JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2015, 45(6) 569–575
doi: 10.1093/jjco/hyv036
Advance Access Publication Date: 7 April 2015
Original Article

OXFORD

Original Article

Efficacy of erlotinib in previously treated patients with advanced non-small cell lung cancer: analysis of the Chinese subpopulation in the TRUST study

Yisheng Huang[1], Li Zhang[2], Yuankai Shi[3], Shenglin Ma[4], Meilin Liao[5], Chunxue Bai[6], Qingyuan Zhang[7], Changli Wang[8], Feng Luo[9], Shiying Yu[10], Shukui Qin[11], Xiuyi Zhi[12], and Caicun Zhou[13,*]

[1]Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, Guangdong Province, [2]Cancer Center of Sun Yat-Sen University, Guangdong Province, [3]Cancer Institute and Hospital, Chinese Academy of Medical Sciences, Beijing, [4]Hangzhou First People's Hospital, Zhejiang Province, [5]Lung Tumor Clinical Medicine Center, Shanghai Chest Hospital, Shanghai, [6]Department of Pulmonary Medicine, Zhongshan Hospital Affiliated with Fudan University, Shanghai, [7]Department of Medical Oncology, Tumor Hospital of Harbin Medical University, Helongjiang Province, [8]Tianjin Tumor Hospital, Tianjin, [9]Department of Oncology, Cancer Center and State Key Laboratory of Biotherapy, West China Hospital of Sichuan University, Sichuan Province, [10]Tongji Medical College, Huazhong University of Science and Technology, Hubei Province, [11]Nanjing Eight One Hospital, Jiangsu Province, [12]Beijing Lung Cancer Center, Capital Medical University, Beijing, and [13]Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, PR China

*For reprints and all correspondence: Caicun Zhou, Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, No. 507 Zhengmin Road, Shanghai 200433, PR China. E-mail: caicunzhoudr@163.com

Received 18 November 2014; Accepted 17 February 2015

Abstract

Objective: This study is to analyze the data of Chinese subpopulation in the Tarceva Lung Cancer Survival Treatment Study (TRUST-China) which was a global Phase IV study designed to provide erlotinib to previously treated patients with Stage IIIB/IV non-small cell lung cancer.

Methods: Patients with pathologically confirmed, unresectable Stage IIIB/IV non-small cell lung cancer who were previously failed on or unsuitable for chemotherapy or radiotherapy were given erlotinib (150 mg/day, oral) until disease progression, intolerable toxicity or death. Efficacy and toxicity of the agent were evaluated.

Results: In total, 519 patients Chinese patients were analyzed. The TRUST-China had similar baseline characteristics to TRUST-Global except the greater percentage of adenocarcinoma and non-smoker cases. The response rate and disease control rate were 24.7 and 75.3%, respectively. Median progression-free survival and overall survival were 6.4 and 15.4 months in the general Chinese population in the TRUST, and 10.2 and 18.9 months in non-smokers with adenocarcinoma ($n = 254$). Median progression-free survival and overall survival were significantly longer in non-smokers with adenocarcinoma than those in other groups ($P \leq 0.0001$ and $P \leq 0.0001$, respectively). Eastern Cooperative Oncology Group Performance Status (≥ 2 vs. ≤ 1, hazard ratio = 1.746, $P < 0.0001$) and histology (squamous cell carcinoma vs. adenocarcinoma, hazard ratio = 1.595, $P = 0.0008$) were independent risk factors that affected survival according to Cox regression multivariate analysis.

Conclusions: We confirmed the efficacy and safety of erlotinib in Chinese patients. Non-smoking patients with adenocarcinoma histology had the best clinical benefits. (NCT00949910).

Key words: non-small cell lung cancer, EGFR mutation, adenocarcinoma, erlotinib, TRUST study

Introduction

Lung cancer is the most common type of tumor causing cancer-related death in the world (1). Approximately 30–50% of patients with non-small cell lung cancer (NSCLC) are initially diagnosed at an advanced stage. These patients usually have a poor prognosis (2–6). In recent years, however, the application of targeted therapies has significantly improved the clinical outcomes of patients with advanced NSCLC (7–10).

Erlotinib is an inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase activity. It was approved in 2004 by the US Food and Drug Administration for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen (11). Various clinical trials have demonstrated that erlotinib can effectively improve the outcomes of patients with advanced NSCLC (11,12). In 2006, erlotinib was approved by the Chinese Food and Drug Administration for the treatment of advanced NSCLC.

