Approval Summary for Erlotinib for Treatment of Patients with Locally Advanced or Metastatic Non–Small Cell Lung Cancer after Failure of at Least One Prior Chemotherapy Regimen

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Abstract

Purpose: To describe the Food and Drug Administration (FDA) review and approval of erlotinib (Tarceva, OSI Pharmaceuticals, Melville, NY) for treatment of patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen.

Experimental Design: The FDA reviewed raw data in electronic format from a randomized controlled clinical trial comparing erlotinib with placebo in patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

Results: Patients were randomized in a 2:1 ratio (erlotinib, $n = 488$ and placebo, $n = 243$). Erlotinib was superior to placebo for survival, progression-free survival, and tumor response rate. Exploratory analyses indicate that epidermal growth factor receptor status may be an important predictor of the erlotinib survival effect. Rash (75% versus 17%) and diarrhea (54% versus 18%) in the erlotnib and placebo group respectively were the most common adverse events. Severe rash occurred in 9% and severe diarrhea in 6% of erlotinib-treated patients and each resulted in study discontinuation in 1% of patients. Dose reductions were required for 10% of patients with rash and 4% of patients with diarrhea.

Conclusions: On November 18, 2004, the FDA granted erlotinib regular approval for treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. The applicant has committed to conduct post-marketing clinical trials to assess further the effect of epidermal growth factor receptor expression, measured with immunohistochemical staining, on erlotinib treatment effect.

Lung cancer is the leading cause of cancer death in both men and women in the United States (1). Initial therapy for advanced non–small lung cancer (NSCLC) is systemic chemotherapy with a two-drug combination regimen that often includes a platinum. Docetaxel and pemetrexed are approved by the Food and Drug Administration (FDA) for use as the second-line chemotherapy. Recently, the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor gefitinib was granted FDA-accelerated approval under subpart H for treatment of advanced NSCLC after failure of both platinum-based and docetaxel chemotherapy, based on a response rate of ~10% in single-arm clinical trials.

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Erlotinib (Tarceva, OSI Pharmaceuticals, Melville, NY) inhibits EGFR tyrosine kinase autophosphorylation by inhibition of the intracellular domain. Studies in cell lines and enzyme assays have both shown that erlotinib inhibits EGFR at concentrations significantly lower than those needed to inhibit *c-src* and *v-abl*. Whereas erlotinib was more selective for EGFR tyrosine kinase than it was for several other tyrosine kinases tested, several other tyrosine kinases in the same family as EGFR were not tested. Although erlotinib seems rather selective for EGFR, insufficient data exist to make a definitive decision regarding selectivity (2–4).

Chemistry and Toxicology

Erlotinib hydrochloride is a quinazolinamine with the chemical name *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine. Erlotonib is formulated as immediate release tablets and is available in three strengths, containing erlotinib hydrochloride (27.3, 109.3, or 164 mg) equivalent to 25, 100, or 150 mg of erlotinib.

The general toxicology of erlotinib has been examined in a wide range of laboratory animals: mouse, rat, dog, and monkey

using the i.v. and oral routes of administration. The primary toxicities seen were gastrointestinal (emesis and loose stool), hepatobiliary (increased bilirubin), and renal (blood in urine).

Clinical Pharmacology

Bioavailability of erlotinib following a 150-mg oral dose is about 60% and peak plasma levels occur 4 hours after dosing. Food increases bioavailability substantially, to almost 100%. Following absorption, erlotinib is ~93% protein bound to albumin and α-1 acid glycoprotein. Erlotinib has an apparent volume of distribution of 232 liters.

A population pharmacokinetic analysis in 591 patients receiving single-agent erlotinib showed a median half-life of 36.2 hours. Time to reach steady-state plasma concentration would therefore be 7 to 8 days. No significant relationships of clearance to patient age, body weight, or gender were observed. Smokers had a 24% higher rate of erlotinib clearance. Following a 100-mg oral dose, 91% of the dose was recovered: 83% in feces (1% of the dose as intact parent) and 8% in urine (0.3% of the dose as intact parent).

In vitro assays of cytochrome *P*450 metabolism showed that erlotinib is metabolized primarily by CYP3A4 and to a lesser extent by CYP1A2 and the extrahepatic isoform CYP1A1. Pretreatment with the CYP3A4 inducer rifampicin decreased erlotinib AUC by about two thirds. Thus, concomitant treatments known to induce CYP3A4 activity should be avoided. If such an alternative treatment is unavailable, an erlotinib dose of >150 mg should be considered. If the erlotinib dose is adjusted upward, the dose will need to be reduced upon discontinuation of rifampicin or other inducers. Cotreatment with the potent CYP3A4 inhibitor ketoconazole increases erlotinib AUC by two thirds. In patients who are being concomitantly treated with a strong CYP3A4 inhibitor, a dose reduction should be considered should severe adverse reactions occur.

