Cetuximab for the Treatment of Advanced Bronchioloalveolar Carcinoma (BAC): An Eastern Cooperative Oncology Group Phase II Study (ECOG 1504)

Suresh S. Ramalingam, Ju-Whei Lee, Chandra P. Belani, Seena C. Aisner, Jill Kolesar, Craig Howe, Mario R. Velasco, and Joan H. Schiller

From Emory University, Winship Cancer Institute, Atlanta, GA; Dana-Farber Cancer Institute, Boston, MA; Penn State Cancer Institute, Hershey, PA; New Jersey Medical School, Newark, NJ; University of Wisconsin, Madison, WI; United Hospital, St. Paul, MN; Decatur Memorial Hospital, Decatur, IL; and University of Texas Southwestern Medical Center, Dallas, TX.

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Corresponding author: Suresh S. Ramalingam, MD, 1365 Clifton Rd NE, Rm C-3090, Atlanta, GA 30322; e-mail: suresh.ramalingam@emory.edu.

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ABSTRACT

Purpose

Inhibitors of the epidermal growth factor receptor (EGFR) tyrosine kinase have demonstrated modest anticancer activity in advanced bronchioloalveolar carcinoma (BAC). We conducted a phase II study to evaluate cetuximab for the treatment of advanced BAC.

Patients and Methods

Patients with advanced-stage pure BAC or adenocarcinoma with BAC features, fewer than two prior chemotherapy regimens, and Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 were eligible. Those with prior EGFR inhibitor therapy were excluded. Cetuximab was given as a weekly intravenous infusion at 250 mg/m² after an initial loading dose of 400 mg/m² in week 1. The primary end point was determination of response rate. *EGFR* and *KRAS* mutations were evaluated by pyrosequencing.

Results

Seventy-two patients were enrolled and 68 met eligibility requirements. Characteristics of patients included median age, 71 years; sex, 57% females; PS 0 or 1, 88% of patients; and smoking status, 19% never-smokers. Central pathology review confirmed the diagnosis in 45 of 49 available specimens. Approximately 50% of patients received more than two cycles of therapy (> 8 weeks). Skin rash was the most common toxicity (grade 3, 15%). The confirmed response rate was 7%, and stable disease was observed in 35%. The median survival and progression-free survival were 13 and 3.3 months, respectively. Only one of the six patients with an *EGFR* mutation and one of the seven patients with a *KRAS* mutation had a partial response.

Conclusion

Cetuximab was associated with modest efficacy in patients with advanced BAC, despite a low response rate. EGFR and KRAS mutations were not predictive of response to cetuximab.

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INTRODUCTION

Bronchioloalveolar carcinoma (BAC) represents a unique subset of non-small-cell lung cancer (NSCLC) characterized by distinct pathologic features and clinical behavior.¹ The incidence of BAC has increased in the past few decades,^{2,3} and it accounts for approximately 5% of all cases of NSCLC. By definition, BAC is characterized by a lepidic growth pattern without any evidence of stromal, vascular, or pleural invasion. These types of tumors are referred to as "pure" BAC. An additional 10% to 20% of the cases of NSCLC have "mixed" BAC that includes adenocarcinoma with BAC features or BAC with invasive features.⁴ In clinical terms, BAC tends to have a more indolent course with favorable

survival outcomes compared with other subtypes of NSCLC.⁵ BAC is also notable for its higher proportion of never-smokers compared with invasive NSCLC.⁶

For patients that present with localized disease, the outcomes for BAC are excellent following surgical resection.⁷ However, presentation as multifocal disease or at an advanced stage is common. The treatment options for patients with surgically unresectable BAC are limited. Systemic chemotherapy appears to be less effective against BAC than against adenocarcinoma or squamous cell carcinoma of the lung, though the evidence is nonconclusive and limited.⁸ A phase II study of paclitaxel as monotherapy in advanced BAC reported a response rate of 14% and a median survival of 12 months.⁹ Agents that

target the epidermal growth factor receptor (EGFR) have demonstrated promising results in patients with advanced BAC. A phase II study by West et al¹⁰ evaluated the anticancer effects of gefitinib as monotherapy in patients with advanced BAC. Six percent of the patients achieved a complete response with a total response rate of 17% in patients who had not received any prior therapy for advanced-stage disease. The overall survival rate at 3 years was 23%. In another phase II study,¹¹ erlotinib was associated with an objective response rate of 22% and a median survival of 17 months in advanced BAC. For patients with an EGFR mutation, the response rate was 83%. On the basis of these observations, EGFR tyrosine kinase inhibitors have emerged as a reasonable therapeutic option for advanced BAC.

