Cetuximab Monotherapy in Patients with Advanced Non-small Cell Lung Cancer After Prior Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy

Joel W. Neal, MD, PhD, Rebecca S. Heist, MD, MPH,* Panos Fidias, MD,* Jennifer S. Temel, MD,* Mark Huberman, MD,† J. Paul Marcoux, MD,‡ Alona Muzikansky, PhD,§ Thomas J. Lynch, MD,‖ and Lecia V. Sequist, MD, MPH**

Introduction: Therapeutic agents directed against the epidermal growth factor receptor (EGFR) signaling pathway have been effective in the treatment of non-small cell lung cancer (NSCLC). Cetuximab is a monoclonal antibody against the EGFR receptor with antitumor activity in NSCLC. This study evaluated the efficacy of cetuximab monotherapy after prior treatment with an oral EGFR tyrosine kinase inhibitor (TKI).

Methods: Eligible patients had stage IIIB, IV, or recurrent NSCLC with progression on the oral EGFR TKIs gefitinib or erlotinib. Cetuximab was administered intravenously at 400 mg/m^2 on day 1 and then 250 mg/m^2 weekly until disease progression or unacceptable toxicity. The primary end point was response rate.

Results: Eighteen patients were enrolled. Patients were heavily pretreated with chemotherapy and TKIs (average number of treatments = 4.2). The response rate was 0/18 (0%), and 28% of patients had confirmed stable disease. Median progression-free survival was 1.8 months (95% confidence interval, 1.6–5.4 months), and median overall survival was 7.5 months (95% confidence interval, 2.2–19 months). Three patients harbored activating *EGFR* mutations, and one of them had stable disease for nearly 6 months on cetuximab. Common toxicities were mild and included fatigue, skin rash, and nausea/vomiting. Two patients developed interstitial lung disease, life threatening in one case.

Conclusions: Cetuximab monotherapy administered after prior EGFR TKI treatment in patients with advanced NSCLC does not yield clinical responses.

Key Words: Non-small cell lung cancer, Cetuximab, Epidermal growth factor receptor, Tyrosine kinase inhibitor.

(*J Thorac Oncol.* 2010;5: 1855–1858)

*Massachusetts General Hospital Cancer Center; †Beth Israel Deaconess Medical Center; ‡Dana-Farber Cancer Institute, §Department of Biostatistics, Massachusetts General Hospital, Boston, Massachusetts; and ‖Yale Cancer Center, New Haven, Connecticut.

Disclosure: Thomas J. Lynch, MD, has served as a paid consultant for Bristol-Myers Squibb and holds a patent in conjunction with Partners Healthcare for EGFR mutation testing.

Address for correspondence: Lecia V. Sequist, Massachusetts General Hospital Cancer Center, 55 Fruit Street, POB 212, Boston, MA 02114. E-mail: lvsequist@partners.org

ISSN: 1556-0864/10/0511-1855

Aberrant activation of the epidermal growth factor receptor (EGFR) tyrosine kinase occurs in a number of epithelial malignancies, including non-small cell lung cancer (NSCLC).[1] The signal network downstream of EGFR plays an important role in multiple tumorigenic processes, including cell cycle progression, angiogenesis, protection from apoptosis, and metastasis.

Two classes of EGFR-directed targeted therapies have demonstrated efficacy in patients with NSCLC. Cetuximab is a monoclonal antibody that binds with high affinity to EGFR, inducing tumor cell death by mechanisms including growth arrest, apoptosis, and antibody-dependent cell-mediated cytotoxicity. Cetuximab has modest single-agent activity in previously treated patients with advanced NSCLC, with a response rate of 4.5%, stable disease (SD) rate of 30%, and time to progression of 2.3 months.[2] In the first-line treatment of metastatic NSCLC, the addition of cetuximab to platinum-containing doublets improves overall survival (OS) by approximately 1 month.[3,4]

The second class of EGFR therapeutics includes the oral tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib, which extend survival by a median of 2 months in unselected, previously treated patients with NSCLC.[5,6] Tumors containing gain-of-function mutations in the *EGFR* gene are particularly sensitive to TKI therapy, and first-line EGFR TKI monotherapy is a viable alternative to chemotherapy in patients with advanced NSCLC harboring *EGFR* mutations.[7]

Preclinical observations had suggested that NSCLC cell lines have differential responses to EGFR TKI therapy and cetuximab,[8] and transgenic mice with inducible *EGFR-mutant* NSCLC responded to prolonged cetuximab treatment.[9] This study was designed to determine whether cetuximab monotherapy has activity in patients previously treated with an EGFR TKI and whether patients with *EGFR* mutations have a higher likelihood of response. Response was chosen for the primary end point to simplify a two-stage design, although progression-free survival (PFS) and OS were prespecified secondary end points.