No data are currently available regarding the influence of hepatic dysfunction and/or hepatic metastases on the pharmacokinetics of erlotinib. As *in vitro* and *in vivo* evidence suggest that erlotinib is cleared primarily by the liver, caution should be used when giving erlotinib to patients with hepatic impairment. Dose reduction or interruption of erlotinib should be considered should severe adverse reactions occur.

Less than 9% of a single dose is excreted in the urine. No clinical studies have been conducted in patients with compromised renal function.

Patients and Methods

Patients. Patients had stage IIIB or IV NSCLC and had failed one or two prior chemotherapy regimens for locally advanced or metastatic disease.

Design. A total of 731 patients were randomized in a 2:1 ratio between erlotinib 150 mg orally daily or placebo. Patients were stratified at enrollment by center, number of prior regimens, prior platinum therapy, best response to prior therapy, and Eastern Cooperative Oncology Group (ECOG) performance status. This multicenter (n = 82 institutions), multinational (n = 17 countries) trial was conducted by the National Cancer Institute of Canada Clinical Trials Group in collaboration with OSI Pharmaceuticals, Inc. (5).

Efficacy end points. The primary end point was survival. Secondary end points were tumor response, tumor response duration, progression-free survival, and quality of life (assessed by patient reported symptoms on the European Organization for Research and Treatment of Cancer QLQ-C30 and QLQ LC-13 questionnaires). The expression of epidermal growth factor receptor levels at diagnosis was correlated with outcomes and response to treatment.

Table 1. Summary of patient baseline characteristics

Characteristics	Erlotinib (n = 488), n (%)	Placebo (n = 243), n (%)
Gender		
Female	173 (35)	83 (34)
Male	315 (65)	160 (66)
Age (y)		
18-39	6 (1)	5 (2)
40-64	293 (60)	148 (61)
≥65	189 (39)	90 (37)
Race		
Caucasian	379 (78)	188 (77)
Black	18 (4)	12 (5)
Asian	63 (13)	28 (12)
Other	28 (5)	15 (6)
ECOG performance status		
0	64 (13)	34 (14)
1	256 (52)	132 (54)
2	126 (26)	56 (23)
3	42 (9)	21 (9)
Weight loss in previous 6 mos (%)		
<5	320 (66)	166 (68)
5-10	96 (20)	36 (15)
>10	52 (11)	29 (12)
Unknown	20 (4)	12 (5)
Smoking history		
Never smoked	104 (21)	42 (17)
Current or ex smoker	358 (73)	187 (77)
Unknown	26 (5)	14 (6)
Histologic classification		
Adenocarcinoma	246 (50)	119 (49)
Squamous	144 (30)	78 (32)
Undifferentiated large cell	41 (8)	23 (9)
Mixed non – small cell	11 (2)	2 (<1)
Other	46 (9)	21 (9)

Statistical methods. The primary survival analysis was survival time, defined as time from randomization to death, using the log-rank test stratified by the randomization stratification factors (number of prior regimens, prior platinum therapy, best response to prior therapy, and ECOG performance status). Median survival was estimated using Kaplan-Meier estimates and the 95% confidence interval (95% CI) was computed using the method of Brookmeyer and Crowley. No interim efficacy analysis was conducted in this study.

Analysis of a secondary end point, progression-free survival defined as the time from randomization to the first observation of disease progression or death due to any cause, was conducted using the stratified log-rank test. Response rate was estimated as the proportion of patients evaluable for response who met the criteria of complete or partial response. The Cochran-Mantel-Haenzel test was used to compare tumor response rates between the two treatment arms. Patient reported outcomes were measured using European Organization for Research and Treatment of Cancer QLQC30 and QLQ-LC13 questionnaires, given at baseline and every 4 weeks while on the study. The

protocol specified analysis was to use ANOVA for repeated measures for domains represented by aggregate scores. The statistical analysis plan included analysis of time from randomization to deterioration in three symptoms: cough, dyspnea, and pain. A 10% worsening from baseline score was considered deterioration.

Results

Baseline characteristics of patients

Summaries of baseline patient characteristics are shown in Tables 1 and 2. Treatment groups are well balanced. Half of the patients had adenocarcinoma. About two thirds of the patients were male. Sixty-seven percent of patients had a baseline ECOG performance status of 0 or 1, 23% had a baseline ECOG performance status of 2, and 9% had a baseline ECOG performance status of 3. Fifty percent of the patients had received only one prior chemotherapy regimen and about 50% had received two prior chemotherapy regimens. About three quarters of the patients were known to have smoked at some time.

Survival by treatment

Survival was significantly longer in the erlotinib group, with a median survival of 6.7 and 4.7 months in the erlotinib and placebo groups, respectively (Fig. 1). The adjusted hazard ratio (HR) for death in the erlotinib group relative to the placebo group (erlotinib/placebo) was 0.73 ($P < 0.001$), using the log-rank test stratified for the four prerandomization stratification factors. One-year survival was 31.2% and 21.5% in the erlotinib and placebo groups, respectively. Survival data were relatively complete with 80% of study patients dead.