The tumor responses to EGFR tyrosine kinase inhibitors (TKIs) are reported to be variant in different subpopulations of patients with NSCLC. Those who are female and have an adenocarcinoma (ADC) histology, Asian ethnicity and a non-smoking history tend to be more sensitive to TKI treatment (13,14). The IPASS (Iressa Pan-Asia Study) study showed that gefitinib (another EGFR-TKI) is more active in the IPASS population (non-smokers or former light smokers with pulmonary ADC in East Asia) than chemotherapy (7). The incidence of mutations in the EGFR TK domain is reported to be much higher in these subgroups of patients, i.e. clinically enriched tumor-EGFR-mutated patients (15). In a subgroup of non-smokers with ADC, EGFR was the most frequently altered gene, with a mutation rate of 49.8% (16). EGFR gene mutations are closely associated with the efficacy of EGFR-TKIs, such as erlotinib and gefitinib (7,17–19).

In the Tarceva Lung Cancer Survival Treatment Study (TRUST), a global Phase IV trial based on >6500 unselected patients with advanced NSCLC, Reck et al. (20) reported TRUST-Global result of the suitability of erlotinib 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. Analysis of the East/South-East Asian subpopulation of the TRUST study showed that erlotinib had superior outcomes and was a well-tolerated treatment for Asian patients with advanced NSCLC (21). Similarly, analysis of the Taiwanese population in the TRUST study also demonstrated the efficacy of erlotinib in a large population of Taiwanese NSCLC patients who had been previously treated with chemotherapy or radiotherapy (22). It was shown that a history of non-smoking or ADC were significantly correlated with response to erlotinib treatment (22). In addition, a large scale retrospective multicenter study in Taiwan revealed that both erlotinib and gefitinib were more effective in the IPASS population than in the non-IPASS population (23). Although a lot of evidence has shown that the EGFR mutation status is the most important factor that determines whether NSCLC patients are sensitive to EGFR-TKIs and Asian NSCLC patients harbor a relatively higher incidence rate of the EGFR mutation, only 9.6% of patients with Stage IIIB or IV disease have undergone EGFR testing in China (24). In the clinic, the majority of Chinese NSCLC patients have an unknown EGFR status when chemotherapy or TKI regimens are selected. Therefore, it is still valuable to identify those subpopulations who are sensitive to erlotinib according to clinical and pathological characteristics.

The objective of this report was to analyze the efficacy and safety data of the Chinese subpopulation of the TRUST study based on histology and smoking history classifications.

Patients and methods

Patients

This study was a part of the global TRUST study and was conducted in a Chinese population (NCT00949910, MO18109 study sponsored by Hoffmann-La Roche) (20). The study protocol was approved by the respective ethics committees at all participating institutions. Informed consent was obtained from all patients before enrollment. This clinical trial was conducted between November 2005 and October 2006 at 16 Chinese medical institutions. The inclusion criteria were as follows: (i) age ≥18 years old; (ii) histologically or cytologically confirmed, unresectable Stage IIIB/IV NSCLC; (iii) 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); (iv) anticipated a life expectancy of 12 weeks or longer; (v) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–3; and (vi) adequate hematological, renal and hepatic function.

The major exclusion criteria were as follows: (i) evidence of unstable systemic disease; (ii) prior treatment with anti-EGFR agents (including TKIs and monoclonal antibodies); (iii) untreated brain metastases (newly diagnosed or pre-existing) or spinal cord compression; (iv) previous malignancies within the last 5 years (other than cervical carcinoma or skin cancer that underwent successful treatment).

Study design and treatment

This was a Phase IV, open-label, single-arm study. Eligible patients received oral 150 mg/day of erlotinib (F. Hoffman-La Roche, Switzerland) until disease progression, intolerable toxicity, withdrawal or death. Dose interruption or reduction in 50 mg/day decrements was allowed in the case of erlotinib-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 overall survival (OS). The incidence and severity of an erlotinib-related rash were also secondary end points for this study.

Clinical evaluation

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) at least every 2 months (by computerized tomography, magnetic resonance imaging or radiography) (25) For patients who were classified as having tumor response, a confirmatory evaluation was carried out 4 weeks after the initial determination of response. The safety and tolerability were evaluated monthly by clinical examination, blood cell count and biochemistry. The AEs and serious AEs (SAEs) of any cause were assessed and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0.