METHODS

We recruited patients to this multicenter, single-arm, phase II clinical trial with Eastern Cooperative Oncology

Group performance status 0 to 2 and stage IIIB, IV, or recurrent NSCLC who were previously treated with erlotinib or gefitinib but failed treatment because of progression or drug intolerance. Patients with asymptomatic, stable brain metastases were eligible.

Patients received intravenous cetuximab, 400 mg/m^2, followed by weekly infusions of 250 mg/m^2. Four weekly treatments constituted one cycle, and CT scans were performed every two cycles to document response. A designation of partial response or SD required confirmation as defined by RECIST. All radiographs were centrally reviewed at Massachusetts General Hospital.

All patients were required to have an available tissue sample for *EGFR* mutation testing, which was performed centrally at a Clinical Laboratory Improvement Amendments-certified laboratory and involved extraction of genomic material from paraffin-embedded tissue, followed by polymerase chain reaction amplification and direct sequencing of exons 19 and 21 as previously described.[10]

The trial used a Simon two-stage design, which enrolled 18 patients in the first stage of accrual. The trial was to proceed to enroll 28 evaluable patients if 1 or more response was observed in the first group. This design provided a 57% chance of early termination if the true response rate was ≤3%. PFS (survival without disease progression or death) and OS were calculated using the Kaplan-Meier method.

The clinical trial protocol was approved and monitored by the local institutional review board at all sites, and all patients provided written informed consent. Data were compiled and analyzed centrally at Massachusetts General Hospital.

RESULTS

Eighteen eligible patients were enrolled in the first stage of the trial between October 2006 and March 2009. Patients were primarily women with heavily pretreated (average number of prior treatments = 4.2) adenocarcinoma (Table 1). Of three patients with tumors harboring *EGFR* mutations, all previously responded to TKI therapy (range, 6–21 months). The remaining patients had SD or progressive disease on prior TKI therapy, with a median treatment duration of 7 months.

After treatment with cetuximab, none of the patients met the criteria for a clinical response, but five patients (28%) had confirmed SD (median, 5.4 months). The remainder of the patients either had progressive disease or unconfirmed SD.

At the time of analysis, the median potential follow-up was 20 months and minimum follow-up was 12 months. No patients remain on treatment, but five patients were still alive. The median PFS is 1.8 months (95% confidence interval, 1.6–5.4 months) (Figure 1*A*), and the median OS is 7.5 months (95% confidence interval, 2.2–19 months) (Figure 1*B*).

Skin-related treatment related toxicity was the most common adverse event (Table 2). Serious events included interstitial lung disease, angina-like chest pain, headache, and shortness of breath/wheezing. One patient had a first-dose infusion reaction that precluded further treatment.

TABLE 1. Characteristics of Patients (n = 18) Treated with Cetuximab

	Patients, *n* (%)
Age (yr)	
Median	66
Range	49–87
Sex	
Male	4 (22)
Female	14 (78)
Smoking history	
Never	5 (28)
>10 pack-years	13 (72)
Brain metastases at enrollment	
No	14 (78)
Yes	4 (22)
Histology	
Adenocarcinoma	15 (83)
NOS	3 (17)
Activating *EGFR* mutation	3 (17)
Ethnicity	
Asian	1 (6)
Other	17 (94)
ECOG PS	
0	4 (22)
1	10 (56)
2	4 (22)
Number of prior systemic therapies	
1–2	1 (6)
3–4	8 (44)
5–6	9 (50)
Previous TKI	
Erlotinib	17[a] (94)
Gefitinib	3[a] (17)
Response to prior TKI (n = 16)	
Complete response	1[b] (6)
Partial response	2[b] (11)
Stable disease	8 (44)
Progressive disease	5 (28)

[a] Two patients received both erlotinib and gefitinib as previous therapy.
[b] These patients had *EGFR* mutations.
NOS, not otherwise specified; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status.

Three patients with *EGFR* mutations were treated with cetuximab. One of three had confirmed SD. The time to progression for these individuals was 1.1, 1.8, and 5.5 months and OS was 1.1, 4.5, and 14 months, compared with a median PFS of 1.8 months and OS of 6.6 months for all patients on the trial.

KRAS mutation status was also available for four patients. Of these, two were positive for *KRAS* mutations and two were wild-type. Three progressed at the 2-month follow-up scan, but one wild-type patient remained on cetuximab for 6 months.