Survival in subgroups: exploratory analyses

The subgroup analyses should be interpreted with caution. The CIs associated with the HRs are large and often include 1.

Table 2. Summary of previous therapy for NSCLC

	Erlotinib (n = 488), n (%)	Placebo (n = 243), n (%)
Previous therapy		
Chemotherapy	488 (100)	243 (100)
Surgery	487 (100)	242 (100)
Radiation	264 (54)	143 (59)
Hormonal therapy	1 (<1)	1 (<1)
Other prior therapy	2 (<1)	2 (<1)
No. prior chemotherapy		
Regimens		
1	243 (50)	121 (50)
2	238 (49)	119 (49)
3	7 (1)	3 (1)
Prior platinum therapy		
No	34 (7)	19 (8)
Yes	454 (93)	224 (92)
Prior taxane therapy		
No	311 (64)	153 (63)
Yes	177 (36)	90 (37)

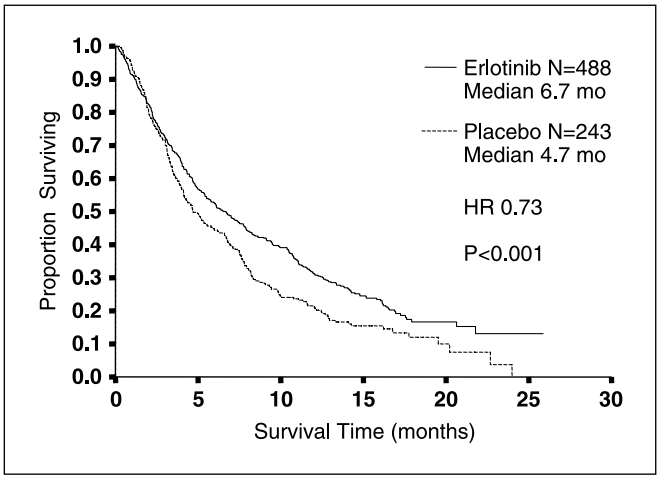

Fig. 1. Survival of all patients by treatment. HR is from the Cox regression model with the following covariates: ECOG performance status, number of prior regimens, prior platinum, and best response to prior chemotherapy. P value is from the two-sided log-rank test stratified by the same four variables.

Exploratory univariate analyses of erlotinib survival effect in subgroups are shown in Fig. 2. The superior erlotinib survival effect is maintained in most subgroups. Notable exceptions are in subgroups who are EGFR receptor negative, are stage IV at initial diagnosis, have no prior platinum treatment, or have tumor histology other than squamous or adenocarcinoma.

Survival by epidermal growth factor receptor status. EGFR expression status was determined by LabCorp using the DAKO EGFR pharmDx kit (Carpinteria, CA), without knowledge of treatment assignment. A positive EGFR expression was defined as having at least 10% of cells staining for EGFR.

Erlotinib was designed to target EGFR. There is therefore great interest in whether erlotinib treatment effect is affected by EGFR status. Exploratory univariate analyses were done in a subgroup of 238 (33%) patients with measured EGFR status (Fig. 2). About 53% of measured patients were EGFR positive. Erlotinib clearly prolonged survival in EGFR-positive patients with median survival on erlotinib 10.7 months and placebo 3.8 months (HR, 0.65; 95% CI, 0.4-1.0; $P = 0.03$). In contrast, in EGFR-negative patients, there was no apparent erlotinib survival effect with median survival on erlotinib 5.2 months and placebo 7.5 months (HR, 1.01; 95% CI, 0.7-1.6, $P = 0.96$). However, the 95% CIs are wide and overlap for the EGFR-positive and EGFR-negative subgroups. Thus, a favorable erlotinib survival effect in the EGFR-negative subgroup can not be excluded.

EGFR-positive status does not seem to be a favorable prognostic factor independent of treatment in this study as shown in Table 3 by a comparison of survival in EGFR-positive and EGFR-negative patients in the placebo group. In the placebo group, median survivals in the EGFR-negative and EGFR-positive patients, respectively, are 7.5 versus 3.8 months (HR, 1.1; $P = 0.56$).

In the erlotinib treatment group, the superior survival of EGFR-positive patients to EGFR-negative patients indicates that EGFR status may be a treatment-dependent disease factor (Table 3).

The importance of any imbalances in known prognostic factors was addressed by performing three Cox proportional hazard analyses in the EGFR-positive and EGFR-negative subgroups. These three Cox proportional hazard analyses are for treatment alone in the model, for treatment using the prerandomization stratification factors in the model, and for treatment using all factors that were imbalanced between treatment groups in the model.

The favorable erlotinib survival effect is consistently seen in all analyses in the EGFR-positive subgroup (Table 4). In the EGFR-negative subgroup, the lack of an erlotinib survival effect is consistent in the treatment only model (HR, 1.01) and in the model with treatment and all of the imbalanced factors (HR, 1.03). But in the model using treatment and the four prerandomization stratification factors, the HR is 0.94, indicating a possible small erlotinib survival effect in the EGFR-negative subgroup (Table 5).