Cetuximab is a chimeric monoclonal antibody against EGFR. It has modest activity as a single agent and has demonstrated improved survival when given in combination with chemotherapy in advanced NSCLC.^{12,13} Cetuximab causes internalization of the EGFR and thereby prevents recycling of the receptor.¹⁴ The Eastern Cooperative Oncology Group (ECOG) conducted a phase II study to evaluate the anticancer effects of cetuximab in patients with advanced BAC.

PATIENTS AND METHODS

Eligibility

Patients with histologic confirmation of BAC or adenocarcinoma with BAC features were eligible. The presence of stage IIIB (pleural or pericardial effusion) or IV disease, measurable disease, age ≥ 18 years, ECOG performance status of 0, 1, or 2, and a life expectancy of more than 3 months were other salient eligibility criteria. Patients had to meet the following laboratory parameters: leukocytes $\geq 3,000/\mu\text{L}$, absolute neutrophil count $\geq 1,500/\mu\text{L}$, platelet count $\geq 100,000/\mu\text{L}$, serum bilirubin within upper limit of institutional normal (ULN), serum AST and ALT within $2.5 \times \text{ULN}$, and serum creatinine within ULN. If the serum creatinine level was above ULN, the estimated creatinine clearance should be greater than $60 \text{ mL/min/1.73 m}^2$. Up to one prior chemotherapy regimen was allowed, but prior therapy with cetuximab or an EGFR tyrosine kinase was not allowed. Patients with untreated or unstable brain metastasis were ineligible. At least a 3-week interval from prior chemotherapy and a 2-week interval from prior radiotherapy must have elapsed before registration. Patients with a known allergic reaction to chimerized or murine monoclonal antibody therapy or those who had documented human antimouse antibodies were excluded. Patients with uncontrolled and serious intercurrent illness and pregnant or lactating women were ineligible. Women of child-bearing potential and sexually active men were required to use adequate contraception during and for 3 months after study therapy. Patients were required to sign a written informed consent form, and the study protocol was approved by the institutional review board of the participating institution.

Treatment Plan

Cetuximab was administered at a loading dose of 400 mg/m^2 intravenously over 120 minutes on week 1 and at 250 mg/m^2 over 60 minutes from week 2 onward. The doses were given every 7 days, but the time lapse between doses was no fewer than 5 days and no more than 7 days. Diphenhydramine hydrochloride 50 mg or a therapeutically equivalent antihistamine was given intravenously 30 to 60 minutes before the first dose of cetuximab. For subsequent doses of cetuximab, premedications were used at the discretion of the treating physician. Treatment cycles were repeated every 4 weeks. Cetuximab was continued until disease progression, unacceptable toxicity, or withdrawal of informed consent. If treatment was interrupted for four consecutive weeks, the patient was removed from the study.

Dose Modifications

All toxicities were graded according to the National Cancer Institute Common Terminology Criteria version 3.0. Before initiation of each new

cycle, patients were required to have an absolute neutrophil count $\geq 1,500/\mu\text{L}$, platelets $\geq 75,000/\mu\text{L}$, skin rash grade ≤ 2 , and resolution of other clinically relevant nonhematologic toxicities to grade 2 or lower with the exception of fatigue, anorexia, and alopecia.

Cetuximab was permanently discontinued for severe infusion reactions. Mild to moderate infusion reactions were managed by slowing the rate of infusion and continued use of antihistamine therapy. Dose reductions by 50% were done for mild to moderate reactions. If the event recurred, study therapy was discontinued permanently. For grade 3 skin rash, cetuximab infusion was held for 1 to 2 weeks and resumed when the symptoms improved. Recurrence of grade 3 rash required a dose reduction by decrements of 50 mg/m^2 . A maximum of two dose reductions were allowed for each patient. Appropriate supportive care measures consistent with optimal patient care were allowed.

Study Procedures

All patients underwent assessment history, physical examination, and performance status assessment at baseline and before initiation of each new cycle. Complete blood count with differential and serum chemistry tests were done at baseline, weeks 1 and 3 of the first cycle, and before initiation of each new cycle thereafter. Serum or urine pregnancy test was done in women of child-bearing potential before study entry. A detailed assessment of smoking status was performed at baseline and every 3 months for all patients enrolled onto the study with a standard questionnaire used by the ECOG thoracic subcommittee. Archived tumor specimens were requested for central verification of pathology and to conduct optional correlative science studies. Imaging studies were performed at baseline and during every two cycles of therapy to assess responses. Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 criteria were used for response assessment.