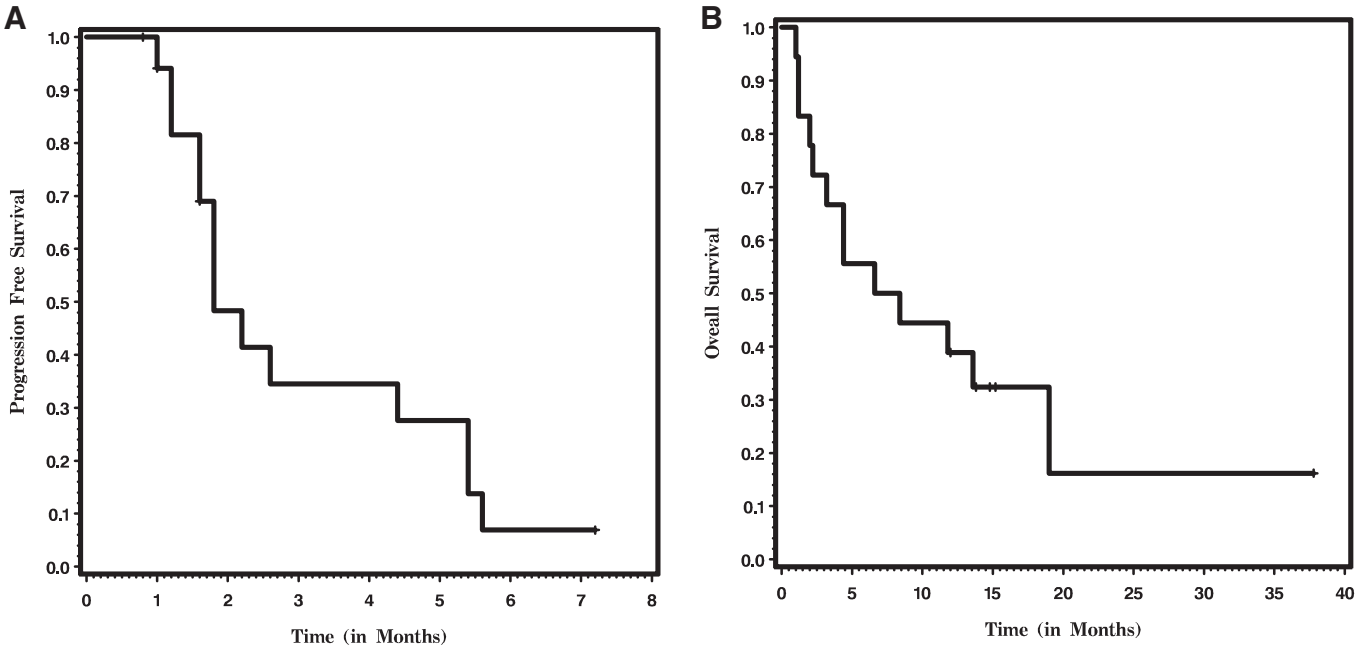

FIGURE 1. Kaplan-Meier curves for progression-free survival (*A*) and overall survival (*B*) among all treated patients.

TABLE 2. Treatment-Related Adverse Events, >10% Frequency or Clinically Significant

	Grade, *n* (%)				
Event	**1**	**2**	**3**	**4**	**Total**
Rash	6 (33)	2 (11)	0	0	8 (44)
Dry skin	5 (28)	0	0	0	5 (28)
Fatigue	2 (11)	2 (11)	0	0	4 (22)
Erythema	4 (22)	0	0	0	4 (22)
Cough	4 (22)	0	0	0	4 (22)
Pruritus	2 (11)	1 (6)	0	0	3 (17)
Nausea	3 (17)	0	0	0	3 (17)
Vomiting	3 (17)	0	0	0	3 (17)
Interstitial lung disease	0	0	1 (6)	1 (6)	2 (11)
Chest pain	1 (6)	0	1[a] (6)	0	2 (11)
Headache	1 (6)	0	1 (6)	0	2 (11)
Diarrhea	2	0	0	0	2 (11)
Wheezing	1 (6)	0	1 (6)	0	2 (11)
Hypersensitivity reaction	0	1[b] (6)	0	0	1 (6)

[a] Cetuximab was discontinued because of grade 3 angina possibly related to study treatment occurring 5 d after treatment.
[b] Cetuximab was discontinued because of hypersensitivity on initial infusion.