Survival by smoking status. Like EGFR status, smoking status does not seem to be a prognostic factor for survival independent of treatment in this study, as shown in Table 3 by the comparison of smokers and nonsmokers in the placebo group (HR, 0.99; $P = 0.95$). In contrast, comparison of smokers and nonsmokers in the erlotinib group shows a strong effect of smoking status favoring nonsmokers (HR, 1.86; $P < 0.0001$).

As shown in Fig. 2, erlotinib prolongs survival in patients who never smoked (erlotinib median, 12.3 months and placebo median, 5.5 months; HR, 0.42; $P < 0.0001$), but the effect in smokers seems to be less (erlotinib median, 5.5 months and placebo median, 4.6 months; HR, 0.87; $P = 0.141$). In this study, patients are considered smokers if they have smoked >100 cigarettes.

In patients who never smoked, EGFR status seems to have a strong effect on survival. In the patient subgroup who never

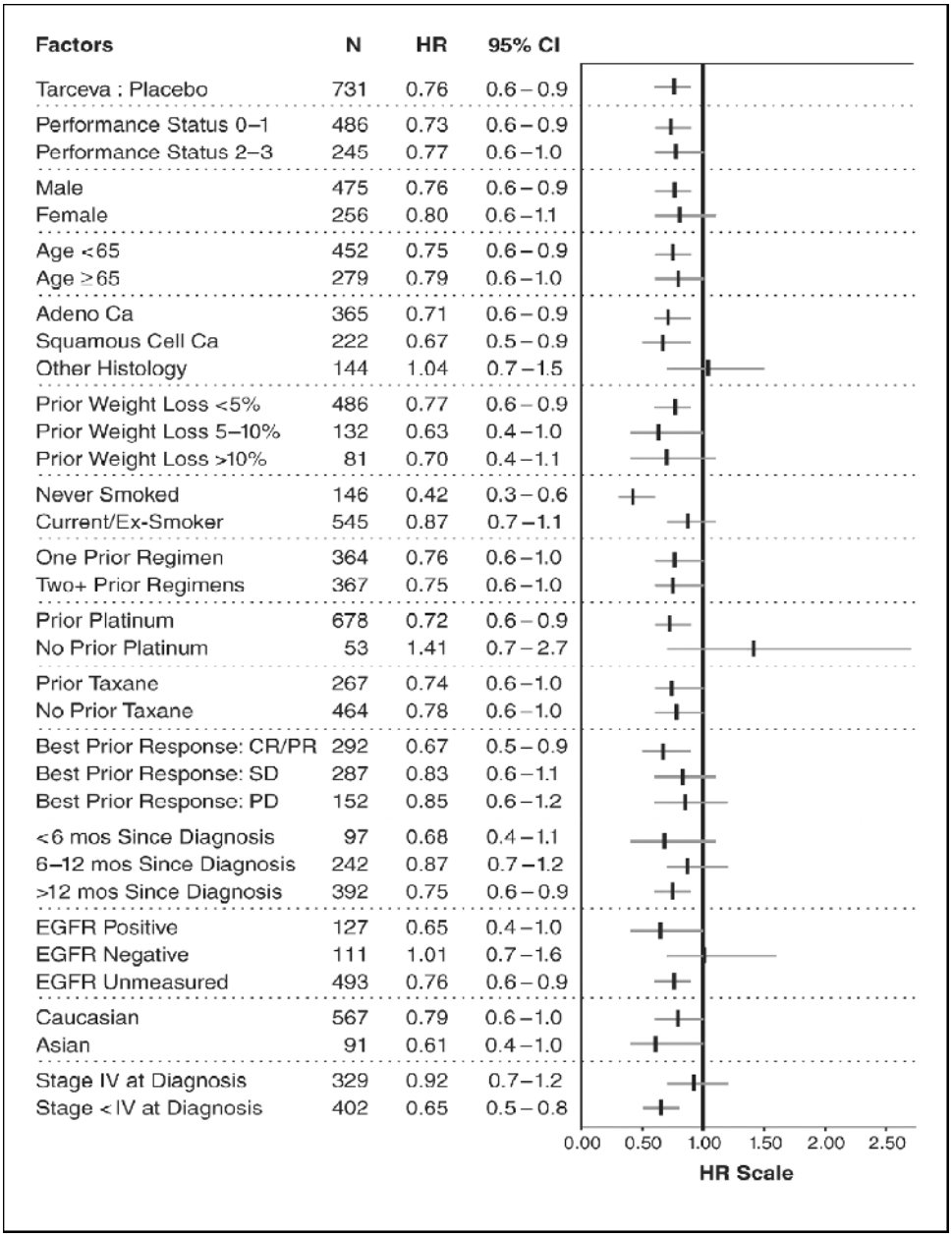

Fig. 2. Death HR (erlotinib/placebo) in subgroups according to pretreatment characteristics. The hash mark on the horizontal bar represents the univariate HR, and the length of the horizontal bar represents the 95% CI. A hash mark to the left of the vertical line corresponds to a HR that is <1.00, which indicates that survival is better in the erlotinib arm compared with the placebo arm in that subgroup. (Reprinted from the Tarceva package insert with the permission of OSI Pharmaceuticals).