Mutation Analyses

EGFR and KRAS mutations were analyzed by standard published methods.^{15,16} Briefly, genomic DNA was extracted from paraffin-embedded tumor samples by marking a tumor area on a hematoxylin and eosin-stained slide and dissecting the tumor area with a sterile needle for subsequent DNA extraction. The polymerase chain reaction (PCR) region spanned exons 12 and 13 in the KRAS gene and exons 18 to 21 in the EGFR gene. The PCRs were performed with PCR master mix (Promega, Madison, WI) to amplify the target sequences. The sequence-specific primers were designed by PyroMark Assay Design software (Qiagen, Valencia, CA). Thermocycler conditions were as follows: initial denaturation at 95°C for 10 minutes, 54 cycles at 94°C for 30 seconds, 52°C for 30 seconds, and 72°C for 1 minute, followed by the final extension of 10 minutes at 72°C . The $5 \mu\text{L}$ of PCR products were visualized on a 2% agarose-ethidium bromide gel before pyrosequencing analysis. The biotinylated PCR products were immobilized on streptavidin-coated Sepharose beads (GE Healthcare, Piscataway, NJ), treated with different washes, and then analyzed with PyroGold reagents (Qiagen) by using specific sequencing primers for EGFR and KRAS on a PSQ 96 MA pyrosequencer (Qiagen).

Statistical Methods

The primary end point of the study was to determine the response rate with cetuximab in patients with advanced BAC. An estimated sample size of 59 eligible patients was required to detect a true response rate of 25% with a 90% power and type I error of 10% (one-sided). The secondary end points included determination of time to progression and overall survival and assessment of toxicity. Another important secondary objective was to conduct biomarker studies on baseline tumor tissue to correlate with efficacy.

All patients were required to have central verification of pathology to be eligible. Only 45 patients had tumor tissue available for verification. Therefore, two analyses were performed. The main analysis included the 41 patients with confirmed pathologic results, and the second analysis included all 68 eligible patients enrolled onto the study. Exact binomial 90% CIs were computed for the response rate. Fisher's exact test was used to evaluate differences in response rates between groups. The Kaplan-Meier estimates were used for event-time distributions. Overall survival and time to progression were compared between groups by using log-rank tests. Landmark analysis was performed to compare the effects of skin rash by grade on overall survival at 3 months and 6 months from registration to minimize lead-time bias. All tests were performed by using SAS 9.2 (SAS Institute, Cary, NC), and all *P* values are two-sided.

RESULTS

The study was open to accrual between August 2005 and December 2008. Of the 72 patients enrolled, four were ineligible because of baseline scan outside the allowed window, absence of measurable disease, stage IIIB disease without effusion, or prior therapy with two regimens, respectively. Tumor tissue was submitted for 49 patients; the diagnosis was confirmed by an independent pathologist in 45 of those patients. In the remaining four patients, inadequate sample, adenocarcinoma without BAC features, carcinoma not otherwise specified, and absence of tumor tissue were the reasons for ineligibility. A total of 68 patients received study therapy.

Patient Baseline Characteristics

Females accounted for more than 50% of the patients (Table 1). A majority of the patients had an ECOG performance status of 0 or 1. Approximately 70% had not received any prior systemic therapy. Nineteen percent of the patients were never-smokers. Eighteen percent of the patients had quit cigarette smoking after the diagnosis, and less than 10% were current smokers. Among women, 32% were never-smokers compared with only 6% among men. There were no

major differences in characteristics between the subgroup with confirmed pathology and the overall patient population. Given the confirmation of diagnosis in more than 90% of the patients with available tumor tissue, we believe that the data from the overall eligible patient groups are equally relevant. The results reported in the following sections were thus based on all 68 eligible and treated patients unless otherwise specified.

Treatment Delivery and Toxicity

The median number of cycles of therapy was two (range, one to 46). Three patients were still on therapy at the time of this report. Twenty-five patients received four or more cycles of therapy. Disease progression was the reason for discontinuation of treatment in approximately 80% of the patients. Six deaths were noted during the study of which five were attributed to disease progression. Cetuximab was tolerated well without any undue toxicity. Toxicities that were possibly, probably, or definitely related to treatment are reported in Table 2. Twenty-four patients had grade 3 toxicity and three patients had grade 4 toxicities. The most common toxicity was skin rash (15%; grade 3). Twenty-six percent of the patients had grade 1 or 2 hypomagnesemia. The overall toxicity profile was consistent with previous reports with cetuximab as monotherapy.

