Erlotinib in Advanced Non-small Cell Lung Cancer

Efficacy and Safety Findings of the Global Phase IV Tarceva Lung Cancer Survival Treatment Study

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Introduction: Erlotinib is a small molecule inhibitor of epidermal growth factor receptor tyrosine-kinase activity that has been shown to significantly increase survival for patients with previously treated advanced non-small cell lung cancer. Here, we report safety and efficacy data from a large, global, open-label, phase IV trial of erlotinib (Tarceva Lung Cancer Survival Treatment).

Methods: Patients who had previously failed on chemotherapy or radiotherapy and were unsuitable for these treatments were treated with oral erlotinib (150 mg/d) until disease progression or unacceptable toxicity.

Results: The disease control rate was 69% in 5394 patients for whom best response data were available. Survival data were available for 6580 patients. Median progression-free and overall survival times were 3.25 months and 7.9 months, respectively. The 1-year survival rate was 37.7%. Among the 6580 patients included in the safety analysis, 799 (12%) experienced one or more erlotinib-related adverse events (AEs, other than prespecified AEs defined in the protocol), and only 4% experienced an erlotinib-related serious AE. Of the 6580 patients for whom data were available, dose reductions were reported in 1096 (17%), the majority (95%) due to an erlotinib-related AE (most commonly rash 65% or diarrhea 10%). Treatment was discontinued for 337 patients (5%) because of erlotinib-related AEs. Incidence of erlotinib-related rash was investigated as a separate end point. Seventy-one percent of patients for whom data were available experienced erlotinib-related rash; of these, the majority of cases were grade 1/2 (59%).

Conclusions: These data confirm the favorable efficacy and safety profile of erlotinib in a large heterogeneous non-small cell lung cancer population.

Key Words: Erlotinib, NSCLC, Phase IV, Efficacy, Safety.

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Erlotinib is a highly potent, orally active, reversible inhibitor of epidermal growth factor receptor (EGFR) tyrosine-kinase (TK) activity. The importance of EGFR in tumor growth and progression has been demonstrated in clinical trials where EGFR inhibition has led to improved efficacy outcomes in patients with non-small cell lung cancer (NSCLC). Erlotinib prolonged overall survival (OS) versus placebo in patients with advanced NSCLC who had received at least one line of chemotherapy (BR.21). Erlotinib was also shown to significantly prolong progression-free survival (PFS), delay symptom deterioration, and provide quality-of-life benefits.[1,2] In the BR.21 trial, the 1-year survival rate was 31.2% with erlotinib and 21.5% with placebo, representing a 45% improvement with erlotinib. Notably, survival benefit was observed across a broad range of patient subgroups. Erlotinib was well tolerated, with rash and diarrhea being the most common toxicities (generally mild or moderate).

Certain groups of patients with NSCLC, such as those with adenocarcinoma histology, women, Asian ethnicity, and non (minimal) smokers are reported to be more likely to have tumor responses to EGFR TK inhibitors (TKIs) than other groups.[3–5] One possible explanation for this observation may be that these groups are also more likely to have activating mutations in the EGFR TK domain,[6,7] which have been shown to be associated with clinical responsiveness to the EGFR TKIs erlotinib[8] and gefitinib.[9–11] In the BR.21 study, patients with *EGFR* gene amplification had a higher response rate than patients with a normal *EGFR* copy number.[12] However, other studies show that the expression of EGFR in tumor cells is not significantly associated with response to EGFR TKIs.[13,14] In the BR.21 study, gender and histology were found to be strong prognostic factors, but neither was predictive of a differential survival benefit with erlotinib compared with placebo.[1,15] Smoking history was the only significant predictive factor. Furthermore, a subanalysis of

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the BR.21 study found that male smokers whose tumors were predominantly of squamous cell histology had a statistically significant survival benefit from erlotinib, compared with placebo.[16]

Erlotinib is approved in more than 80 countries for the treatment of NSCLC for patients who have received at least one line of prior chemotherapy. The Tarceva Lung Cancer Survival Treatment (TRUST) study was a large international, open-label, phase IV study of erlotinib, designed to allow access to erlotinib monotherapy for patients with advanced stage IIIB/IV NSCLC who had previously failed on or were considered unsuitable to receive standard chemotherapy or radiotherapy and were ineligible for other erlotinib trials. In each country, recruitment continued until erlotinib was granted a license. A total of 513 centers across 51 countries have participated in this trial. The study provided an opportunity to evaluate the efficacy and safety of erlotinib in a broad patient population in a real-life clinical setting. The impact of patient characteristics on clinical outcomes with erlotinib was also assessed by examining specific patient subgroups presumed to be predisposed to beneficial or detrimental outcomes during treatment with EGFR TKIs (albeit in an uncontrolled setting). Here, we report final data from the global population of the TRUST study.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

