Efficacy and Safety of Erlotinib in 1242 East/South-East Asian Patients with Advanced Non-small Cell Lung Cancer

Tony Mok, MD, FRCPC, Yi-long Wu, MD, FACS,† Joseph Siu-kie Au, PhD, FRCR,‡ Caicun Zhou, MD, PhD,§ Li Zhang, MD,‖ Reury-Perng Perng, MD, PhD, FCCP,¶ and Keunchil Park, MD, PhD#*

Introduction: Erlotinib is an epidermal growth factor receptor tyrosine kinase inhibitor that significantly increases survival for patients with previously treated advanced non-small cell lung cancer. Epidermal growth factor receptor tyrosine kinase inhibitors have been reported to be particularly effective in Asian patients and may have a distinct safety profile in this population compared with non-Asian patients. We report safety and efficacy data from a subpopulation of East/South-East (E/SE) Asian patients enrolled in a global, open-label, phase IV trial of erlotinib (Tarceva Lung Cancer Survival Treatment study).

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

Results: Best response data were available for 1118 E/SE Asian and 4276 non-E/SE Asian patients. The overall response rates were 27% versus 10%, respectively ($p < 0.0001$). The disease control rates were 78% versus 66%, respectively ($p < 0.0001$). Survival data were available for 1242 E/SE Asian and 5338 non-E/SE Asian patients. The median progression-free survival times were 5.78 months versus 2.92 months, respectively (hazard ratio = 0.66, $p < 0.0001$). The median overall survival times were 14.7 months versus 6.8 months, respectively (hazard ratio = 0.57, $p < 0.0001$). One-year survival rates were 58.3% and 32.7%, respectively. Safety data were available for 1242 E/SE Asian patients. Seventeen percent of these patients experienced one or more erlotinib-related adverse event (AE) (other than the most frequently occurring AEs prespecified in the protocol) and 2% experienced an erlotinib-related serious AE. Dose reductions were reported for 171 (14%) patients.

Conclusion: Erlotinib is an effective and well-tolerated treatment for Asian patients with advanced non-small cell lung cancer.

Key Words: Erlotinib, NSCLC, Phase IV, Asia, TRUST.

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The epidermal growth factor receptor (EGFR) is part of a receptor family linked to a complex intracellular signaling network, which is central to cellular processes that are relevant to tumor growth, development, and apoptosis inhibition in non-small cell lung cancer (NSCLC). As such, EGFR is a rational target for therapeutic intervention in NSCLC. Single-agent erlotinib is the only EGFR tyrosine kinase inhibitor (TKI) proven to significantly prolong overall survival (OS) in patients with NSCLC after failure of cytotoxic chemotherapy.[1] In BR.21, a randomized, placebo-controlled, phase III trial in 731 patients with advanced NSCLC who had received at least one line of chemotherapy, erlotinib ($n = 488$) significantly prolonged survival, delayed symptom deterioration, and provided quality of life benefits compared with placebo.[1,2]

Patients with Asian ethnicity are a population who respond well to EGFR TKI therapy. Multiple retrospective studies from Asia report high response rates and impressive survival duration after treatment with EGFR TKIs.[3,4] In two recent prospective studies of erlotinib and gefitinib, approximately 12% and 20% of the total populations were Asian, respectively.[1,5] In retrospective subgroup analyses of Asian patients in both studies, median OS was longer with EGFR TKI therapy than with best supportive care (erlotinib hazard ratio [HR] 0.7, $p = 0.01$; gefitinib HR 0.66, $p = 0.01$). The high incidence of exon 19 and 21 *EGFR* mutations in Asian populations (49.5% in patients with early-stage resectable adenocarcinoma and 37.6% in advanced-stage adenocarcinoma) is the main explanation for these superior outcomes.[6,7] By comparison, the *EGFR* mutation rate in Western populations is 15 to 17%.[8,9] Furthermore, the safety profile of EGFR TKIs in Asian populations may also be different from that seen in other populations. For example, the incidence of interstitial lung disease (ILD) may be higher in Japanese patients than in other Asian populations.[10] This observation remains to be validated prospectively in an Asian population.