Statistical analysis

The overall response rate (ORR) 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 the start of treatment until the date of death (irrespective of cause). Comparisons of demographic, clinical and pathological variables were performed using the χ^2 test. The Kaplan–Meier method was used to analyze survival data, and statistical differences were evaluated by the log-rank test. Unless otherwise stated, the results are expressed as medians with 95% confidence intervals (95% CIs). A 0.05 nominal significance level without multiplicity adjustment was adopted. Multivariate Cox regression proportional hazards analysis was used to determine the association between risk factors (age, gender, ECOG PS, stage of disease, histology and smoking status) and PFS and OS in each group. All tests were two-sided, and analyses were carried out using SAS software, version 8.2 (SAS Institute Inc., USA).

Results

Patient characteristics

A total of 519 patients with advanced NSCLC were enrolled in this study (TRUST-China, 223 females and 296 males). The mean age was 57 years old (ranging from 24 to 82 years old). The majority of patients had an ECOG PS of 1 (61.8%, $n = 321$), were in Stage IV (82.3%, $n = 427$), and had ADC (77.3%, $n = 401$). Furthermore, 302 patients (58%) were treated with erlotinib in this trial as the second-line treatment, and 216 patients (42%) as the third-line treatment. The Chinese subpopulation in this study had similar baseline characteristics to TRUST-Global (Table 1) except that the Chinese population had a greater percentage of ADC as well as non-smoker cases.

Table 1. Characteristics of the Chinese population and the global population in the TRUST Study

Characteristics	TRUST-China ($n = 519$) No. of patients (%)	TRUST-Global ($n = 6586$) No. of patients (%)
Age (years)		
Mean (range)	57 (24–82)	63 (19–91)
Gender		
Male	296 (57.0)	3976 (60.4)
Female	223 (43.0)	2608 (39.6)
ECOG PS		
0	94 (18.1)	1473 (22.4)
1	321 (61.8)	3508 (53.3)
2	81 (15.6)	1236 (18.8)
3	23 (4.4)	360 (5.5)
Stage of disease		
III B	92 (17.7)	1377 (20.9)
IV	427 (82.3)	5190 (78.8)
Histology		
Squamous cell carcinoma	95 (18.3)	1555 (23.6)
Adenocarcinoma	401 (77.3)	3967 (60.3)
Large cell carcinoma	3 (0.6)	382 (5.8)
Others	20 (3.9)	679 (10.3)
Erlotinib treatment		
First line	1 (0.2)	872 (13.2)
Second line	302 (58.2)	3225 (49.0)
Third line	216 (41.6)	2432 (36.9)
Smoking status		
Non-smoker	284 (54.7)	2005 (30.4)
Smoker (previous or current)	235 (45.3)	4572 (69.4)

All data are expressed as numbers of patients (%), unless otherwise indicated. ECOG PS, Eastern Cooperative Oncology Group performance status.

Tumor response

The best overall response data were available in 479 patients, in which CR was observed in only 1 patient (0.2%), PR in 127 patients (26.5%), objective response rate (ORR = CR + PR) in 128 patients (26.7%), SD in 263 patients (54.9%) and the DCR (CR + PR + SD) was 81.6% PD was observed in 88 patients (18.4%). Two patients were not evaluable and 38 patients were not evaluated.

PFS and OS

Survival data were available for all 519 patients. Median PFS and OS were 6.4 months (95% CI: 5.5–7.9 months) and 15.4 months (95% CI: 14.2–17.7 months) respectively, which were longer than those in the TRUST-global study population (median PFS: 3.3 months; median OS: 8.2 months).

Survival in selected subgroups

Patient PFS and OS were further evaluated based on gender, smoking history and histological classifications (Supplementary data, Tables S1 and S2). Being a female, non-smoker or having ADC favored a longer PFS and OS in comparison to being a male, smoker, or having squamous cell carcinoma (SCC)/other histology, respectively. The study population was divided into groups according to histological type: ADC, large cell carcinoma (LCA), SCC and other histological types (Fig. 1). Patients with ADC had a median PFS of 8.4 months (95% CI: 7.2–9.7) and a median OS of 16.6 months (95% CI: 14.7–18.9). The median PFS and OS for SCC were 3.1 months (95% CI: 2.76–3.98) and 8.6 months (95% CI: 6.14–13.4), respectively. Statistically significant differences were observed between the ADC group and the non-ADC (SCC + LCA + other types) group, in terms of both PFS and OS, and the results are presented in Fig. 1 ($P \leq 0.0001$ for both).