Patients aged 18 years or older with histologically or cytologically confirmed, unresectable, stage IIIB/IV NSCLC who had received at least one previous course of standard chemotherapy or radiotherapy or were unsuitable for chemotherapy (and could not participate in another trial with erlotinib) were eligible for TRUST. Additional criteria included Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 3; an estimated life expectancy of 12 weeks or more; and adequate hematological, renal, and hepatic function (serum bilirubin must have been $\leq$1.5 upper limit of normal). At least 3 weeks must have elapsed from the last dose of previous therapy, and patients must have recovered from any toxic effects of such therapies before enrolment. Patients who had fully recovered from previous surgery were eligible. Women of child-bearing potential were required to test negative for pregnancy and agree to birth control precaution.

Key exclusion criteria included any evidence of unstable systemic disease (including active infection, grade 4 hypertension, unstable angina, congestive heart failure, and hepatic, renal, or metabolic disease); prior treatment with anti-EGFR agents (including small molecules or monoclonal antibodies); previous malignancies within the last 5 years (other than cervical carcinoma or skin cancer that underwent successful treatment); untreated brain metastases (newly diagnosed or preexisting) or spinal cord compression; and any significant ophthalmologic abnormalities (including severe dry eye syndrome, keratoconjunctivitis sicca, Sjögren syndrome, severe exposure keratitis, or any other disorder likely to increase the risk of corneal epithelial lesions).

The study complied with the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent was obtained from all patients, and the protocol was approved at all participating centers by respective ethics committees.

Study Design and Treatment

This was a phase IV, open-label, single-arm study. Oral erlotinib (F. Hoffman-La Roche, Switzerland) was administered once daily at a dose of 150 mg to all patients until disease progression, unacceptable toxicity, or death. Dose interruption or reduction (in 50 mg/d decrements) was permitted in the event of treatment-related adverse events (AEs). The primary objective was to provide access to erlotinib (before approval) for patients with stage IIIB/IV NSCLC who had failed or were unsuitable for chemotherapy or radiotherapy. Secondary objectives were to assess safety, best response, PFS, and OS. The incidence and severity of erlotinib-related rash was also a secondary end point for this study.

Clinical Assessments

Outcomes included best response as per investigator assessment (complete response [CR], partial response [PR], or stable disease [SD]), PFS, OS, and safety. Clinical and laboratory assessments were conducted at baseline, then every 4 weeks throughout the study. Tumor response was assessed using RECIST,[17] at least every 2 months (by computerized tomography, magnetic resonance imaging, or x-ray). For tumors classed as responding, a confirmatory evaluation was carried out 4 weeks after the initial determination of response.

For safety and tolerability evaluations, AEs and serious AEs (SAEs) of any cause were assessed and graded using National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0. Treatment-related AEs were reported if they were not included on a list of prespecified AEs defined in the study protocol (pruritus, dry skin, diarrhea, nausea, vomiting, stomatitis, abdominal pain, fatigue, dyspnea, cough, anorexia, infection, conjunctivitis, and keratoconjunctivitis sicca). All treatment-related SAEs were reported (regardless of whether the AE was included on the prespecified list). The incidence and severity of erlotinib-related rash were recorded as a secondary end point. The incidence and severity of interstitial lung disease were recorded by exclusion diagnosis based on investigator assessment according to NCI-CTC version 3.0 (pneumonitis and pulmonary infiltrates were applicable). All erlotinib-related AEs or SAEs resulting in treatment withdrawals were recorded (regardless of whether the AE was included on the prespecified list). Erlotinib-related AEs or SAEs leading to dose reduction or modification were also monitored (unless they were included on the list of prespecified AEs). In the event of an erlotinib-related AE that was not controlled by best supportive care or not tolerated due to any reason (regardless of severity), dose reductions were permitted (see earlier). Within 2 weeks of a dose reduction, erlotinib-related toxicity must have improved by $\geq$1 NCI-CTC grade and be NCI-CTC grade $\leq$2 (or $\leq$1 for ocular toxicity), or a further dose reduction was required. Dose reescalation was only

permissible if the reason for reduction was erlotinib-related rash and if the rash was grade ≤2.