*Department of Oncology, Prince of Wales Hospital, Hong Kong, China; †Guangdong Lung Cancer Institute, Guangdong General Hospital, Guangzhou, China; ‡Department of Clinical Oncology, Queen Elizabeth Hospital, Hong Kong; §Department of Oncology, Shanghai Pulmonary Hospital, Shanghai, China; ‖Sun Yat-Sen University Cancer Centre, Guangzhou, China; ¶Taipei Veterans General Hospital, Taipei, Taiwan; and #Samsung Medical Centre, Sungkyunkwan University School of Medicine, Seoul, South Korea.

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Address for correspondence: Keunchil Park, MD, PhD, Samsung Medical Centre, Sungkyunkwan University School of Medicine, Seoul, South Korea. E-mail: kpark@skku.edu

Tony Mok and Yi-long Wu contributed equally to this study.

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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 that was 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 who were ineligible for other erlotinib trials. In each country involved, recruitment continued until erlotinib was granted a license.

Recruitment into the TRUST study ceased as of June 28, 2007. A total of 6665 patients were enrolled into the study at 513 centers across 51 countries worldwide. Of the 1242 patients recruited within the East/South-East (E/SE) Asian region (China, Taiwan, Hong Kong, Korea, Thailand, Malaysia, and Indonesia), 1241 were of Asian ethnicity. For the purposes of this analysis, we report data from all 1242 patients who were recruited in the E/SE Asian region to investigate the hypothesis that treatment outcomes in this subgroup would be superior to those observed in a largely non-Asian population (2% of patients recruited in other regions were Asian). The E/SE Asian population from TRUST provides the largest prospective data set available to determine the efficacy and safety of erlotinib in Asian patients with advanced NSCLC and to explore potential predictive factors for better response and longer survival in this population.

PATIENTS 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 childbearing potential were required to test negative for pregnancy and agree to birth control precautions.

Key exclusion criteria included the following: any evidence of unstable systemic disease (including active infection; grade four 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's 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. Hoffmann-La Roche, Basel, 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 for patients with stage IIIB/IV NSCLC who had failed or were unsuitable for chemotherapy/radiotherapy before approval. Secondary objectives were to assess safety, best response, progression-free survival (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 and then every 4 weeks throughout the study. Tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST)[11] at least every 2 months (by computerized tomography, magnetic resonance imaging, or radiography). For patients who were classified as having tumor response, 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 was recorded as a secondary end point. The incidence and severity of ILD was 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 in 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 above). Within 2 weeks of a dose reduction, erlotinib-related

toxicity must have improved by ≥1 NCI-CTC grade and be NCI-CTC grade ≤2 (or ≤1 for ocular toxicity), or a further dose reduction was required. Dose re-escalation 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 (ORR) was defined as the sum of CR and PR. A patient was classified as having SD if they had a response assessment of CR, PR, or SD at more than one visit but were not confirmed as having a 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). Clinical outcomes, including ORR, DCR, PFS, 1-year survival, and OS, were also available for the global TRUST non-E/SE Asian population for comparison with the TRUST E/SE Asian population. Clinical outcomes were collected for all E/SE Asian patients, including those who received erlotinib as first-line treatment.

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 the following: gender (male/female); age (<65 years/≥65 years); ECOG PS (PS 0 or 1/PS 2 or 3); stage (stage IV/stage IIIB); histology (adenocarcinoma or bronchoalveolar carcinoma [adeno/BAC]/squamous cell carcinoma); treatment line (second line/third line); smoking status (nonsmoker [NS = smoked ≤100 cigarettes in their lifetime]/current or former smoker [C/FS = smoked >100 cigarettes in their lifetime]). Given that 1241 of 1242 patients were Asian, ethnicity was not considered as a baseline factor in this analysis. 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 2, 2004, and June 28, 2007, a total of 6665 patients were enrolled in the TRUST study, including 1345 patients of Asian ethnicity and 5320 patients of non-Asian ethnicity. The study database was locked (cut-off date) on April 17, 2009. Of the 1345 Asian patients enrolled in the TRUST study, we report data from the subpopulation of patients who were recruited in E/SE Asia (n = 1242), including those from the following seven countries/regions: mainland China (n = 519); Taiwan (n = 300); South Korea (n = 201); Hong Kong (n = 179); Thailand (n = 30); Indonesia (n = 8); and Malaysia (n = 5). The E/SE Asian study population (n = 1242) comprised all patients who had received at least one dose of erlotinib (regardless of whether major protocol violations occurred). The median duration of follow-up was 4.57 months (range, 0–37.06 months) for 1239 E/SE Asian patients and 2.20 months (range, 0–43.36) for 5309 non-E/SE Asian patients with a known end date (the remaining 3 E/SE Asian patients and 29 non-E/SE Asian patients were not included in this analysis, mainly because they were lost to follow-up [E/SE Asian patients n = 3, 100%; non-E/SE Asian patients n = 19, 66%]).