Based on the combination of histology and smoking status (smoker or non-smoker), non-smokers with ADC had a significantly longer PFS (mPFS: 10.2 months, 95% CI: 8.4–11.6 months) in comparison to smokers with ADC, smokers with SCC or non-smokers with SCC ($P = 0.0003$, $P < 0.0001$, $P = 0.0001$, respectively). However, the PFS among smokers with ADC, smokers with SCC and non-smokers

with SCC were not statistically different (all $P > 0.05$) (Table 2 and Fig. 2A). We further analyzed the patient OS based on the combination of histology and smoking status. Non-smokers with ADC had a significantly longer OS (median OS: 18.9 months, 95% CI: 15.7–21.7 months) in comparison to patients in the other three groups (all $P \leq 0.0001$) (Table 2 and Fig. 2B).

Multivariate analysis of ADC and SCC populations

Multivariate risk factor analysis was performed for OS using the Cox regression model with the data from patients with ADC or SCC ($n = 496$) and showed that ECOG PS (ECOG PS ≥2 vs. ≤1, hazard ratio [HR]: 1.746, 95% CI: 1.352–2.233, $P < 0.0001$) and histology (SCC vs. ADC, HR: 1.595, 95% CI: 1.207–2.091, $P = 0.0008$) were independent risk factors that affected patient survival (Table 3).

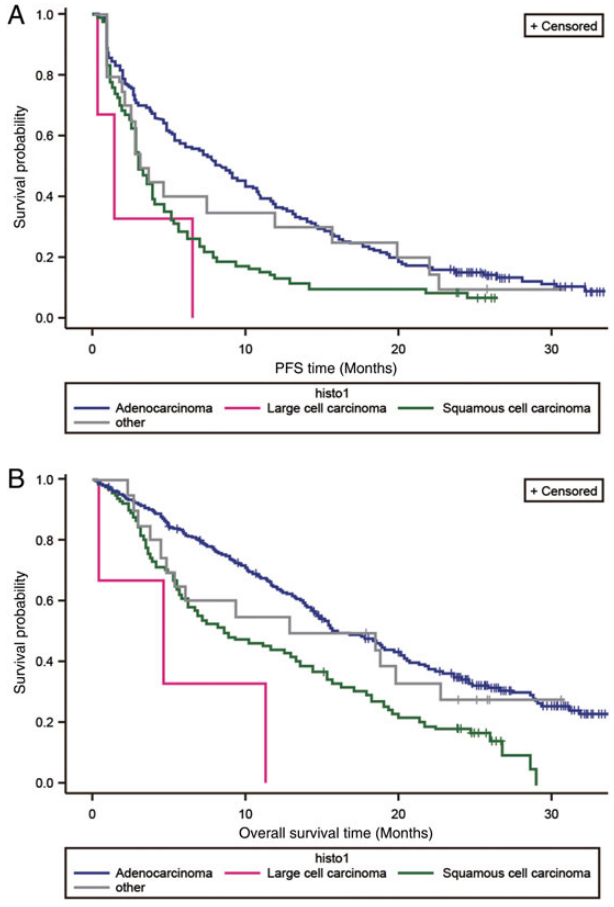

Figure 1. Kaplan–Meier survival plots according to histology type of the patients receiving erlotinib as the second-line therapy: (A) progression-free survival and (B) overall survival.

Safety and tolerability

Safety and tolerability data were available for 519 patients. Of these, 118 patients (23%) had at least one any grade AE and 40 patients (7.7%) had at least one Grade 3–4 AEs. Forty patient (7.7%) died mainly due to disease progression ($n = 16$), respiratory failure ($n = 13$) or lung infection ($n = 7$) (Table 4), in which only one death caused by erlotinib-related interstitial lung disease. Seventy-three patients (14%) had at least one SAE, most of which were caused by the disease progression, respiratory, thoracic and mediastinal disorders, infections or other complications. Only three patients (<1%) had at least one erlotinib-related SAE, including one with Grade 3 perianal abscess, one with Grade 3 abnormal liver function and one with interstitial lung disease complicated with respiratory failure and eventually died during the study. Erlotinib-related AEs resulting in treatment withdrawal occurred in 6 patients (1.2%) because of rash ($n = 1$), interstitial lung disease ($n = 1$), hepatobiliary disorders ($n = 1$), encephalatrophy ($n = 1$), hematuria ($n = 1$), perianal abscess ($n = 1$). Approximately 84% of the patients ($n = 436$) experienced a rash, in which 22 patients had a Grade 3/4 rash (Table 4).