Statistical Analysis

The overall response rate was defined as the sum of CR and PR. A patient was assigned SD if they had a response assessment of CR, PR, or SD at ≥1 visit but were not confirmed as CR or PR (SD criteria must be met for ≥28 days). The disease control rate (DCR) was defined as the sum of CR, PR, and SD. PFS was determined from the date of erlotinib initiation until the date of first documented progression according to RECIST objective tumor assessment or until the date of death for any reason in the absence of disease progression. OS was determined from the date of start of treatment until date of death (irrespective of cause).

Differences in OS and PFS according to clinical or disease characteristics were analyzed using the log-rank test. Multivariate analyses were performed for PFS and OS using the Cox regression model and for DCR using the logistic regression model. Baseline characteristics investigated for the analyses comprised gender (male/female); age (<65 years/≥65 years); ethnicity (Asian/other); ECOG PS (PS 0 or 1/PS 2 or 3); stage (stage IV/stage IIIB); histology (adenocarcinoma or bronchoalveolar carcinoma/squamous cell carcinoma); smoking status (nonsmoker [smoked ≤100 cigarettes in their lifetime]/current or former smoker [smoked >100 cigarettes in their lifetime]). Patients with a missing value for any of the baseline characteristics were excluded from the multivariate analysis. For PFS, OS, and DCR analyses, factors were included in the model using a stepwise approach: the criteria for entry into the model being a p value ≤0.25 and the criteria for remaining in the model being a p value ≤0.15.

RESULTS

Patients

Between November 2004 and June 2007, a total of 6665 patients were enrolled. The study database was locked (cutoff date) on April 17, 2009. The study population (n = 6580) comprised all patients who had received at least one dose of erlotinib. At the time of the data cutoff, 471 patients had not experienced disease progression; 170 of these patients continued to receive erlotinib and 301 had discontinued erlotinib treatment (mainly because of patient refusal [n = 86], symptomatic deterioration [n = 84], lost to follow-up [n = 62], or study-related AE [n = 35]). The safety population (n = 6580) comprised all patients who received at least one dose of erlotinib at the cutoff date. The median duration of follow-up was 2.56 months (range: 0–43.36 months) for the 6548 patients with a known end date (the remaining 32 patients had no valid end date, mainly because of lost to follow-up [n = 22, 69%]).

Baseline patient and disease characteristics for the study population are summarized in Table 1. Sixty percent of the patients were men, and 77% were white. Seventy-six percent of patients were PS 0 to 1, and the majority (69%) were current/former smokers. Most patients had nonsquamous tumor histology (76%), and 79% of patients had stage IV disease. Thirty-seven percent of patients received erlotinib as third-line therapy, 49% as second-line therapy, and 13% of patients had no previous treatments and, therefore, received erlotinib as first-line therapy.

TABLE 1. Baseline Characteristics of Patients in the TRUST Study (n = 6580)

Characteristics	
Median age, years (range)	63 (19–91)
Gender, *n* (%)	
Male	3974 (60)
Female	2606 (40)
Ethnic origin, *n* (%)	
White	5057 (77)
Asian	1345 (20)
Black	29 (<1)
Other[a]	149 (2)
ECOG PS, *n* (%)	
0	1473 (22)
1	3504 (53)
2	1235 (19)
3	360 (5)
No data	8 (<1)
Stage, *n* (%)	
Stage IIIB	1376 (21)
Stage IV	5185 (79)
Other	15 (<1)
No data	4 (<1)
Histology, *n* (%)	
Adenocarcinoma	3590 (55)
Bronchoalveolar carcinoma	372 (6)
Large-cell carcinoma	382 (6)
Squamous cell carcinoma	1552 (24)
Other	681 (10)
No data	3 (<1)
Prior lines of chemotherapy, *n* (%)	
None	869 (13)
One	3224 (49)
Two	2428 (37)
Other	59 (<1)
Smoking history, *n* (%)	
NS	2004 (30)
C/FS	4567 (69)
No data	9 (<1)

[a] Includes patients with "Indian" ethnicity.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; NS, nonsmoker; C/FS, current or former smoker; TRUST, Tarceva Lung Cancer Survival Treatment.