DISCUSSION

Cetuximab monotherapy demonstrated no responses, a SD rate of 28%, and PFS of 1.8 months in a population of patients previously treated with EGFR TKI therapy. Of note, the patient population in this study was heavily pretreated, possibly biasing toward a lower likelihood of response to any additional therapy. Despite this, our results are fairly similar to those previously reported in a phase II study of single-agent cetuximab in less-refractory patients.[2]

When this trial was initiated, it was hoped that patients with tumors harboring *EGFR* mutations may be more sensitive to cetuximab therapy as preclinical models suggested that cetuximab may be active against *EGFR* mutant cell lines. In addition, a published report described a patient with an exon 19 deletion mutation who responded to cetuximab before gefitinib or erlotinib therapy.[11] Among our three patients with *EGFR* mutations, we saw no responses. One patient with an exon 19 deletion and prior complete response to erlotinib lasting 10 months achieved SD on cetuximab for 6 months, which was one of the longest periods of benefit from treatment in our study. Furthermore, repeat biopsy of this patient's tumor after TKI therapy had demonstrated an acquired T790M resistance mutation. In preclinical work, mice harboring xenograft tumors containing an exon 19 deletion and T790M had dramatic tumor responses when treated with the combination of cetuximab and the irreversible EGFR TKI, BIBW2992.[12] Although concurrent EGFR blockade with cetuximab and a TKI may be challenging because of overlapping toxicities, clinical trials using such combinations and modeled after the preclinical models are underway in patients with acquired TKI resistance.[13,14]

Although cetuximab seems to be a modestly effective drug in combination with chemotherapy for first-line treatment of NSCLC, the search for predictive biomarkers has been disappointing. Biomarkers that have been tested include increased *EGFR* gene copy number, EGFR protein expression by immunohistochemistry, and *KRAS* mutations, but none have been validated in NSCLC.[3,4,15] Hopefully, future investigations will be able to identify an effective biomarker to help select patients most likely to respond to cetuximab and other anti-EGFR antibodies.

ACKNOWLEDGMENTS

Supported by BMS/ImClone, study number BMS CA225023.

REFERENCES

1. Herbst RS, Heymach JV, Lippman SM. Lung cancer. *N Engl J Med* 2008;359:1367–1380.
2. Hanna N, Lilenbaum R, Ansari R, et al. Phase II trial of cetuximab in patients with previously treated non-small-cell lung cancer. *J Clin Oncol* 2006;24:5253–5258.
3. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet* 2009;373:1525–1531.
4. Lynch TJ, Patel T, Dreisbach L, et al. Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099. *J Clin Oncol* 2010;28:911–917.
5. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123–132.
6. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005;366:1527–1537.
7. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–957.
8. Mukohara T, Engelman JA, Hanna NH, et al. Differential effects of gefitinib and cetuximab on non-small-cell lung cancers bearing epidermal growth factor receptor mutations. *J Natl Cancer Inst* 2005;97:1185–1194.
9. Ji H, Li D, Chen L, et al. The impact of human EGFR kinase domain mutations on lung tumorigenesis and in vivo sensitivity to EGFR-targeted therapies. *Cancer Cell* 2006;9:485–495.
10. Sequist LV, Joshi VA, Janne PA, et al. Epidermal growth factor receptor mutation testing in the care of lung cancer patients. *Clin Cancer Res* 2006;12(14 Pt 2):4403s–4408s.
11. Cho BC, Im CK, Park MS, et al. Phase II study of erlotinib in advanced non-small-cell lung cancer after failure of gefitinib. *J Clin Oncol* 2007;25:2528–2533.
12. Regales L, Gong Y, Shen R, et al. Dual targeting of EGFR can overcome a major drug resistance mutation in mouse models of EGFR mutant lung cancer. *J Clin Invest* 2009;119:3000–3010.
13. Ramalingam S, Forster J, Naret C, et al. Dual inhibition of the epidermal growth factor receptor with cetuximab, an IgG1 monoclonal antibody, and gefitinib, a tyrosine kinase inhibitor, in patients with refractory non-small cell lung cancer (NSCLC): a phase I study. *J Thorac Oncol* 2008;3:258–264.
14. Cetuximab in Patients with Lung Adenocarcinoma Receiving Erlotinib That Have Developed "Acquired Resistance" to Erlotinib. Available at: http://clinicaltrials.gov/ct2/results?term=NCT00716456. Accessed January 20, 2010.
15. Khambata-Ford S, Harbison CT, Hart LL, et al. Analysis of potential predictive markers of cetuximab benefit in BMS099, a phase III study of cetuximab and first-line taxane/carboplatin in advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:918–927.