Table 1. Patient Baseline Characteristics

Characteristic	Pathology Confirmed (%) (n = 41)	All Eligible Patients (%) (n = 68)
Sex		
Male	49	43
Age, years		
Median	70	71
Range	26-90	26-90
ECOG performance status		
0	39	41
1	49	47
2	12	12
Race/ethnicity		
White	81	85
African American	17	13
Other	2	2
Stage IIIB to IV	56	57
Recurrent	44	43
Histology		
BAC unspecified	29	27
Mucinous BAC	34	32
Nonmucinous BAC	17	16
Adenocarcinoma with BAC	20	18
Prior therapy		
Chemotherapy	24	32
Radiotherapy	5	7
Percent weight loss in previous 6 months		
< 5	86	79
5-10	10	15
> 10	42	5
Smoking status		
Never-smoker	19	19
Former smoker	76	78
Current smoker	5	3

Abbreviations: ECOG, Eastern Cooperative Oncology Group; BAC bronchioloalveolar carcinoma.

Table 2. Adverse Events*

Toxicity	Adverse Events (%)†	
	Grade 1 to 2	Grade 3
Hypersensitivity reaction	6	1
Anemia	36	
Fatigue	54	8
Fever	11	
Weight loss	15	
Dry skin	24	3
Nail changes	14	
Pruritus	19	
Rash/desquamation	31	
Rash (acne/acneiform)	71	15
Hand-foot reaction	11	1
Anorexia	21	
Constipation	22	
Diarrhea	32	1
Stomatitis	15	
Nausea	31	1
Altered taste	13	
Vomiting	11	
Alkaline phosphatase	11	
Creatinine	11	1
Hyperglycemia	44	
Hypomagnesemia	26	
Hyperkalemia		1
Neuropathy-sensory	8	1
Headache	14	1
Cough	7	1
Dyspnea	7	6
Hypoxia		1
Pneumonitis		1
Worst degree	61	33

*Worst grade of toxicity reported in at least 10% of the patients or of grade 3 severities, deemed by the treating physician as treatment-related.
†Three grade 4 toxicities were reported (fatigue, creatinine, and thrombosis).

Table 3. Efficacy

Variable	Pathology Confirmed (n = 41)		All Eligible Patients (n = 68)	
	No.	%	No.	%
Partial response	3	7	5	7
Stable disease	17	42	24	35
Progression	14	34	27	40
Nonevaluable	7	17	12	18
Median overall survival, months	17.9		13	
Median time to progression, months	3.8		3.3	

Efficacy

Among the 41 patients with central confirmation of pathologic diagnosis, there were three partial responses (7%; 90% CI, 2% to 18%). Two had adenocarcinoma with BAC histology, and the third patient had nonmucinous BAC. For all treated patients (n = 68), there were five objective responses (7%; 90% CI, 3% to 15%; Table 3). There were no statistically significant differences in response rate based on sex, race, or smoking status. Although none of the patients with mucinous BAC experienced a partial response, the differences in response rate between patients with mucinous BAC and those with nonmucinous BAC were not statistically significant. At the time of analysis, 20 patients were still alive. The median follow-up was approximately 30

months. The median overall survival was 17.9 months (95% CI, 10.6 to 31.5 months) and 13 months (95% CI, 8 to 24 months) respectively for patients with pathology confirmation and all treated patients (Fig 1). Figure 2 represents the PFS outcomes with cetuximab therapy. There was no significant difference in survival based on smoking status or histologic subtypes.

A landmark analysis was conducted at 3 months and 6 months after initiation of study therapy to determine the association between skin rash and overall survival. For patients who developed a grade 3 skin rash by 3 months, the median survival was 37.4 months compared with 9.5 and 3.6 months for those with grade 1 or 2 rashes, respectively. These differences were not statistically significant because the actual number of events was small ($P = .16$). Similar trends were observed at the 6-month time point.

Mutation Analysis

Tumor samples from 42 patients were analyzed for *EGFR* and *KRAS* mutation. Two patients harbored the L858R mutation and four had the deletion mutation in exon 19. None of the samples had the T790 mutation. One objective response was noted in a patient with exon 19 deletion and none in those with L858R. The median time to progression (6 months v 3.7 months; $P = .052$) and overall survival (23.2 months v 17.9 months; $P = .85$) were favorable for patients with an *EGFR* mutation compared with those with *EGFR* wild-type, but the differences did not reach significance. Of the seven patients with the *KRAS* G12 mutation, one had a partial response.

Fig 1. Overall survival in (A) pathology confirmed patients and (B) all eligible and treated patients.

Fig 2. Time to progression (Prog) in (A) pathology confirmed patients and (B) all eligible and treated patients.