Response and Survival

Best overall response data were available for 5394 patients, including 206 patients (4%) who were not evaluable as response data were not collected at the first evaluation, and their tumors were not evaluable for response at the second evaluation (Table 2). The remaining 1186 patients could not be included in the response analyses, because no best response data were reported (mainly because of symptomatic deterioration [36%] or death due to malignant disease [22%]). The overall response rate with erlotinib

TABLE 2. Response Data in the Overall TRUST Population (n = 6580)

	n (%)
Best response data available, n = 5394	
Complete response (CR)	45 (<1)
Partial response (PR)	668 (12)
Objective response rate (ORR = CR + PR)	713 (13)
Stable disease (SD)	2992 (55)
Disease control rate (DCR = CR + PR + SD)	3705 (69)
Progressive disease (PD)	1483 (27)
Not evaluable (NE)	206 (4)
No best response data available, n = 1186	
Remaining patients in the study population for whom no best response data were reported due to	
Symptomatic deterioration	424 (36)
Death due to malignant disease	262 (22)
Patient refusal	179 (15)
Study drug-related AE	143 (12)
Death due to other reason	68 (6)
Other	49 (4)
Lost to follow-up	48 (4)
PD	10 (<1)
Death due to toxicity	2 (<1)
Not known	1 (<1)
Total (all patients)	6580 (100)

TRUST, Tarceva Lung Cancer Survival Treatment; AE, adverse event.

was 13%, and the DCR was 69%. Survival data were available for 6580 patients. Median PFS was 3.25 months (n = 6580; 95% confidence interval: [CI]: 3.06–3.42) (Figure 1*A*). Median OS was 7.9 months (n = 6580; 95% CI: 7.59–8.28), with 18.8% of patients censored at the time of data cutoff (Figure 1*B*). The 1-year survival rate was 37.7% (95% CI: 36.5–38.9).

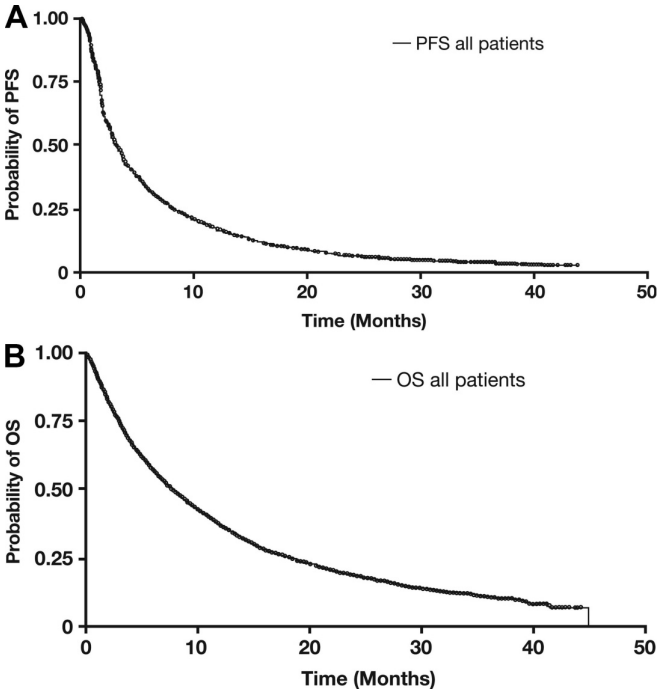

FIGURE 1. Progression-free survival (*A*) and overall survival (*B*) in patients receiving erlotinib (n = 6580).

Response and Survival in Selected Subgroups

Response and survival data for erlotinib in subgroups, defined on the basis of gender, histology, and smoking status, are shown in Table 3. Tumor response rate varied considerably between the different subgroups, from 4% in male current/former smokers with squamous cell carcinoma to 28% in female nonsmokers with nonsquamous tumors. There was also notable variability in the DCR, which ranged from 59% in male nonsmokers with squamous tumors to 79% in female nonsmokers with nonsquamous tumors. The observed median PFS ranged from at least 2.33 months (in male nonsmokers with squamous tumors) to 7.19 months (in female nonsmokers, with nonsquamous tumors). Median PFS for patients with erlotinib-related rash of grades 2 to 4 was 5.49 months versus 2.60 months for grades 0 to 1 (hazard ratio: 0.59, 95% CI: 0.56–0.62, $p < 0.0001$), respectively.

At the time of data cutoff, OS data were mature (<25% censored observations) for all but one subgroup (female nonsmokers with nonsquamous tumors). Median OS ranged from 5.03 months (in male nonsmokers with squamous tumors) to 15.54 months (in female nonsmokers with nonsquamous tumors).

Multivariate Analyses

Multivariate analyses were performed for PFS and OS using the Cox regression model and for DCR using the logistic regression model. For both the PFS and OS analyses, data were available for 4729 patients, with 1851 patients excluded because of missing values (Table 4). Of the patients included in the PFS and OS analyses, 348 patients did not experience progression, and 919 were alive at the last observation. Data for these patients were censored. The Cox regression analysis showed that poor ECOG PS (≥2), smoking, non-Asian ethnicity, squamous cell histology, stage IV disease, and age <65 years were all predictive of early disease progression. With the exception of age, the same characteristics along with male gender were also predictive of shorter OS. A multivariate logistic regression analysis for DCR was also performed. Data were available for 3960 patients, with 2620 patients excluded because of missing values. The optimal model for DCR showed that nonsmokers with stage IIIB disease, ECOG PS 0/1, and Asian ethnicity had significantly better prognosis in terms of DCR (Table 4).