Baseline disease characteristics are summarized in Table 1. Over half of the E/SE Asian patients (54%) were male and 55% were NS. Adenocarcinoma was the most common histology (70%). Eighty percent of patients had advanced stage IV disease and 81% had a PS of 0 to 1. Nine percent of patients were chemonaive, 57% had received one former line of treatment, and 34% had received two or more lines of prior treatment. Of the 111 patients who received erlotinib as first-line therapy, 53% were male, 46% were NS, 65% had adenocarcinoma, 74% had stage IV disease, and 74% had a PS of 0 to 1.

Response and Survival

Best response data were available for 1118 E/SE Asian and 4276 non-E/SE Asian patients, including 21 (2%) E/SE and 185 (4%) non-E/SE Asian patients who were not evaluable because 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 124 E/SE and 1062 non-E/SE Asian patients could not be included in the response analyses because no best response data were available (mainly due to symptomatic deterioration [40%] or patient refusal [23%] in the E/SE population and symptomatic deterioration [35%] and death due to malignant disease [23%] in the non-E/SE Asian population). Both the ORR and DCR were significantly higher in these patients compared with non-E/SE Asian patients (n = 4276), ORR: 27% versus 10% ($p < 0.0001$); DCR: 78% versus 66% ($p < 0.0001$), respectively.

PFS was significantly longer in E/SE Asian versus non-E/SE Asian patients: 5.78 months (n = 1242; 95% confidence interval [CI]: 5.39–6.57) versus 2.92 months (n = 5338; 95% CI: 2.79–3.02), respectively (HR = 0.66, 95% CI: 0.62–0.70, $p < 0.0001$) (Figure 1*A*).

Median OS for E/SE Asian versus non-E/SE Asian patients was 14.7 months (n = 1242; 95% CI: 13.8–15.5) versus 6.8 months (n = 5338; 95% CI: 6.5–7.1), respectively (HR = 0.57, 95% CI: 0.53–0.62, $p < 0.0001$) (Figure 1*B*). At the time of data cutoff, the 1-year survival rates were 58.3% (28.3% censored) and 32.7% (16.6% censored), respectively.

Response and Survival in Selected Subgroups

In a separate analysis, response and survival data for subgroups, defined on the basis of gender, histology (squamous or nonsquamous cell carcinoma), and smoking status (C/FS or NS), were assessed (data not shown). Females with adenocarcinoma attained the highest tumor response rates (42% for C/FSs and 35% for NSs). The lowest DCR (38%) was observed in the subgroup of male NSs with squamous

TABLE 1. Baseline Demographic and Clinical Characteristics in TRUST

Characteristic	E/SE Asian Population (n = 1242)	Non-E/SE Asian Population (n = 5338)
Age, yr, median (range)	60 (22–87)	63 (19–91)
Gender, *n* (%)		
Male	668 (54)	3306 (62)
Female	574 (46)	2032 (38)
Ethnic origin, *n* (%)		
Caucasian/white	1 (<1)	5056 (95)
Asian[a]	1241 (100)	104 (2)
Other[b]	0 (0)	178 (3)
ECOG PS, *n* (%)		
0	204 (16)	1269 (24)
1	803 (65)	2701 (51)
2	181 (15)	1054 (20)
3	54 (4)	306 (6)
No data	0 (0)	8 (<1)
Stage, *n* (%)		
Stage IIIB	251 (20)	1125 (21)
Stage IV	991 (80)	4194 (79)
Other	0 (0)	15 (<1)
No data	0 (0)	4 (<1)
Histology, *n* (%)		
Adenocarcinoma	867 (70)	2723 (51)
Bronchoalveolar carcinoma	32 (3)	340 (6)
Large cell carcinoma	12 (<1)	370 (7)
Squamous cell carcinoma	221 (18)	1331 (25)
Other	110 (9)	571 (11)
No data	0 (0)	3 (<1)
Prior lines of chemotherapy, *n* (%)		
None	111 (9)	758 (14)
One	704 (57)	2520 (47)
Two	420 (34)	2008 (38)
Other	7 (<1)	52 (<1)
Smoking status, *n* (%)		
NS	689 (55)	1315 (25)
C/FS	553 (45)	4014 (75)
No data	0 (0)	9 (<1)

