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Determinants of Tumor Response and Survival With Erlotinib in Patients With Non–Small-Cell Lung Cancer

Román Pérez-Soler, Abraham Chachoua, Lisa A. Hammond, Eric K. Rowinsky, Mark Huberman, Daniel Karp, James Rigas, Gary M. Clark, Pedro Santabárbara, and Philip Bonomi

From the Montefiore Medical Center/Albert Einstein College of Medicine, Bronx; New York University School of Medicine, New York, NY; Institute for Drug Development, San Antonio, TX; Beth Israel Deaconess Medical Center and Deaconess Medical Center, Boston, MA; Dartmouth-Hitchcock Medical Center, Lebanon, NH; OSI Pharmaceuticals Inc, Boulder, CO; and Rush Cancer Institute, Chicago, IL.

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Román Pérez-Soler, MD, Department of Oncology, Hofheimer 100, Montefiore Medical Center/Albert Einstein College of Medicine, 111 E 210th St, Bronx, NY 10467; e-mail: rperezso@montefiore.org.

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ABSTRACT

Purpose
Erlotinib is a highly specific epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor. This phase II study of erlotinib in patients with HER1/EGFR-expressing non–small-cell lung cancer previously treated with platinum-based chemotherapy evaluated tumor response, survival, and symptom improvement.

Patients and Methods
Fifty-seven patients received an oral, continuous daily dose of 150 mg of erlotinib. Assessments of objective response used WHO and Response Evaluation Criteria in Solid Tumors criteria. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, supplemented with a lung cancer module, Quality of Life Questionnaire LC13, was used to measure health-related quality of life. Additional analyses were performed to identify predictors of response and survival.

Results
The objective response rate was 12.3% (95% CI, 5.1% to 23.7%). Responses were observed regardless of type or number of prior chemotherapy regimens. Median survival time was 8.4 months (95% CI, 4.8 to 13.9 months), and the 1-year survival rate was 40% (95% CI, 28% to 54%). Erlotinib therapy was associated with tumor-related symptom improvement. The drug was well tolerated; drug-related cutaneous rash and diarrhea were observed in 75% and 56% of patients, respectively. One patient experienced toxicity consisting of severe grade 3 rash and diarrhea. Time since diagnosis and good performance status were significant predictors of survival in a multivariate Cox proportional hazards model, whereas HER1/EGFR staining intensity was not. Additionally, survival correlated with the occurrence and severity of rash.

Conclusion
Erlotinib was active and well tolerated in this patient population, and further clinical development is clearly warranted. Cutaneous rash seems to be a surrogate marker of clinical benefit, but this finding should be confirmed in ongoing and future studies.

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INTRODUCTION

Several human malignancies are associated with aberrant or overexpressed epidermal growth factor receptor (HER1/EGFR).[1-3] HER1/EGFR tyrosine kinase serves as a potential target for therapeutic intervention in human tumors including ovarian, head and neck, breast, bladder, lung, and other squamous cell carcinomas.[4-7] Overexpression of HER1/EGFR has been directly related to chemoresistance and poor prognosis.[8-10] Several studies have shown that HER1/EGFR expression or overexpression is common in non–small-cell lung cancer (NSCLC) tumor samples.[9-17]

Erlotinib (Tarceva; OSI-774; OSI Pharmaceuticals, Melville, NY) is a potent and selective inhibitor of HER1/EGFR tyrosine kinase. It is a direct and reversible enzyme inhibitor in vitro, with a median inhibitory concentration of 2 nmol/L (0.79 ng/mL). Erlotinib reduces HER1/EGFR autophosphorylation in intact tumor cells with a median inhibitory concentration of 20 nmol/L (7.9 ng/mL), inhibits epidermal growth

factor-dependent cell proliferation at nanomolar concentrations, and blocks cell-cycle progression at the G_1 phase.[18]

Oral administration of erlotinib to mice reduced the level of HER1/EGFR autophosphorylation in human tumor xenografts by over 70% for more than 12 hours. Daily administration markedly inhibited the growth of HN5 human head and neck tumor and A431 squamous cell carcinoma xenografts in athymic mice, with near complete inhibition of tumor growth during a 20-day treatment regimen at the highest doses.[19]

In two phase I erlotinib dose-escalation studies in patients with advanced solid malignancies,[20] 14 patients achieved stable disease. The most common adverse events were diarrhea and rash, regardless of dose and schedule. Diarrhea was considered the dose-limiting adverse event. The maximum-tolerated dose and recommended phase II dose was 150 mg once daily on a continuous dosing schedule.