Safety and Tolerability

Overall safety data were available for 6580 patients, of whom 54% had one or more AE of any cause (excluding the prespecified AEs defined in the protocol). Twelve percent of patients had one or more erlotinib-related AE (excluding the prespecified AEs defined in the protocol) (Table 5). Erlotinib-related AEs (any grade; excluding the prespecified AEs defined in the protocol) that were reported in more than 20 patients included mouth ulceration; paronychia; alanine aminotransferase increase; aspartate aminotransferase increase; blood bilirubin increase; dysgeusia; and alopecia (Table 5).

TABLE 3. Response and Survival in Selected Patient Subgroups, Defined on the Basis of Gender, Histology, and Smoking Status

	Group 1, Male C/FS with SCC	Group 2, Male NS with SCC	Group 3, Male C/FS with Nonsquamous Tumors	Group 4, Male NS with Nonsquamous Tumors	Group 5, Female C/FS with SCC	Group 6, Female NS with SCC	Group 7, Female C/FS with Nonsquamous Tumors	Group 8, Female NS with Nonsquamous Tumors
n (evaluable for response)[a]	944	78	1731	410	153	83	805	1183
CR, *n* (%)	0 (0)	1 (1)	5 (<1)	9 (2)	0	1 (1)	3 (<1)	26 (2)
PR, *n* (%)	42 (4)	8 (10)	144 (8)	78 (19)	8 (5)	13 (16)	75 (9)	300 (25)
SD, *n* (%)	616 (65)	37 (47)	954 (55)	224 (55)	87 (57)	38 (46)	417 (52)	614 (52)
PD, *n* (%)	246 (26)	28 (36)	559 (32)	85 (21)	56 (37)	26 (31)	274 (34)	208 (18)
NE, *n* (%)	40 (4)	4 (5)	69 (4)	14 (3)	2 (1)	5 (6)	36 (4)	35 (3)
ORR (%)	4	12	9	21	5	17	10	28
DCR (%)	70	59	64	76	62	63	61	79
n (evaluable for survival)[b]	1164	99	2216	488	193	94	994	1323
PFS (mo)	2.83	2.33	2.73	6.01	2.35	2.97	2.46	7.19
OS (mo)	5.98	5.03	5.95	13.21	5.19	9.40	7.26	15.54[c]

[a] Nine patients were not included in this analysis because of unknown smoking status (seven with response data available and two with response data "not done").
[b] Nine patients were not included in this analysis because unknown smoking status.
[c] Data not mature.
C/FS, current or former smokers; SCC, squamous cell carcinoma; NS, nonsmokers; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; OS, overall survival.

TABLE 4. Multivariate Analyses for Progression-Free Survival, Overall Survival, and Disease Control Rate

Factor (Cox Regression Model)	Hazard Ratio	95% CI	*p*
Factors for PFS, *n* = 4729			
Stage of disease (IV:IIIB)	1.23	1.14–1.32	<0.0001
Histology (SCC:adeno/BAC)	1.19	1.11–1.28	<0.0001
Smoking status (C/FS:NS)	1.58	1.47–1.69	<0.0001
Ethnicity (non-Asian:Asian)	1.34	1.25–1.45	<0.0001
Age (<65 yr:≥65 yr)	1.08	1.01–1.14	0.0210
ECOG PS (2 or 3:0 or 1)	1.42	1.32–1.52	<0.0001
Factors for OS, *n* = 4729			
ECOG PS (2 or 3:0 or 1)	2.01	1.86–2.16	<0.0001
Smoking status (C/FS:NS)	1.53	1.40–1.66	<0.0001
Ethnicity (non-Asian:Asian)	1.55	1.43–1.68	<0.0001
Histology (SCC:adeno/BAC)	1.26	1.17–1.36	<0.0001
Stage of disease (IV:IIIB)	1.22	1.13–1.33	<0.0001
Gender (male:female)	1.11	1.03–1.20	0.0054
Factor (Logistic Regression Model)	**Odds Ratio[a]**	**95% CI**	***p***
Factors for DCR, *n* = 3960			
Ethnicity (non-Asian:Asian)	1.54	1.29–1.83	<0.0001
Smoking status (C/FS:NS)	1.60	1.37–1.88	<0.0001
Stage of disease (IV:IIIB)	1.29	1.09–1.53	0.0037
ECOG PS (2 or 3:0 or 1)	1.26	1.06–1.50	0.0086

[a] For response:no response.
PFS, progression-free survival; CI, confidence interval; SCC, squamous cell carcinoma; BAC, bronchoalveolar carcinoma; C/FS, current or former smoker; NS, nonsmoker; ECOG PS, Eastern Cooperative Oncology Group performance status; OS, overall survival; DCR, disease control rate.