[a] Includes patients from China, Taiwan, Hong Kong, Korea, Thailand, Malaysia, and Indonesia.
[b] Includes patients with "Indian" ethnicity.
TRUST, Tarceva Lung Cancer Survival Treatment; E/SE, East/South-East; ECOG PS, Eastern Cooperative Oncology Group performance status; NS, nonsmoker; C/FS, current or former smoker.

TABLE 2. Best Response to Erlotinib in Patients Recruited into TRUST

	E/SE Asian Population (n = 1118), *n* (%)	Non-E/SE Asian Population (n = 4276), *n* (%)
Complete response (CR)	9 (<1)	36 (<1)
Partial response (PR)	295 (26)	373 (9)
Objective response rate (ORR = CR + PR)	304 (27)	409 (10)
Stable disease (SD)	571 (51)	2421 (57)
Disease control rate (DCR = CR + PR + SD)	875 (78)	2830 (66)
Progressive disease (PD)	222 (20)	1261 (29)
Not evaluable (NE)	21 (2)	185 (4)
Total (CR + PR + SD + PD + NE)	1118 (100)	4276 (100)
Remaining patients in the study population for whom no best response data were available, mainly due to	124	1062
Symptomatic deterioration	49 (40)	375 (35)
Patient refusal	28 (23)	
Death due to malignant disease	—	247 (23)

[a] Only the two most frequently reported reasons are listed.
TRUST, Tarceva Lung Cancer Survival Treatment; E/SE, East/South-East.

cell carcinoma (no responses were reported); however, there were only 13 patients in this category. Variability in the DCR between the other groups ranged from 62% (female NSs with squamous cell tumors) to 86% (female NSs with nonsquamous cell tumors). Across all subgroups examined, the median PFS and OS ranged from 1.7 months and 3.9 months (both in the subgroup of male NSs with squamous tumors) to 9.2 months and 20.3 months, respectively (both in the subgroup of female NSs with nonsquamous tumors). Median PFS and OS were generally higher among all female subgroups compared with male subgroups.

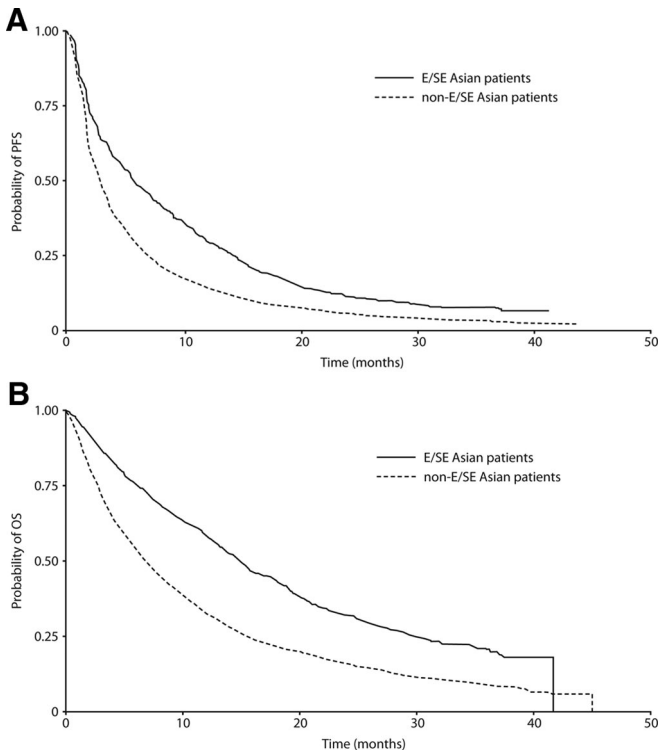

FIGURE 1. Progression-free survival (*A*) and overall survival (*B*) in TRUST E/SE Asian patients (n = 1242) versus TRUST non-E/SE Asian patients (n = 5338).

