGFR*-driven lung adenocarcinoma. Although no RECIST partial responses were seen, 85% (11 of 13) of patients had stable disease, the median PFS was 3 months, and there were objective tumor shrinkages suggesting that combined EGFR blockade may have clinical value. Although the combination of erlotinib and cetuximab led to stable disease in most patients, the absence of prolonged disease stabilization and the observed toxicities (31% of patients discontinued due to rash) make this combination unlikely to be of significant clinical benefit for patients with acquired resistance. *In vitro* data suggest that second-generation irreversible inhibitors that covalently bind *EGFR* (unlike gefitinib and erlotinib, which compete with ATP in a reversible manner) may be able to overcome T790M-mediated resistance. One such irreversible, dual EGFR and HER2 inhibitor, afatinib (BIBW2992), is currently in phase III study as initial treatment in patients with lung adenocarcinoma and primary *EGFR* mutations. Data in mice with L858R and T790M erlotinib-resistant lung tumors show that the combination of afatinib and cetuximab together, but neither agent alone, induced dramatic shrinkage of tumors, because together they efficiently

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depleted both phosphorylated and total EGFR (41). On the basis of these data, a phase I trial of afatinib with cetuximab for patients with acquired resistance to erlotinib is underway (clinicaltrials.gov NCT01090011).

Disclosure of Potential Conflicts of Interest

Y.Y. Janjigian has received research funding from Boehringer-Ingelheim and is a consultant for Genentech/Roche; C.G. Azzoli has received research funding from Genentech; M.G. Kris is a consultant for Lilly, Boehringer-Ingelheim and Pfizer; W. Pao is a consultant and patent holder with Molecular MD and a consultant for Lilly, Bristol-Myers Squibb and Symphony Evolution; V.A. Miller has received research funding from and is a consultant for Boehringer-Ingelheim, Genentech/Roche, OSI, Pfizer, and Lilly; G.J. Riely has received research funding from Bristol-Myers Squibb and is a consultant for Boehringer-Ingelheim and AstraZeneca.

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