TABLE 5. Erlotinib-Related Adverse Events (Any Grade)[a] Reported in >20 Patients (*n* = 6580)[b]

Events	Any Grade, *n* (%)	Grades 3–4, *n* (%)
Patients with any erlotinib-related AE	799 (12)	173 (3)
Blood and lymphatic system disorders	34 (<1)	8 (<1)
Eye disorders	71 (1)	5 (<1)
Gastrointestinal disorders	108 (2)	16 (<1)
Mouth ulceration	27 (<1)	0
General disorders and administration site conditions	56 (<1)	20 (<1)
Hepatobiliary disorders	32 (<1)	11 (<1)
Infections and infestations	174 (3)	21 (<1)
Paronychia	137 (2)	5 (<1)
Investigations	133 (2)	22 (<1)
Alanine aminotransferase increased	23 (<1)	3 (<1)
Aspartate aminotransferase increased	22 (<1)	2 (<1)
Blood bilirubin increased	56 (<1)	7 (<1)
Metabolism and nutrition disorders	28 (<1)	13 (<1)
Musculoskeletal and connective tissue disorders	28 (<1)	0
Nervous system disorders	93 (1)	8 (<1)
Dysgeusia	31 (<1)	0
Respiratory, thoracic, and mediastinal disorders	78 (1)	23 (<1)
Skin and subcutaneous tissue disorders	189 (3)	17 (<1)
Alopecia	102 (2)	0

[a] As defined by NCI-CTC criteria v3.0.
[b] Other than the most frequently occurring prespecified events.
AE, adverse event.

Of the seven patients (<1%) who had erlotinib-related interstitial lung disease (grades 1–2, *n* = 2; grades 3–4, *n* = 4; grade 5, *n* = 1), two deaths occurred. Only 4% of patients had one or more erlotinib-related SAEs; diarrhea was the most common single SAE, occurring in 1% of patients (Table 6).

Dose reduction of erlotinib was reported in 1096 (17%) of the 6580 patients for whom data were available. In the majority (95%) of these cases, the dose was reduced due to an erlotinib-related AE, most commonly rash (65%) or diarrhea (10%). In the overall safety population (*n* = 6580), treatment

TABLE 6. Erlotinib-Related Serious Adverse Events (Any Grade)[a] Reported in >20 Patients (n = 6580)

Events	Any Grade, n (%)	Grades 3–4, n (%)
Patients with any erlotinib-related SAE	274 (4)	209 (3)
Gastrointestinal disorders	121 (2)	89 (1)
Diarrhea	67 (1)	49 (<1)
Nausea	24 (<1)	11 (<1)
General disorders and administration site conditions	26 (<1)	18 (<1)
Infections and infestations	22 (<1)	16 (<1)
Metabolism and nutrition disorders	27 (<1)	18 (<1)
Respiratory, thoracic and mediastinal disorders	37 (<1)	30 (<1)
Skin and subcutaneous tissue disorders	40 (<1)	31 (<1)
Rash	31 (<1)	26 (<1)

[a] As defined by NCI-CTC criteria v3.0.
SAE, serious adverse event.

TABLE 7. Erlotinib-Related Adverse Events Leading to Treatment Withdrawal in ≥1% Patients (n = 6580)

Events	Any Grade,[a] n (%)	Grades 3–4, n (%)
Patients with any AE leading to withdrawal	337 (5)	213 (3)
Gastrointestinal disorders	121 (2)	74 (1)
Diarrhea	74 (1)	42 (<1)
Skin and subcutaneous tissue disorders	133 (2)	78 (1)
Rash	113 (2)	67 (1)

[a] As defined by NCI-CTC criteria v3.0.
AE, adverse event.

was discontinued due to erlotinib-related AEs in 337 (5%) of patients. The most common AEs leading to discontinuation were rash (2%) and diarrhea (1%) (Table 7). Treatment-related SAEs resulting in death occurred in 24 patients (<1%), mainly because of respiratory, thoracic, and mediastinal disorders (n = 10) or infections and infestations (n = 4).