TABLE 3. Multivariate Analyses for PFS, OS, and DCR

Factor (Cox Regression Model)	HR	95% CI	p
Factors for PFS (n = 1022)			
Histology (SCC: adeno/BAC)	1.66	1.40–1.98	<0.001
Smoking status (C/FS: NS)	1.46	1.27–1.68	<0.001
ECOG PS (2 or 3: 0 or 1)	1.27	1.07–1.50	0.0058
Factors for OS (n = 1022)			
ECOG PS (2 or 3: 0 or 1)	1.80	1.50–2.16	<0.0001
Histology (SCC: adeno/BAC)	1.72	1.43–2.06	<0.0001
Gender (male: female)	1.32	1.08–1.63	0.0075
Smoking status (C/FS: NS)	1.32	1.07–1.63	0.0094
Factor (Logistic Regression Model)	**Odds Ratio[a]**	**95% CI**	**p**
Factors for DCR (n = 930)			
Smoking status (C/FS: NS)	1.61	1.15–2.26	0.0058
Histology (SCC: adeno/BAC)	1.54	1.03–2.29	0.0348

[a] For response: no response.

PFS, progression-free survival; OS, overall survival; DCR, disease control rate; SCC, squamous cell carcinoma; adeno, adenocarcinoma; BAC, bronchoalveolar carcinoma; HR, hazard ratio; CI, confidence interval; C/FS, current or former smoker; NS, nonsmoker; ECOG PS, Eastern Cooperative Oncology Group performance status.

Multivariate Analyses

Multivariate analyses were performed using the Cox regression model for PFS and OS and using the logistic regression model for DCR (Table 3). For both the PFS and OS analyses, data were available for 1022 E/SE Asian patients, with 220 patients excluded because of missing data. For the PFS analysis, 113 patients had not experienced progression at the last observation, and their data were therefore censored. The model for PFS was optimized to include the following characteristics: smoking status, baseline ECOG PS, and histology. In this population, NSs who had a baseline ECOG PS of 0/1 and adeno/BAC histology were more likely to experience longer PFS compared with patients in other subgroups. For the OS analysis, data were censored for the 301 patients who were still alive at last contact. The optimal model for OS included gender in addition to the characteristics mentioned above. Females, NSs, with a baseline ECOG PS of 0/1, and adeno/BAC histology were more likely to experience longer survival compared with patients in other subgroups. For both the PFS and OS optimal models, the factors mentioned above were shown to be statistically significant ($p < 0.05$). For the DCR analysis using the logistic regression model, data were available for 930 patients of whom 730 experienced disease control. A further 312 patients were excluded because of missing data. The optimal model for DCR included smoking status and histology; NSs with adeno/BAC histology were more likely to experience disease control. Both these factors were shown to be statistically significant ($p < 0.05$) by logistic regression analysis.

Of particular interest is the subgroup of E/SE Asian patients who received erlotinib as first-line therapy. Of 111 patients, 37% were NSs with adenocarcinoma and approximately 26% of the first-line therapy group had poor PS (PS 2/3), with a median age of 72 years, compared with 60 years in the overall E/SE Asian population. The tumor response rate in this population was 31%, and the median OS was 11.5 months (95% CI: 7.6–14.3).

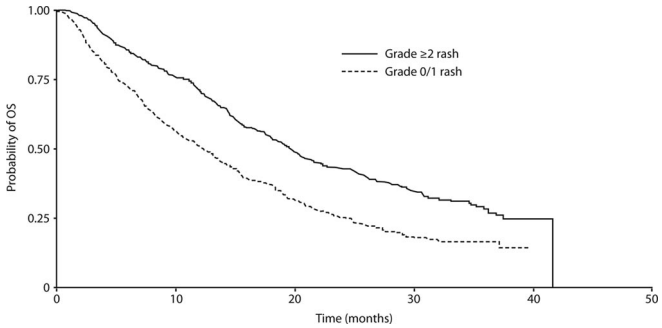

FIGURE 2. Overall survival according to rash (grade 0/1 versus grade ≥2; n = 1186).