Discussion

In the present study, we further confirmed the efficacy and safety profile of erlotinib in Chinese NSCLC patients who did not respond to previous chemotherapy, especially in the patients with ADC and a non-smoking history. Previous studies on EGFR-TKI treatment in patients with NSCLC have illustrated that these agents are likely more effective in patients with certain clinical characteristics, such as being female and a non-smoker and having ADC histology and an Asian origin (26). Among all clinical features, a history of smoking was identified as a predominant risk factor that affected the efficacy of TKIs. It is likely that the majority of female patients was non-smokers and had a higher incidence of ADC (27–30).

Importantly, in the current study, we demonstrated that the subpopulation of Chinese patients with ADC histology and a non-smoking history had a better PFS (10.2 months) and OS (18.9 months) following erlotinib therapy compared with other Chinese subpopulations. Although the data of the Asian subpopulation from the East or South-East region from the TRUST study have been reported, showing that being a non-smoker or having an ADC histology is associated with a longer PFS and OS (21), the EGFR mutation rate/clinicopathological characteristics are different among different Asian ethnic groups [31]. To the best of our knowledge, this is the longest survival time observed in patients treated with TKIs after failure to respond to previous treatment in a clinically enriched population.

Previous studies have demonstrated that Asian patients with advanced NSCLC have a longer survival time (7). In addition, Shepherd et al. (12) have shown that the median OS in patients treated with erlotinib who did not respond to a previous first-line chemotherapy

Table 2. Survival in selected patient subgroups defined on the basis of histology and smoking status ($n = 496$)

	Median PFS (months)	95% CI	Median OS (months)	95% CI
Non-smoker with ADC ($n = 254$)	10.2	8.4–11.6	18.9	15.7–21.7
Non-smoker with SCC ($n = 21$)	1.8	1.0–3.2	10.2	3.0–19.5
Smoker with ADC ($n = 147$)	4.9	3.9–7.8	13.7	11.6–15.5
Smoker with SCC ($n = 74$)	3.6	2.8–5.1	8.2	6.1–13.4

PFS, progression-free survival; OS, overall survival; ADC, adenocarcinoma; SCC, squamous cell carcinoma; CI, confidence interval.