Results from pharmacokinetic studies showed that erlotinib is highly protein bound in humans (92% to 95%). The primary route of metabolism is oxidation by the hepatic cytochromes CYP3A4 and CYP3A5 and the pulmonary cytochrome CYP1A1. A potential for drug-drug interaction exists when erlotinib is coadministered with drugs that are highly protein bound or are CYP3A4 inhibitors or inducers.

The high frequency of overexpression of HER1/EGFR in NSCLC provides a scientific rationale for evaluating the therapeutic effect of erlotinib in this tumor type. In addition, there is a clear need for new therapeutics to treat patients with NSCLC, especially those patients with advanced disease who have a poor prognosis after failure of platinum-based chemotherapy. The majority of these patients will not benefit from additional chemotherapy, including taxane regimens. The current study was planned to estimate the objective tumor response rate of erlotinib administered as a single agent to patients with advanced (stage IIIB or IV) or recurrent metastatic HER1/EGFR-positive NSCLC who were previously treated with platinum-based combination chemotherapy. Secondary objectives were to estimate the stable disease rate, duration of response, time to disease progression, overall and 1-year survival, health-related quality-of-life (HRQOL) outcomes, and safety profile of erlotinib in this population.

PATIENTS AND METHODS

Eligibility Criteria

The study population included male and female patients 18 years of age or older. The main criteria for inclusion were documented stage IIIB or IV advanced or recurrent metastatic NSCLC, disease progression or relapse after platinum-based therapy, measurable disease, and documentation of HER1/EGFR positivity. Additional criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and adequate bone marrow, hepatic, and renal function (total bilirubin and creatinine $\leq 1.5 \times$ the upper limit of normal). Patients with brain metastases were eligible if they were clinically stable for at least 8 weeks.

Procedures Performed at Screening

The procedures performed at screening included a complete medical and surgical history, standard laboratory studies, ECG, pregnancy test with a negative result, tumor assessment, determination of HER1/EGFR status by immunohistochemistry in a tumor specimen conducted by a central laboratory (IMPATH, Los Angeles, CA), with HER1/EGFR positivity defined as more than 10% of cells staining positive, and administration of an HRQOL questionnaire. All patients gave written informed consent in accordance with policies of local human subjects committees before screening and initiation of therapy.

Procedures Performed During the Study

Procedures that were to be completed at weeks 2, 4, 6, and 8, every 4 weeks throughout the study, and at the time of study discontinuation included an interval history and reassessment of performance status, brief physical and skin examination, weight, and vital signs, complete blood count with differential and platelet count, blood biochemistry, and urinalysis. Ophthalmologic evaluations were to be repeated after 4 weeks of erlotinib therapy, within 2 weeks after any dose escalation, and at the time of study discontinuation only if a change from baseline had been detected with subsequent examinations.

Treatment Plan

Patients received erlotinib at an initial dose of 150 mg in a tablet formulation supplied by the sponsor (OSI Pharmaceuticals) that was self-administered orally once daily on a continuous basis. The dose was taken in the morning with up to 200 mL of water. The dose could be increased to 200 mg/d in patients who had received at least 4 weeks of continuous dosing at 150 mg/d and did not experience any drug-related adverse events during the previous 4-week cycle. The dosage was to be decreased in 25- or 50-mg decrements if the patient experienced drug-related ocular toxicities of any National Cancer Institute Common Toxicity Criteria grade, had any drug-related adverse events subjectively considered intolerable, had any Common Toxicity Criteria $\geq$ grade 3 drug-related adverse events not controlled with optimal supportive medication, or had undergone dose reduction for a drug-related adverse event that did not improve by at least one grade level to less than grade 3 within 2 weeks. Therapy could be continued after dose reduction to the minimum daily dose of 25 mg despite drug-related toxicity if the investigators and sponsor felt it was in the patient's interest.

Erlotinib treatment was planned for a minimum of 8 weeks and was to continue for a maximum of 52 weeks unless disease progression or unmanageable toxicity occurred. Patients with stable or responding disease for whom additional therapy beyond 52 weeks was deemed to be of potential benefit could continue erlotinib.