In a separate analysis, the incidence and severity of erlotinib-related rash was monitored among the 6580 patients for whom safety data were available. These data were recorded separately on the case report forms. Erlotinib-related rash was observed in 71% of patients. The majority (59%) of cases were mild or moderate (grade 1/2) in severity, 12% were grades 3 to 4, and <1% were classified as unknown (grade of rash not reported).

DISCUSSION

The results of this international phase IV trial reflect clinical experience with erlotinib in a wide range of more than 6500 patients with advanced NSCLC. Differences in local clinical practice and the broad eligibility criteria for this study resulted in a large and heterogeneous patient population. The conclusions from the study must be tempered by the limitations of the open-label, nonplacebo controlled, single-arm study design, one consequence of which is that no distinction can be made between prognostic and predictive factors.

Our analyses confirm that erlotinib is an effective and well-tolerated option for eligible patients with advanced NSCLC. The PFS and OS in this study were 3.25 months and 7.9 months, respectively, and the DCR was 69%.

The criteria used for selecting the most appropriate therapy for a patient are of particular interest to physicians. Tumors with *EGFR* mutations have been shown to be highly responsive to EGFR TKIs.[8,11,18] Although patients whose tumors have these mutations are likely to obtain a greater magnitude of benefit from EGFR TKIs such as erlotinib, it is important to note that the absence of these mutations does not necessarily result in a lack of benefit with erlotinib therapy. In the recent phase III SATURN study of erlotinib maintenance therapy in patients obtaining clinical benefit from standard first-line chemotherapy, erlotinib significantly prolonged both PFS and OS in patients whose tumors did not harbor *EGFR* mutations.[19,20] As there was still some uncertainty about the relevance of biomarkers to EGFR TKIs when the TRUST study was designed, biomarker investigations were only conducted as exploratory analyses. Collection of tumor samples in this study was optional, and, as a result, only a small number of TRUST patients provided samples suitable for *EGFR* mutation analyses (4.4%; Roche, data on file).

Current options for second-line treatment for patients with advanced NSCLC include conventional chemotherapy with docetaxel or pemetrexed, or targeted therapy with erlotinib, or in some regions, gefitinib. Alternatively, some patients may elect to receive best supportive care or to participate in a clinical trial. Clearly, patient characteristics such as likelihood of response, in addition to the efficacy and safety of the treatment, are among the primary considerations for the selection of an appropriate therapy. This study, as well as others, shows that erlotinib is generally well tolerated. The class effect of skin toxicity may also be predictive of response.

The results suggest that erlotinib can benefit a wide range of patients, including those who have previously been thought unlikely to benefit from treatment with EGFR TKIs. Although response rates were particularly high for some groups (nonsmokers with nonsquamous tumors) and lower for others (current/former smokers with squamous cell carcinoma), the DCR was at least 59% in all subgroups. The median PFS in the eight predefined subgroups ranged from 2.33 to 7.19 months and was not substantially shorter than that for the overall study population (3.25 months) in any of the subgroups. These PFS data compare favorably with the median PFS of 1.8 months reported for the placebo arm of the BR.21 trial,[1] indicating that all subgroups were likely to have obtained some benefit from treatment with erlotinib. Similarly, results from the phase III BR.21 study indicated that erlotinib conferred a clinical benefit to most patient subgroups, although certain subgroups seem to have an enhanced benefit from erlotinib therapy.[1]

There were no unexpected safety findings relating to erlotinib in this study. As the prespecified expected treatment-related AEs were not recorded (unless they resulted in premature treatment withdrawal), it is not possible to com-

ment on the frequency or severity of these events. Most AEs were generally mild to moderate. The most common reasons for erlotinib-related dose reductions or discontinuations were rash and diarrhea; both of which are well-known class effects of EGFR inhibitors.

Previous studies have shown a strong correlation between the degree of rash experienced by patients and survival benefit, indicating that rash may be surrogate marker of efficacy for erlotinib and other EGFR inhibitors.[21] In our study, comparison of PFS between patients who experienced mild or no rash (grades 0–1) versus patients who experienced a higher degree of rash (grades 2–4) showed that the PFS for the high-grade rash group was at least twice as long in duration compared with the low grade or no rash group. These results are supportive of the proposed predictive relationship between rash and EGFR inhibitor benefit. Based on the lack of prospective data, the difficulties to adequately assess rash (because of dynamic changes in the rash during treatment with erlotinib) and on our experiences with the efficacy of erlotinib (even in patients without rash), it may not be valid to use rash as a selection criterion for or against treatment in clinical practice. Standard conventional assessments (i.e., tumor imaging) should remain the measure of efficacy.