Table 3. Subgroup univariate analyses within treatment groups

Treatment	Factor	*n*	Median (mo)	HR (95% CI)	*P*
Placebo	EGFR+	49	3.8	1.1 (0.72-1.86)	0.56
	EGFR−	37	7.5		
Erlotinib	EGFR+	78	10.7	0.74 (0.52-1.07)	0.11
	EGFR−	74	5.2		
Placebo	Smoke+	187	4.6	0.99 (0.69-1.41)	0.95
	Smoke−	42	5.6		
Erlotinib	Smoke+	358	5.5	1.86 (1.42-2.44)	<0.0001
	Smoke−	104	12.3		

smoked and were EGFR positive, erlotinib prolongs survival (median erlotinib, 13.6 months and placebo, 3.1 months; HR, 0.27; 95% CI, 0.11-0.67; $P = 0.003$). This subgroup is small with only 18 erlotinib patients and 12 placebo patients. There are too few EGFR-negative patients who never smoked to do a reliable analysis.

In the patients who smoked, the effect of EGFR status on survival is less clear. In the patient subgroup who smoked and were EGFR positive, the erlonitib favorable survival effect seems maintained, although it is not statistically significant (erlotinib median, 9.5 months and placebo, 3.8 months; HR, 0.87; 95% CI, 0.53-1.43; $P = 0.56$). But in the patient subgroup who smoked and were EGFR negative, there is no apparent erlonitib survival effect (erlotinib median, 4.1 months and placebo, 5.3 months; HR, 1.02; 95% CI, 0.64; 1.67, $P = 0.93$).

Survival by skin rash status. Favorable survival was associated with occurrence of a skin rash while on erlotinib treatment (Fig. 3). In erlotinib-treated patients with no reported skin rash, a grade 1 skin rash and a grade ≥2 skin rash, the median survivals respectively were 2.2, 6.9, and 11.1 months ($P = 0.0001$, three-way comparison).

It is always treacherous to compare outcomes based on response to treatment as opposed to baseline variables. The erlotinib skin rash may only be identifying patients who would have had good survival without erlotinib treatment. But the erlotinib patients who did not develop a skin rash had a survival so short that it is very unlikely that erlotinib caused any meaningful survival increase.

In addition, an exploratory survival analysis comparing erlotinib- and placebo-treated patients who were not reported to develop a skin rash shows that placebo was actually better than erlotinib in patients who did not develop a skin rash (Fig. 4). There were imbalances in prognostic factors favoring the placebo treatment group. To adjust for the imbalances in prognostic factors, Cox proportional hazard analyses were done using treatment only in the model, the four prerandomization stratification factors in the model, and all prognostic factors with imbalances between treatment groups (smoking history, ECOG performance status, and response to prior treatment) in the model; Table 6). In these analyses, adjusting for the imbalances in prognostic factors, the survival advantage for the placebo group decreased but remained highly statistically significantly better than the erlotinib group.

In the 75% of erlotinib patients who developed a skin rash, the median time to onset of skin rash was 8 days. The rash developed within 3 weeks of starting treatment in 87% and within 30 days in 93% of erlotinib patients.

Progression-free survival

Progression-free survival was superior in the erlotinib group (medians, 9.9 and 7.9 weeks; HR, 0.59; 95% CI, 0.50-0.70; $P < 0.001$, two-sided log-rank test stratified by prerandomization stratification factors).

Tumor response

Tumor response rates in patients with measurable disease at study entry who received at least one dose of erlotinib or placebo were erlotinib 8.9% and placebo 0.9% ($P < 0.001$, two-sided Fishers exact test; Table 7). In erlotinib-treated patients, the tumor response rate was 12% in EGFR-positive patients and 3% in EGFR-negative patients (Table 8).

Tumor response in erlotinib treated patients was associated with skin rash. In erlotinib patients with no reported skin rash, a grade 1 skin rash or a grade 2 to 4 skin rash, respectively, the objective tumor response rates were 1%, 9%, and 13% (Table 9).

Quality of life

The FDA decided not to include any quality of life claims or information in the erlotinib label. The main reasons are as follows. The applicant's main analyses focused on cough, dyspnea, and pain and used individual items of the European Organization for Research and Treatment of Cancer QLQ-C30 and QLQ LC-13 instruments for assessing them. Individual items are not validated for use separately from the instruments as a whole. The measures used for evaluation of the cough, dyspnea, and pain items of the instruments are not consistent with the FDA's previous experience and advice for patient-reported outcomes. Various components of the instruments purporting to measure similar or related aspects of quality of life gave inconsistent or conflicting results.