Tumor Measurements

Measurements of disease sites by clinical examination and radiographic imaging studies (x-ray, computed tomography scan, and magnetic resonance imaging) were collected at baseline before erlotinib therapy. The same methods were used every 8 weeks during the study to assess response. If a patient achieved a complete or partial response, tumor measurements were repeated 4 weeks later to confirm the response.

HRQOL

HRQOL was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, version 3.0.[21] An additional lung cancer module, Quality of Life Questionnaire LC13, was used and is composed of 13 items; it is intended for use among a wide range of lung cancer patients varying in disease stage and treatment modality. Four additional questions were added to assess the effect of any rash, skin pain, and itching, and their impact on daily activities. These four questions were combined into a single rash score.

The HRQOL questionnaire was administered at baseline, every 2 weeks during the first 2 months and monthly thereafter, at the end of study, and at the 1-month and 3-month follow-up visits. The questionnaire was to be completed during office visits before any other evaluations or assessment of adverse events. Changes in HRQOL scores during the study were compared with the baseline score.

Criteria for Evaluation of Efficacy

The primary efficacy variable was the overall response rate, which was defined as the percentage of patients with complete or partial responses. Responses were determined by the investigators according to WHO criteria.[22]

Evaluation of the objective tumor response was performed every 8 weeks during treatment. Stable disease, duration of overall response, time to progression, and survival were assessed at 2-week intervals for the first 2 months, every 4 weeks until study discontinuation, and at 1-month and 3-monthly intervals after treatment. Patients who met the criteria for complete or partial response had their response confirmed at least 4 weeks after the first determination of response. In addition, responses were also evaluated by the sponsor (OSI Pharmaceuticals) according to Response Evaluation Criteria in Solid Tumor (RECIST) criteria.[23]

Statistical Analysis

This was a single-arm, open-label, multicenter phase II study. A Gehan two-stage design was used to determine sample size.[24] It was anticipated that a total of 37 patients would be enrolled to ensure that 33 patients would be fully assessable for response. With 33 patients, the response rate of interest (10%) would be estimated with a maximum SE of 9%. A total of 57 patients were accrued to compensate for patients who had early progression and/or death before completing 8 weeks of study therapy. All 57 patients were included in all efficacy and safety analyses. The parameters of interest were estimated and presented with their 95% CIs using exact methods. All time-to-event variables, including duration of response and progression-free and overall survival, were analyzed using Kaplan-Meier product-limit survival estimates. Pretreatment characteristics were analyzed in univariate and multivariate logistic regression models for their ability to predict objective response and in univariate and multivariate Cox proportional hazards models for their ability to predict survival. Multivariate models were constructed using stepwise variable selection techniques. Changes in HRQOL from baseline, including impact of disease-related symptoms and rash, were evaluated using paired *t* tests. All analyses were performed using SAS/STAT User's Guide version 8.2 for Windows (SAS Institute, Cary, NC).

RESULTS

A total of 84 patients were screened for the study; 57 were enrolled and treated with erlotinib. The most common reasons that screened patients were not enrolled onto the study were HER1/EGFR status (eight patients were negative, one was too weak, and five had no tissue specimens available) and rapid deterioration (four patients). The 57 patients were accrued from January 25, 2000, until February 14, 2001. All patients were assessable for tumor response and toxicity. Table 1 shows the characteristics of the patient population. The median age was 62 years (range, 31 to 83

Table 1. Summary of Baseline Patient and Disease Characteristics

Demographic and Disease Characteristic	No. of Patients (N = 57)	%
Sex		
Female	34	59.6
Male	23	40.4
Race		
White	52	91.2
Black	2	3.5
Hispanic	2	3.5
Asian	1	1.8
Age		
31-39 years	3	5.3
40-64 years	33	57.9
65-69 years	7	12.3
≥ 70 years	14	24.6
ECOG performance status		
0	6	10.5
1	44	77.2
2	7	12.3
Smoking classification		
Smoker	5	8.8
Ex-smoker	42	73.7
Never smoked	10	17.5
NSCLC stage		
IV	48	84.2
IIIB	9	15.8
Histologic classification		
Adenocarcinoma	35	61.4
Large cell	11	19.3
Squamous cell	9	15.8
NOS	2	3.5
Pathologic grade		
Poorly differentiated	24	42.1
Moderately differentiated	18	31.6
Well differentiated	8	14.0
Not assessable/not available	7	12.3
HER1/EGFR expression		
Strong	32	56.1
Weak to strong	19	33.3
Weak	6	10.5
HER1/EGFR stain		
10-19% cells	4	7.0
20-39% cells	17	29.8
40-59% cells	9	15.8
60-79% cells	6	10.5
80-100% cells	21	36.8

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non–small-cell lung cancer; NOS, not otherwise specified; HER1/EGFR, epidermal growth factor receptor.