The results of this global phase IV trial of erlotinib in more than 6500 unselected patients with advanced NSCLC confirm the suitability of erlotinib for use in patients who are unsuitable for standard chemotherapy or have experienced disease progression. These data confirm the favorable survival and safety profile of erlotinib in a global patient population and across a broad range of patient subgroups.

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REFERENCES

1. Shepherd FA, Rodrigues Pereira J, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123–132.
2. Bezjak A, Tu D, Seymour L, et al. Symptom improvement in lung cancer patients treated with erlotinib: quality of life analysis of the National Cancer Institute of Canada Clinical Trials Group Study BR. 21. *J Clin Oncol* 2006;24:3831–3837.
3. Birnbaum A, Ready N. Gefitinib therapy for non-small cell lung cancer. *Curr Treat Options Oncol* 2005;6:75–81.
4. Shah NT, Kris MG, Pao W, et al. Practical management of patients with non-small-cell lung cancer treated with gefitinib. *J Clin Oncol* 2005;23:165–174.
5. Goodin S. Erlotinib: optimizing therapy with predictors of response? *Clin Cancer Res* 2006;12:2961–2963.
6. Hsieh RK, Lim KH, Kuo HT, et al. Female sex and bronchioloalveolar pathologic subtype predict EGFR mutations in non-small cell lung cancer. *Chest* 2005;128:317–321.
7. Tsao AS, Tang XM, Sabloff B, et al. Clinicopathologic characteristics of the EGFR gene mutation in non-small cell lung cancer. *J Thorac Oncol* 2006;1:231–239.
8. Rosell R, Moran T, Queralt C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med* 2009;361:958–967.
9. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2004;350:2129–2139.
10. Van Zandwijk N, Mathy A, Boerrigter L, et al. EGFR and KRAS mutations as criteria for treatment with tyrosine kinase inhibitors: retro- and prospective observations in non-small-cell lung cancer. *Ann Oncol* 2007;18:99–103.
11. Mok T, Wu Y-L, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–957.
12. Tsao MS, Sakurada A, Cutz JC, et al. Erlotinib in lung cancer-molecular and clinical predictors of outcome. *N Engl J Med* 2005;353:133–144.
13. Cappuzzo F, Gregorc V, Rossi E, et al. Gefitinib in pretreated non–small-cell lung cancer (NSCLC): analysis of efficacy and correlation with HER2 and epidermal growth factor receptor expression in locally advanced or metastatic NSCLC. *J Clin Oncol* 2003;21:2658–2663.
14. Parra HS, Cavina R, Latteri F, et al. Analysis of epidermal growth factor receptor expression as a predictive factor for response to gefitinib ('Iressa', ZD1839) in non-small-cell lung cancer. *Br J Cancer* 2004;9:91:208–212.
15. Clark GM. Prognostic factors versus predictive factors: examples from a clinical trial of erlotinib. *Mol Oncol* 2008;1:406–412.
16. Clark GM, Zborowski DM, Santabarbara P, et al. Smoking history and epidermal growth factor receptor expression as predictors of survival benefit from erlotinib for patients with non-small-cell lung cancer in the National Cancer Institute of Canada Clinical Trials Group study BR. 21. *Clin Lung Cancer* 2006;7:389–394.
17. Therasse P, Eisenhauer EA, Verweij J. RECIST revisited: a review of validation studies on tumour assessment. *Eur J Cancer* 2006;42:1031–1039.
18. Murray S, Dahabreh IJ, Linardou H, et al. Somatic mutations of the tyrosine-kinase domain of epidermal growth factor receptor and tyrosine-kinase inhibitor response to TKIs in non-small-cell lung cancer: an analytical database. *J Thorac Oncol* 2008;3:832–839.
19. Brugger W, Triller N, Blasinska-Morawiec M, et al. Biomarker analyses from the phase III placebo-controlled SATURN study of maintenance erlotinib following first-line chemotherapy for advanced NSCLC. *J Clin Oncol* 2009;27(Suppl 15):411s(Abstract 8020).
20. Cappuzzo F, Coudert B, Wierzbicki R, et al. Efficacy and safety of erlotinib as first-line maintenance in NSCLC following non-progression with chemotherapy: results from the phase III SATURN study. *J Thorac Oncol* 2009;4(Suppl 1):S289 (Abstract A2.1).
21. Wacker B, Nagrani T, Weinberg J, et al. Correlation between development of rash and efficacy in patients treated with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in two large phase III studies. *Clin Cancer Res* 2007;13:3913–3922.