Table 4. Cox's proportional hazard model in the EGFR-positive patients (erlotinib, $n = 78$; placebo, $n = 49$)

Analyses	HR (95% CI)	*P**
Treatment only	0.646 (0.430-0.969)	0.0333
Prerandomization stratification factors (4) †	0.607 (0.401-0.918)	0.018
Factors imbalanced between erlotinib and placebo (6) ‡	0.609 (0.400-0.927)	0.0205

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*P value not adjusted for multiplicity.
†Prior response (CR/PR versus SD/PD).
‡Factors imbalanced between erlotinib and placebo: baseline ECOG performance status (0-1 versus 2-3), response to prior therapy (CR/PR versus SD/PD), number of prior regimens (1 versus 2), age (≤60 versus >60), sex, and histology (adenocarcinoma versus others).

Table 5. Cox's proportional hazard model in EGFR-negative patients (erlotinib, $n = 74$; placebo $n = 37$)

Analyses	HR (95% CI)	P*
Treatment only	1.012 (0.651-1.572)	0.958
Prerandomization stratification factors (4)†	0.937 (0.596-1.472)	0.776
Factors imbalanced between erlotinib and placebo (6)‡	1.033 (0.652-1.636)	0.890

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*P value not adjusted for multiplicity.
† Prior response (CR/PR versus SD/PD).
‡ Factors imbalanced between erlotinib and placebo: baseline ECOG performance status (0-1 versus 2-3), response to prior therapy (CR/PR versus SD/PD), number of prior therapies (1 versus 2), smoking history (yes versus no), sex, and histology (adenocarcinoma versus others).

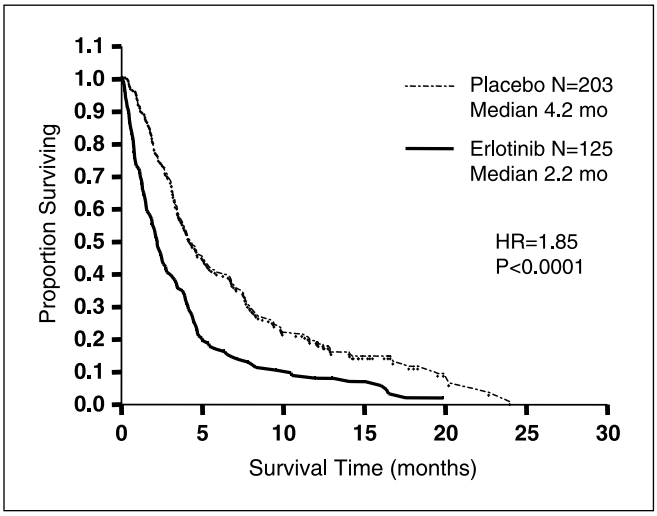

Fig. 4. Survival by treatment in patients without skin rash (univariate analysis).

Safety

All evaluations of safety, dose intensity, erlotinib exposure, and dose reductions were based on the Safety Population (i.e., patients who received at least one dose of erlotinib).

The erlotinib mean relative dose intensity was 92% with a range from 29% to 101%. Thirty-five per cent of erlotinib patients were on drug for >16 weeks and 6% for >52 weeks.

Dose reduction to 100 mg occurred in 15% of erlotinib patients with further reduction to 50 mg in 4% of patients, compared with 1% and <1% in placebo patients. Discontinuation due to toxicity occurred in 5% of patients in the erlotinib group and 2% in the placebo group.

The overall incidence per patient of adverse events regardless of causality was similar in the two treatment arms (99% erlotinib versus 96% placebo). Severe events (National Cancer Institute Common Toxicity Criteria grade 3 or 4) occurred in 62% of patients in the erlotinib group compared with 58% in the placebo group. Adverse events considered treatment-related by the investigator occurred in 85% of patients in the erlotinib group and 51% in the placebo group.

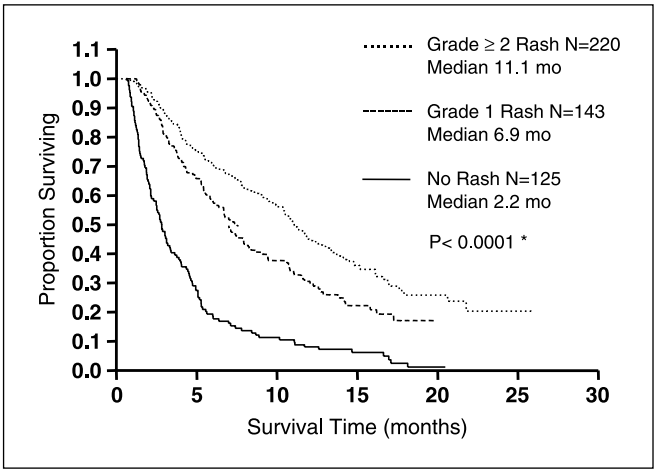

Fig. 3. Survival erlotinib patients by skin rash status (univariate analysis). Three-way comparison. Two-way comparison: no rash versus grade ≥2 rash (*, $P < 0.0001$). Two-way comparison: no rash versus grade 1 rash (*, $P < 0.0001$).