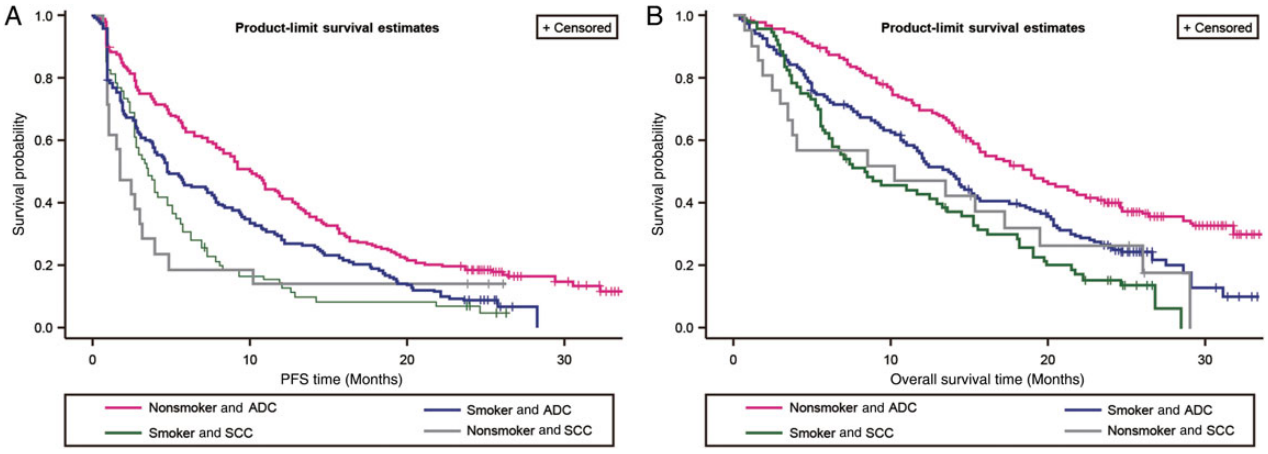

Figure 2. (A) Kaplan–Meier progression-free survival (PFS) plots according to histology and smoking status in patients treated with erlotinib in the TRUST study. PFS is superior in the subgroup of non-smokers with ADC ($n = 254$) compared with the other three subgroups, including smokers with ADC ($n = 147$), non-smokers with SCC ($n = 21$) and smokers with SCC ($n = 74$). ADC, adenocarcinoma; SCC, squamous cell carcinoma. Smokers with ADC vs. non-smokers with ADC: $P = 0.0003$; smokers with ADC vs. smokers with SCC: $P = 0.9979$; smokers with ADC vs. non-smokers with SCC: $P = 0.7290$; non-smokers with ADC vs. smokers with SCC: $P < 0.0001$; non-smokers with ADC vs. non-smokers with SCC: $P = 0.0001$; smokers with SCC vs. non-smokers with SCC: $P = 0.0551$. (B) Kaplan–Meier overall survival (OS) plots according to histology and smoking status in patients treated with erlotinib in the TRUST study. OS is superior in the subgroup of non-smokers with ADC ($n = 254$) compared with the other three subgroups, including smokers with ADC ($n = 147$), non-smokers with SCC ($n = 21$) and smokers with ADC ($n = 74$). Smokers with ADC vs. non-smokers with ADC: $P = 0.0001$. Smokers with ADC vs. smokers with SCC: $P = 0.9818$. Smokers with ADC vs. non-smokers with SCC: $P = 0.6354$. Non-smokers with ADC vs. smokers with SCC: $P < 0.0001$. Non-smokers with ADC vs. non-smokers with SCC: $P < 0.0001$. Smokers with SCC vs. non-smokers with SCC: $P = 0.0133$.

Table 3. Multivariate risk factor analysis for prognosis in patients with ADC or SCC ($n = 496$)

Factor	Variables	Hazard ratio	95% CI	*P* value
Gender	Female vs. male	0.854	0.645–1.134	0.2739
Age	≥65 years vs. <65 years	1.21	0.965–1.511	0.0947
ECOG PS	≥2 vs. ≤1	1.746	1.352–2.233	<0.0001
Histology	SCC vs. ADC	1.595	1.207–2.091	0.0008
Smoking history	C/FS vs. NS	1.289	0.967–1.724	0.0851
Stage of disease	Stage IIIB vs. Stage IV	1	0.750–1.312	0.9975

C/FS, current/former smoker; NS, non-smoker.

was 6.7 months, compared with 4.7 months in control patients. The median PFS was 2.2 months and 1.8 months in erlotinib-treated and control subjects, respectively. While in 91 Asian patients, those receiving erlotinib had a response rate of 18.9% and a median OS of 13.6 months. The survival time in this group of patients was longer than that of other patients with a non-Asian origin. Fan et al. (23) reported that Taiwanese patients with advanced NSCLC who were treated with erlotinib had a higher disease control rate, longer PFS and longer OS compared with patients treated with gefitinib. The median PFS in patients treated with erlotinib was 4.6 months. Erlotinib treatment resulted in a longer median PFS (7.2 months) in the IPASS subpopulation (non-smokers or former light smokers with ADC) (23). In addition, Mok et al. (21) have shown that the Asian subpopulation from the East or South-East region had a median OS of 14.7 months and a median PFS of 5.8 months. Similarly, our study revealed that the median OS of Chinese patients from the TRUST study was 15.4 months, which is almost twice as long as that in the global population (8.2 months). Likewise, the median PFS in the Chinese population is reported to be twice as long as that in the global population (6.4 vs. 3.3 months). The results of our current study are consistent with these previous findings (12,21) and may be attributed to a higher EGFR mutation rate in these clinically enriched populations.

Moreover, the mutation rate of EGFR in NSCLC was 28.4% (147/517) in Chinese patients, in a subgroup of non-smokers with ADC (clinically enriched tumor-EGFR exon 19- or 21-mutated patients); and EGFR was the most frequently altered gene, with a mutation rate of 49.8% (16). Rosell et al. (17) have reported that EGFR mutations were found in 16.6% of patients with lung cancer, and mutations were more frequent in women (69.7%), in non-smokers (66.6%), and in those with ADC (80.9%). Compared with conventional chemotherapy, erlotinib is more effective against advanced EGFR mutation-positive NSCLC (8,9,31). Although EGFR mutation testing is well-established clinical process of lung cancer treatment, the EGFR mutation testing rate for lung cancer treatment in China is only ~10% (24). Many NSCLC Chinese patients are treated with unknown EGFR status due to the low awareness and low test rate. Clinical characteristics are still important factors to choose the regimen. The TRUST-China subset analysis is valuable for Chinese clinical practice of NSCLC.