Efficacy data for patients with erlotinib-related rash were available for all 1242 E/SE Asian patients. Of these, 1021 patients (82%) experienced rash of any grade (36% grade 0 to 1, 46% grade 2 to 4). Median OS for patients with erlotinib-related rash of grade 2 to 4 was 19.5 months (95% CI: 17.8–21.1) versus 12.2 months for patients with grade 0 to 1 rash (95% CI: 10.6–13.6, HR = 0.60; $p < 0.0001$) (Figure 2).

Safety and Tolerability

Safety data were available for all 1242 E/SE Asian patients of whom 532 (43%) had one or more AE regardless of causality. Seventeen percent of patients experienced an erlotinib-related AE (other than the most frequently occurring AEs predefined in the protocol; Table 4); of these patients, 87% had an AE that was grade 1 or 2 in severity. Only 31 (2%) patients had an SAE considered to be related to treatment. These included gastrointestinal disorders (diarrhea or abdominal pain) and skin and subcutaneous tissue disorders (includes rash; Table 5). ILD occurred in two patients (0.16%); one patient had grade 2 ILD that resolved spontaneously and the other patient had grade 4 ILD that did not improve despite treatment withdrawal.

TABLE 4. Erlotinib-Related Adverse Events (Any Grade)[a] Reported in ≥1% of Patients (n = 1242)[b]

Event	Any Grade, n (%)	Grade 3–4, n (%)
Patients with any erlotinib-related AE	207 (17)	27 (2)
Gastrointestinal disorders	34 (3)	0 (0)
Mouth ulceration	24 (2)	0 (0)
Infections and infestations	79 (6)	6 (<1)
Paronychia	75 (6)	3 (<1)
Investigations	55 (4)	3 (<1)
Alanine aminotransferase increased	17 (1)	2 (<1)
Aspartate aminotransferase increased	15 (1)	1 (<1)
Blood bilirubin increased	21 (2)	1 (<1)
Nervous system disorders	16 (1)	0 (0)
Skin and subcutaneous tissue disorders	27 (2)	3 (<1)
Blood and lymphatic system disorders	15 (1)	4 (<1)
Eye disorders	14 (1)	1 (<1)
Respiratory, thoracic, and mediastinal disorders	15 (1)	5 (<1)

[a] As defined by NCI-CTC criteria v3.0.

[b] Other than the most frequently occurring pre-specified events.

AE, adverse event; NCI-CTC, National Cancer Institute Common Toxicity Criteria.

TABLE 5. Erlotinib-Related Serious Adverse Events[a] (Any Grade) Reported in >1 Patient (n = 1242)

Event	Any Grade, n (%)	Grade 3–4, n (%)
Patients with any erlotinib-related SAE	31 (2)	26 (2)
Gastrointestinal disorders	8 (<1)	7 (<1)
Abdominal pain	2 (<1)	2 (<1)
Diarrhea	4 (<1)	3 (<1)
General disorders and administration site conditions	4 (<1)	3 (<1)
Infections and infestations	4 (<1)	3 (<1)
Respiratory, thoracic and mediastinal disorders	5 (<1)[b]	3 (<1)
Pneumonitis	2 (<1)	2 (<1)
Skin and subcutaneous tissue disorders	8 (<1)	6 (<1)
Rash	6 (<1)	4 (<1)

[a] As defined by NCI-CTC criteria v3.0.
[b] One grade 5 event occurred (respiratory failure).
SAE, serious adverse event; NCI-CTC, National Cancer Institute Common Toxicity Criteria.

This patient subsequently had respiratory failure and died. Both cases were considered to be erlotinib related.

Dose reductions were reported for 171 patients (14%); 164 (13%) of these patients required a dose reduction due to erlotinib-related AE. The majority (71%) of the 171 dose reductions were necessitated by an erlotinib-related skin rash. Another 10 patients required a dose reduction for diarrhea (<1%), and one patient required a dose reduction for hepatic dysfunction (hyperbilirubinemia; <1%). The majority of all dose reductions (167 patients; 13%) were to 100 mg/d, with only 22 (2%) patients requiring further reduction to 50 mg/d. AEs resulting in treatment withdrawal occurred in 31 (2%) patients; all AEs and groups of AEs (by body system) that resulted in treatment withdrawal occurred in <1% of patients. Three (<1%) patient deaths occurred due to a treatment-related event; one patient each due to pneumonia (grade 3), pneumonitis (grade 3), and respiratory failure (grade 5).