Rash (75% versus 17%) and diarrhea (54% versus 18%) in the erlotinib and placebo group, respectively, were the most common adverse events regardless of causality. Most were grade 1 and 2 in severity and manageable without intervention. Severe rash occurred in 9% and severe diarrhea occurred in 6% of erlotinib-treated patients and each resulted in study discontinuation in 1%. Dose reductions were required for 10% of patients with rash and 4% of patients with diarrhea.

The incidence of interstitial lung disease-like events was 0.8% in both the erlotinib and placebo groups. The onset of symptoms ranged from 6 days to 9 months after initiating erlotinib therapy.

There was no apparent hematologic toxicity associated with erlotinib therapy. The possibility of an interaction between erlotinib and warfarin was monitored in patients on such anticoagulants. Erlotinib patients on warfarin frequently showed INR values outside the therapeutic range. INR shifts from baseline to values that are associated with increased risk for bleeding complication (i.e., INR ≥ 4) were seen in 26% and 21% of warfarin-treated patients in the erlotinib and placebo groups, respectively. Whether patients received warfarin or not, reports of clinically recognized bleeding occurred in 24% of erlotinib-treated patients and 17% of those given placebo. Most were inconsequential grade 1 episodes of hemoptysis and epistaxis. Severe bleeding cases include eight erlotinib patients (2%) with serious gastrointestinal hemorrhage and none in placebo patients. Concurrent warfarin administration was present in two of these eight patients.

Eye disorders were more frequent in the erlotinib group than in the placebo group (27% versus 9%). Most were conjunctivitis and keratoconjunctivitis sicca (dry eyes) experienced by the erlotinib patients at an incidence of 12% each, compared with 2% and 3%, respectively, in the placebo patients. The worst severity was grade 3, occurring in < 1% in each arm. Keratitis was reported in 3% of erlotinib patients compared with 1% of placebo patients. All except one case was grade <2 and none were reported as medically significant or resulting in discontinuation of protocol therapy. Concomitant ophthalmologic preparations such as artificial tears were given to 11% of the patients in the erlotinib group and 1% in the placebo group.

Table 6. Cox proportional hazard analyses in patients with no reported rash (erlotinib, $n = 125$; placebo, $n = 203$)

Analyses	HR (95% CI)	P^*
Treatment only (erlotinib versus placebo)	1.852 (1.465-2.340)	<0.0001
Prerandomization stratification factors (4)†	1.641 (1.290-2.088)	<0.0001
Factors imbalanced between erlotinib and placebo (3)‡	1.539 (1.200-1.974)	0.0007

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*P value not adjusted for multiplicity.
†Prior response (CR/PR versus SD/PD).
‡Factors imbalanced between erlotinib and placebo: baseline ECOG (0-1 versus 2-3), response to prior therapy (CR/PR versus SD/PD), and smoking history (yes versus no).

Discussion

Erlotinib trial and exploratory analyses. Erlotinib was developed to target the EGF receptor. It is therefore of great interest to determine whether patients can be selected for erlotinib treatment based on EGFR status. Measured EGFR status was not an entry criterion for the randomized placebo-controlled trial and only about one third of the patients had EGFR status measured.

In favor of doing exploratory analyses of the treatment effect of EGFR status is the strong prior assumption that EGFR status is important because erlotinib was developed to target EGFR. Also in favor of such analyses is that patients were not selected for EGFR measurement based on any study outcome and that the HRs for erlotinib survival effect were very similar in the entire study population, the subgroup with measured EGFR and the subgroup with unmeasured EGFR, indicating that patients with measured EGFR were representative of all study patients.

Against doing such analyses is that only one third of study patients had EGFR status measured and that patients were not randomized based on EGFR status, resulting in imbalances of known prognostic factors between treatments in some of the subgroups.

The authors believe the exploratory analyses of the treatment effect of EGFR status should be presented. However, confirmation in independent studies is necessary before any conclusions can be drawn.

Effect of epidermal growth factor receptor status on treatment effect in other trials. EGFR status measured by immunohistochemistry was not a predictor of tumor response in previous lung cancer clinical trials with erlotinib or gefitinib, a related EGFR tyrosine kinase inhibitor. Two single-arm gefitinib trials comparing 250 and 500 mg daily (6) and one single-arm erlotinib trial of 150 mg daily (7) assessed the relationship of tumor membrane EGFR staining and tumor response in patients with NSCLC treated with gefitinib or erlotinib as second-line or third-line chemotherapy. These trials did not show a relationship between EGRF expression and tumor response. The present study is the only one where EGRF status measured by immunohistochemistry has been assessed to determine if it predicts for treatment effect on survival.

EGFR status as measured by somatic mutations of *EGFR* has been reported to predict erlotinib and gefitinib tumor response. No study has assessed EGFR status measured by somatic mutations to determine if it predicts for treatment effect on survival with EGFR inhibitors.

In a study by Lynch et al., eight of nine gefitinib treated NSCLC patients whose tumor responded had documented mutations in the tyrosine kinase domain of the *EGFR* gene. None of seven patients who failed to respond to gefitinib treatment had a gene mutation. All responding patients had bronchoalveolar carcinoma or adenocarcinoma (8).