In our study, the majority of the Chinese patients were non-smokers (54.7%), which is greater than the global population based on the TRUST study (30.5%). Mok et al. (21) have shown that there are more non-smokers than smokers (55% vs. 45%) in the Asian subgroup. The higher proportion of non-smokers is likely to contribute to better clinical outcomes in patients with an Asian origin.

Table 4. Adverse events (AEs) in the Chinese subpopulation ($n = 519$)[a]

Events	No. of patients	%
Patients with at least one AE	118	22.7
Grade 1	19	3.7
Grade 2	19	3.7
Grade 3	27	5.2
Grade 4	13	2.5
Grade 5[b]	40	7.7
Patients with at least one SAE[c]	73	14.1
Respiratory, Thoracic and mediastinal disorders	25	4.8
Infections and infestations	7	1.3
Cardiac disorders	7	1.3
General disorders and administration site conditions	10	1.9
Nervous system disorders	7	1.3
Patients with at least one erlotinib-related SAE	3	0.6
Patients with erlotinib-related AEs leading to withdrawal	6	1.2
Patients with erlotinib-related AEs leading to death	1[d]	0.2
Deaths during the treatment or within 30 days post study	53	10.2
Rash	436	84
Grade 1/2	414	79.8
Grade 3/4	22	4.2

SAE, serious AEs.

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

[b]Majority of death caused by disease progression ($n = 16$), respiratory failure ($n = 13$) or lung infection ($n = 7$).

[c]SAEs in ≥7 patients listed.

[d]This patient died due to interstitial lung disease and respiratory failure.

Multivariate analyses within the Asian subgroup have demonstrated that smoking status is an important risk factor that influences patient survival (21). Similarly, the percentage of Chinese NSCLC patients with ADC was also higher than that in the TRUST-global population (73.4% vs. 54.6%, Table 1). It is well known that the EGFR mutation rate is relatively higher in NSCLC patients with ADC or non-smokers. This fact can explain why non-smokers with ADC had the longest PFS and OS and why PFS and OS for the Chinese subpopulation in the TRUST study were better than those in the global population. The safety profile of erlotinib in this study was consistent with previous reports (21). Shepherd et al. (12) have reported that a skin rash occurred in 75% of patients in their study; while in our study, 84% of Chinese patients developed a skin rash following erlotinib treatment. The incidence of a skin rash in our study was slightly higher than that in the TRUST study, which was 70.6% in the global population. The incidence of interstitial lung disease-like events was 0.8% in both the erlotinib and placebo groups in the BR21 study (12). In the global TRUST study (21), clinically significant adverse events of rash and interstitial lung disease in the Asian subgroup were observed in four patients (<1%) and one patient (<0.1%), respectively. In the present study, one patient experienced a Grade 3/4 rash (<0.1%) and one developed Grade 3/4 interstitial lung disease (<0.1%). Our study together with previous reports have further confirmed the safety of erlotinib in patients with advanced NSCLC.

One limitation of this study is the lack of EGFR mutation information and analysis. The Chinese patients were enrolled from 2006 to 2007 in this study during which the EGFR mutation testing was not widely adapted in clinic and it is difficult to do retrospective EGFR mutation testing now since there was no enough tumor sample left for this kind of testing. Considering the very low EGFR testing rate during current clinical treatment for Chinese NSCLC, the analysis of the combination of smoking status and histological characteristics in TKI therapy still provides clinical benefits to NSCLC patients (32).

Conclusion

Our TRUST study of the Chinese population further confirmed that erlotinib is effective and safe in treating patients with advanced NSCLC. More importantly, our study demonstrated that the subpopulation of Chinese patients with ADC histology and a non-smoking history had the longest survival time following erlotinib treatment. Thus, good performance status and ADC histology were determined as favorable clinical features for erlotinib treatment.

Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org.