DISCUSSION

We confirm the superior outcomes with erlotinib in this patient population, compared with the TRUST overall global population (includes E/SE Asian and non-E/SE Asian patients) (Reck et al., unpublished data). The median PFS for the E/SE Asian population was 5.78 months compared with 2.92 months for the non-E/SE Asian population and 3.25 months for the overall global population (Reck et al., unpublished data). The median OS was 14.7, 6.8, and 7.9 months, respectively (Reck et al., unpublished data). The ORR was significantly higher for the E/SE Asian patients (27%), compared with the non-E/SE Asian patients (10%) or the overall global population (13%) (Reck et al., unpublished data). The conclusions from the study must be tempered by the limitations of the open-label, nonplacebo-controlled, single-arm study design.

In this study, 111 patients (9%) received erlotinib as first-line therapy, compared with 13% of the overall global population (Roche, data on file). In the E/SE Asian patients, we found no significant differences in PFS between patients who received erlotinib as first-line treatment, compared with those who received erlotinib as second-/third-line treatment. This finding supports data from Spanish patients with known *EGFR* mutation status where tumor response rates to erlotinib as first- and second-line therapy were 73.5% and 67.4%, respectively (p = 0.35). In these patients, there were also no significant differences in PFS and OS between those receiving first-line erlotinib and those receiving second-line erlotinib.[9] In patients who received first-line erlotinib therapy, we report a tumor response rate of 31% and a median survival time of 11.5 months. Patients who receive first-line therapy would usually be expected to have better survival outcomes than those treated second-line therapy or later. In our study, the most likely explanation for the shorter median OS in this subgroup (11.5 months) compared with the overall E/SE Asian population (14.7 months) is that most of these patients were not eligible for chemotherapy because of advanced age and/or poor PS. Patients who are preselected on the basis of poor PS may have shorter survival with EGFR TKI therapy.[12,13]

Multivariate analyses for PFS and OS showed that smoking status (NS), histology (adeno/BAC), and gender (females) were all predictive of longer survival with erlotinib. The benefit obtained in these patients, in addition to E/SE Asian patients who received first-line erlotinib therapy, is likely to be driven by the presence of higher rates of *EGFR* mutations. In subgroup analyses based on gender, smoking status, and histology, all subgroups including C/FS, males, and patients with squamous cell histology obtained a survival benefit with erlotinib. Patients in these subgroups are less likely to harbor activating *EGFR* mutations.[14] This finding is compatible with SATURN data in which patients with *EGFR* wild-type disease obtained a survival benefit with erlotinib compared with placebo.[15] However, the reason for such benefit remains to be explored.

This analysis of TRUST is the first study that establishes skin rash as a predictive factor for improved PFS and OS with erlotinib in an Asian population. The PFS and OS for patients who experienced grade ≥2 rash was found to be significantly longer than that for patients experiencing grade 0/1 rash. This finding is consistent with the TRUST global population (Reck et al., unpublished data; Roche, data on file) and is supportive of the suggested link between the grade of rash and the efficacy of EGFR inhibitor-based therapy.[16,17] Although skin rash was the major toxicity in our study, it is crucial that Asian patients who develop skin rash continue to receive erlotinib therapy, because they are the population that obtain the greatest benefit from this therapy. Active and vigorous management of skin rash are therefore an essential aspect of treatment.

No new safety signals were identified in this study. Because the prespecified expected treatment-related AEs were not recorded (unless they resulted in premature treatment withdrawal), it is not possible to comment on the frequency or severity of these events. However, the results reported here support the favorable safety profile of erlotinib seen in previous clinical trials. Despite reports of a higher risk of ILD in Japanese patients, we found that the incidence of ILD in the E/SE Asian population was low and similar to that observed in the global population (<1% in both cases) (Reck et al., unpublished data).

In summary, our data from more than 1200 E/SE Asian patients confirm the role of erlotinib in the management of NSCLC in this population. The superior outcomes compared with the non-E/SE population are likely to be driven by the higher *EGFR* mutation rate in the Asian population. These results complement data from the overall global population and confirm the favorable safety profile of erlotinib.

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