Paez et al. reported clinical and/or symptomatic responses to gefitinib in five of five NSCLC patients with somatic *EGFR* tyrosine kinase domain mutations, whereas none of four patients without mutations had a response (9).

Pao et al. studied both gefitinib and erlotinib treated NSCLC patients. Seven of 10 gefitinib responding patients had somatic EGFR tyrosine kinase mutations, whereas none of eight gefitinib refractory tumors were mutation positive. Five of seven erlotinib responding patients were mutation positive, whereas all 10 erlotinib nonresponding patients were mutation negative. Mutations were most commonly observed in patients with adenocarcinoma with or without bronchoalveolar carcinoma features and in patients who never smoked (10).

Survival effect and skin rash. In the present erlotinib study, skin rash was associated with a favorable survival and objective tumor response in erlotinib-treated patients. Erlotinib patients who do not develop a skin rash have worse survival than placebo patients who do not develop a skin rash.

Perez-Soler et al. also reported skin rash is associated with a favorable survival in a phase 2 single-arm trial of 57 erlotinib-treated patients with NSCLC (11). Saltz et al. also

Table 7. Tumor response

Treatment	CR (%)	PR (%)	SD (%)
Erlotinib ($n = 424$)	4 (1)	34 (8)	150 (35)
Placebo ($n = 210$)	1 (.5)	1 (.5)	56 (27)

NOTE: Patients with measurable disease at study entry who received at least one dose of erlotinib or placebo. CR + PR, $P < 0.0001$ (Fisher's exact test). CR + PR + SD, $P < 0.0001$ (Fisher's exact test).
Abbreviations: CR, complete response; PR, partial response; SD, stable disease.

Table 8. Erlotinib tumor response by EGFR status

EGFR	n	CR or PR (%)	No response (%)
Negative	61	2 (3)	59 (97)
Positive	69	8 (12)	61 (88)
Unknown	294	28 (10)	266 (90)

Abbreviations: CR, complete response; PR, partial response.

Table 9. Erlotinib tumor response by skin rash grade

Rash grade	*n*	CR (%)	CR or PR (%)	No response
0	107	0 (0)	1 (1)	109 (99)
1	121	0 (0)	11 (9)	110 (91)
≥2	196	4 (2)	26 (13)	170 (87)

Abbreviations: CR, complete response; PR, partial response.

reported skin rash is associated with a favorable survival, using the EGFR blocking antibody, cetuximab, in two trials in advanced colorectal cancer, one trial in advanced head and neck cancer, and one trial in advanced pancreatic cancer (12).

In the 75% of erlotinib patients in the present trial who developed skin rashes, the median time to onset of rash was 8 days. Most skin rashes developed within 3 weeks of starting erlotinib (87%) or within 30 days (93%). In erlotinib patients who do not develop a skin rash or show some clinical improvement within 30 days, consideration could be given to altering treatment in some way.

Erlotinib concurrent with chemotherapy. Two large placebo-controlled studies in over 2,000 patients with advanced NSCLC without prior chemotherapy comparing carboplatin and paclitaxel with or without concurrent erlotinib (13) and gemcitabine and cisplatin with or without concurrent erlotinib (14) showed no improvement in survival, PFS, or tumor response with use of erlotinib. Thus, erlotinib should not be given concurrently with cytotoxic chemotherapy drugs for treatment of NSCLC.

Regulatory Basis for Approval

Erlotinib was approved for treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen, based on the results of one randomized placebo-controlled clinical study. Erlotinib was superior to placebo for survival, PFS, and objective tumor response.

Given the clear survival effect of erlotinib, the main regulatory issue for this application was whether there was sufficient evidence to indicate erlotinib only for patients with EGFR-positive tumors. Such a limitation would seem logical, as EGFR status might be expected to predict treatment outcome because erlotinib was designed to target this receptor and subgroup analyses showed that EGFR status was a strong predictor of improved survival with erlotinib. However, EGFR status was measured in only about one third of the patients and it was not possible to conclude with certainty that EGFR-negative patients did not benefit from erlotinib. The FDA therefore decided not to restrict the indication to EGFR-positive patients.

The manufacturer of erlotinib has committed itself to conduct two post-marketing studies in patients with advanced NSCLC to assess whether pretreatment information on immunohistologic staining with the DAKO kit predicts erlotinib treatment outcome. This pretreatment information will be required for study entry.

For several reasons (cost, avoiding needless toxicity, and directing therapy to likely responders), it is critical to the extent possible to identify the patients who will respond to the treatment. In an era of increasingly targeted therapy, it seems likely that it will be possible to do this. There has been a concern that manufacturers who can show an effect in an overall unselected population may be reluctant to provide targeting information. In the randomized trial supporting this application, provision of material for determining EGFR status was voluntary and not a study entry criterion. In the future, the FDA must work proactively with manufacturers to ensure that potential targeting information is available. This means that such availability must be a requirement for study entry.

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