Table 2. Summary of Previous Therapy for NSCLC

Characteristic	No. of Patients (N = 57)	%
Prior therapy for NSCLC		
Chemotherapy	57	100.0
Surgery	51	89.4
Radiation therapy, primary/metastatic	42	73.7
Hormonal/immunologic therapy	5	8.7
Time from initial diagnosis to erlotinib therapy		
< 6 months	5	8.8
6-12 months	16	28.1
> 12 months	36	63.2
Median, months	17.7	
Range, months	4.2-136.6	
No. of prior chemotherapy regimens		
1	10	17.5
2	24	42.1
3 or more	23	40.4
Median, No. of prior regimens	2	
Range, No. of prior regimens	1-8	
No prior platinum therapy	2	3.5
Prior platinum-based treatment	55	96.5
Prior docetaxel treatment	15	26.3
Time from last regimen to erlotinib therapy		
< 6 months	44	77.2
6-12 months	8	14.0
> 12 months	5	8.8
Median, months	3	
Range, months	0.5-26	

Abbreviation: NSCLC, non–small-cell lung cancer.

years), and the majority of patients (63%) had been diagnosed with NSCLC more than 12 months before study enrollment. The median time from initial diagnosis to study entry was 17.7 months (range, 4 to 137 months). The advanced stage of disease in these patients was characterized by multiple sites of distant metastases and the presence of lung cancer signs and symptoms at baseline. Fifty-four patients (95%) reported symptoms at baseline, including fatigue (67%), dyspnea (61%), and cough (60%).

Before study entry, the patients had received various therapies (Table 2). Eighty-two percent of patients had received two or more chemotherapy regimens. Fifteen patients (26%) had received prior docetaxel. All but two patients had been treated with at least one platinum-based combination chemotherapy regimen. One of the two patients who had not received platinum therapy had been treated with gemcitabine-based combinations, and the other patient had been treated with two regimens of paclitaxel. The majority of patients (44 of 57 patients, 77%) had documented disease progression during or within 6 months of their last chemotherapy regimen.

Tumor Response and Survival

Table 3 lists the antitumor response data. Two patients achieved a complete response, and five had a partial response, as determined by both WHO and RECIST criteria. The objective response rate (complete + partial response) was 12.3% (95% CI, 5.1% to 23.7%). On the basis of RECIST criteria, 22 patients (39%) had stable disease and 28 patients (49%) had disease progression as their best tumor response. The number of prior chemotherapy regimens had no effect on response rates (12.8% for patients with two or more prior chemotherapy regimens *v* 12.3% for the whole group). One of the seven responders had not received prior platinum therapy; this 83-year-old patient, who had pre-existing neuropathy contraindicating platinum therapy, had previously received two gemcitabine-based combinations, one of which included docetaxel. Of the 15 patients previously treated with docetaxel, four (27%) achieved complete or partial responses, and an additional five (33%) had stable disease. Of the 44 patients with documented disease progression within 6 months of their last chemotherapy treatment, three (7%) subsequently achieved a partial response with erlotinib, and 16 (36%) had stable disease.

Thirty-five patients enrolled had adenocarcinoma, four of whom responded to therapy (11.4%; one complete and three partial responses). Of the remaining 22 patients,

Table 3. Response to Erlotinib

Response	Investigator Best Response (WHO criteria)		Sponsor Best Response (RECIST criteria)	
	No. of Patients	%	No. of Patients	%
CR	2	3.5	2	3.5
PR	5	8.8	5	8.8
Stable disease	20	35.1	22	38.6
Progressive disease	28	49.1	28	49.1
Not assessable	2	3.5	—	—
Overall response rate, CR + PR	7	12.3	7	12.3
95% CI, %	5.1 to 23.7		5.1 to 23.7	

Abbreviations: RECIST, Response Evaluation Criteria in Solid Tumor; CR, complete response; PR, partial response.