DISCUSSION

EGFR tyrosine kinase inhibitors are commonly used in the United States for the treatment of patients with advanced BAC.^{8,17} Erlotinib and gefitinib have both demonstrated response rates of 10% to 22% and a median survival of 13 to 17 months in patients with BAC.^{10,11,18} Our study was designed to evaluate the efficacy of targeting the external domain of the EGFR with cetuximab for the treatment of advanced BAC or adenocarcinoma with BAC. The overall response rate with cetuximab was low at 7%, but the median time to progression and overall survival were comparable to that of the EGFR tyrosine kinase inhibitors in advanced BAC. In general, responses are difficult to assess in BAC because this disease has unique radiographic features that make it hard to assess the anticancer effects of new agents in BAC.¹⁹ Even progression-free survival could be influenced by the varying course of disease based on individual subtypes of BAC and the frequency of imaging studies. We considered both of these factors in choosing the end points for this study. Another limitation of our study is that information on poststudy therapy was not collected. It is likely that many patients received an EGFR tyrosine kinase after progression that could have had an effect on the overall survival results.

An important strength of this study is that the pathologic diagnosis was confirmed by an independent pathologist in 45 of the 49 patients with available tumor tissue. We have reported the results separately for those with a confirmed diagnosis and for all treated patients. At the time of conception of this study, the presence of activating mutations in the *EGFR* was not known.²⁰ Therefore, *EGFR* and *KRAS* mutation analysis was done post hoc in nearly two thirds of the participants. Interestingly, only one of the six patients with an activating mutation in the *EGFR* experienced an objective response with cetuximab. This is in stark contrast to erlotinib, which was associated with a response rate of more than 80% in patients with BAC who had an *EGFR* mutation.¹¹ The differential sensitivity of *EGFR*-mutated NSCLC cells to tyrosine kinase inhibitors and monoclonal antibodies has been reported in a preclinical study.²¹ Compared with gefitinib, cetuximab had relatively minimal effect on inhibition of phosphorylation of downstream signals in vitro. The low response rate with cetuximab in patients with *EGFR* mutations in this study provides clinical affirmation for these preclinical observations. One patient with a *KRAS* mutation experienced a partial response in our study, which is also different from the tyrosine kinase inhibitors. These important observations highlight the differential mechanism(s) of anticancer effects between cetuximab and the tyrosine kinase inhibitors. Of note, *KRAS* mutations are frequently present in advanced BAC.

This study also substantiates the observation from prior studies that objective responses with EGFR inhibitors are not seen in mucinous BAC.¹⁷ Nearly a third of the patients enrolled onto this study had the mucinous subtype, among which there were no partial responses. It is notable that none of the patients with mucinous BAC who were treated with EGFR tyrosine kinase inhibitors on the three studies reported to date had a complete or partial response. Mucinous BAC tends to present with a multicentric pattern and lobar consolidation,

and it is often associated with debilitating symptoms.²² *EGFR* mutations are not frequent in mucinous BAC. It will be necessary to study new classes of anticancer agents for this subgroup of patients.

Though cetuximab has enhanced efficacy when used with chemotherapy, no predictive markers have been described for patient selection in NSCLC. A recent analysis of tumor specimens from the FLEX study²³ noted a correlation between efficacy with cetuximab and EGFR protein expression. A composite score of EGFR expression based on the number of positively stained cells and the intensity of staining was used and, accordingly, a score of ≥ 200 was predictive of a higher response rate with chemotherapy in combination with cetuximab. The correlation with progression-free survival and overall survival has not been reported. If this observation can be validated, it could potentially help with patient selection for cetuximab therapy. As was observed in the FLEX study,¹³ we also found a favorable correlation between the severity of skin rash and efficacy of cetuximab, though it was not statistically significant. The biologic reasons behind this observation are not entirely clear.

In conclusion, cetuximab has modest efficacy in the treatment of advanced BAC and is likely effective in a different molecular subset than the EGFR tyrosine kinase inhibitors.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception and design: Suresh S. Ramalingam, Chandra P. Belani, Joan H. Schiller

Provision of study materials or patients: Suresh S. Ramalingam, Chandra P. Belani, Jill Kolesar, Craig Howe, Mario R. Velasco

Collection and assembly of data: Suresh S. Ramalingam, Chandra P. Belani, Ju-Whei Lee, Seena C. Aisner, Jill Kolesar, Craig Howe, Mario R. Velasco, Joan H. Schiller

Data analysis and interpretation: Suresh S. Ramalingam, Ju-Whei Lee, Seena C. Aisner, Jill Kolesar, Craig Howe, Mario R. Velasco, Joan H. Schiller

Manuscript writing: All authors

Final approval of manuscript: All authors

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