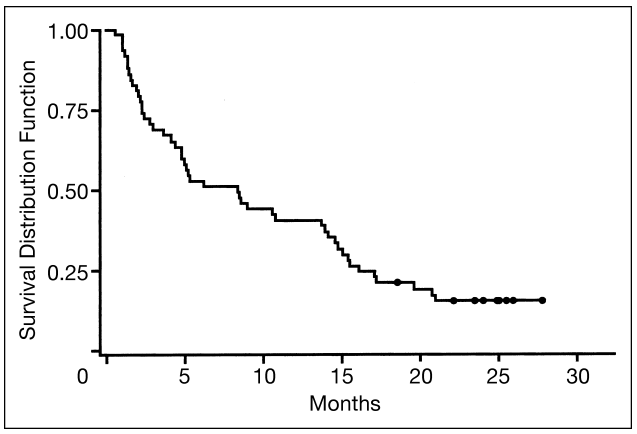

Fig 1. Overall survival of patients treated with erlotinib. Bullets represent patients still alive at time of analysis.

11 had large-cell carcinoma, nine had squamous cell carcinoma, and two were not specified; three patients responded to therapy (13.6%), two with large-cell carcinoma (one complete and one partial response) and one with squamous cell carcinoma (partial response). Four of the seven responding patients had adenocarcinoma (one complete response and three partial responses). Histologies were not further classified by subtype; specifically, BAC or BAC-like features were not characterized.

The median duration of response was 19.7 weeks (range, 11.7 to 80.3 weeks). Progression-free survival was measured from the first erlotinib administration to the date of disease progression, start of subsequent anticancer treatment, death, or date of last contact, whichever occurred first. With five patients censored in the analysis, the median progression-free survival time was 9 weeks (95% CI, 8 to 15 weeks). With nine patients still alive and censored in the analysis, the median overall survival time was 8.4 months (95% CI, 4.8 to 13.9 months), and the 1-year survival rate was 40% (95% CI, 28% to 54%; Fig 1).

Determinants of Tumor Response and Survival

Several pretreatment characteristics were analyzed in univariate and multivariate logistic regression models for their ability to predict the objective response rate. Table 4 shows the results of these analyses. Time from last chemotherapy was the only pretreatment characteristic that significantly predicted the objective response rate in the multivariate analysis ($P = .033$), although time since initial diagnosis was marginally predictive ($P = .086$).

The same pretreatment characteristics were analyzed in univariate and multivariate Cox proportional hazards models for their ability to predict survival (Table 5). Time since initial diagnosis and ECOG performance status were the only pretreatment characteristics that predicted survival in the multivariate model.

Patients previously treated with docetaxel as second-line therapy had a higher objective response rate compared with the entire group (26.7% *v* 12.3% overall, respectively), a similar median survival time of 8.6 months (95% CI, 2.2 to 20.8 months), and a 1-year survival rate of 47% (95% CI, 21.3% to 73.4%).

Exploratory analyses were conducted to investigate any potential relationship between rash and clinical outcomes. For these analyses, rash was defined as MedDRA (Medical Dictionary for Regulatory Activities, version 5.0; MedDRA MSSO, Reston, VA) codes that contain the terms rash, dermatitis, or acne. Rash was experienced by all seven patients who had an objective response and by 21 (95%) of 22 patients who had stable disease, but only 15 (54%) of 28 patients (54%) who had progressive disease experienced rash (data not shown). Thus, rash was necessary but was not a sufficient condition for tumor response in this study.

Table 4. Univariate and Multivariate Logistic Regression Analyses to Predict Response (CR + PR)

Factors	Univariate *P*	Multivariate *P*	OR	95% CI
Factors in the final model				
Time from last chemotherapy < 6 *v* ≥ 6 months	.021	.033	6.1	1.2 to 32.0
Factors not in the final model				
Time since initial diagnosis, < 12 months *v* ≥ 12 months	.031	.086		
HER1/EGFR staining intensity, weak, weak/strong, strong	.28	.19		
Stage of disease, IIIB *v* IV	.22	.28		
Sex, male *v* female	.50	.39		
No. of prior chemotherapy regimens, 1 *v* ≥ 2	.81	.50		
Age, > 70 *v* ≤ 70 years	.50	.65		
Histology, adenocarcinoma *v* other	.80	.79		
ECOG performance status, 0, 1, 2	.34	.90		

Abbreviations: CR, complete response; PR, partial response; OR, odds ratio; HER1/EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group.

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