Acknowledgements

We thank all patients who participated in this study. We sincerely thank Dr Yunzhong Zhu from Beijing Chest Hospital, Dr Guoliang Jiang from Tumor Hospital affiliated with Fudan University and Dr Longyun Li from Peking Union Medical Hospital to provide helps on this study. Support for third-party editorial support for this manuscript was provided by Shanghai Roche Pharmaceuticals Limited.

Funding

The TRUST study was sponsored by F. Hoffmann-La Roche.

Conflict of interest statement

None declared.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011;61:69–90.
2. Novaes FT, Cataneo DC, Ruiz Junior RL, Defaveri J, Michelin OC, Cataneo AJ. Lung cancer: histology, staging, treatment and survival. *J Bras Pneumol* 2008;34:595–600.
3. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010;60:277–300.
4. Sant M, Aareleid T, Berrino F, Bielska Lasota M, Carli PM, Faivre J, et al. EUROCARE-3: survival of cancer patients diagnosed 1990–94—results and commentary. *Ann Oncol* 2003;14(Suppl 5):v61–118.
5. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–8.
6. Scagliotti GV, De Marinis F, Rinaldi M, Crino L, Gridelli C, Ricci S, et al. Phase III randomized trial comparing three platinum-based doublets in advanced non-small-cell lung cancer. *J Clin Oncol* 2002;20:4285–91.
7. Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, et al. Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–57.
8. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer

(EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239–46.
9. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011;12:735–42.
10. Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel–carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542–50.
11. Johnson JR, Cohen M, Sridhara R, Chen YF, Williams GM, Duan J, et al. 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. *Clin Cancer Res* 2005;11:6414–21.
12. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353:123–32.
13. Shah NT, Kris MG, Pao W, Tyson LB, Pizzo BM, Heinemann MH, et al. Practical management of patients with non-small-cell lung cancer treated with gefitinib. *J Clin Oncol* 2005;23:165–74.
14. Goodin S. Erlotinib: optimizing therapy with predictors of response? *Clin Cancer Res* 2006;12:2961–3.
15. Tsao AS, Tang XM, Sabloff B, Xiao L, Shigematsu H, Roth J, et al. Clinicopathologic characteristics of the EGFR gene mutation in non-small cell lung cancer. *J Thorac Oncol* 2006;1:231–9.
16. An SJ, Chen ZH, Su J, Zhang XC, Zhong WZ, Yang JJ, et al. Identification of enriched driver gene alterations in subgroups of non-small cell lung cancer patients based on histology and smoking status. *PLoS One* 2012;7:e40109.
17. Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, et al. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med* 2009;361:958–67.
18. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, 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;350:2129–39.
19. Van Laethem K, Pannecouque C, Vandamme AM. Mutations at 65 and 70 within the context of a Q151M cluster in human immunodeficiency virus type 1 reverse transcriptase impact the susceptibility to the different nucleoside reverse transcriptase inhibitors in distinct ways. *Infect Genet Evol* 2007;7:600–3.
20. Reck M, van Zandwijk N, Gridelli C, Baliko Z, Rischin D, Allan S, et al. Erlotinib in advanced non-small cell lung cancer: efficacy and safety findings of the global phase IV Tarceva Lung Cancer Survival Treatment study. *J Thorac Oncol* 2010;5:1616–22.
21. Mok T, Wu YL, Au JS, Zhou C, Zhang L, Perng RP, et al. Efficacy and safety of erlotinib in 1242 East/South-East Asian patients with advanced non-small cell lung cancer. *J Thorac Oncol* 2010;5:1609–15.
22. Perng RP, Yang CH, Chen YM, Chang GC, Lin MC, Hsieh RK, et al. High efficacy of erlotinib in Taiwanese NSCLC patients in an expanded access program study previously treated with chemotherapy. *Lung Cancer* 2008;62:78–84.
23. Fan WC, Yu CJ, Tsai CM, Huang MS, Lai CL, Hsia TC, et al. Different efficacies of erlotinib and gefitinib in Taiwanese patients with advanced non-small cell lung cancer: a retrospective multicenter study. *J Thorac Oncol* 2011;6:148–55.
24. Xue C, Hu Z, Jiang W, Zhao Y, Xu F, Huang Y, et al. National survey of the medical treatment status for non-small cell lung cancer (NSCLC) in China. *Lung Cancer* 2012;77:371–5.
25. Therasse P, Eisenhauer EA, Verweij J. RECIST revisited: a review of validation studies on tumour assessment. *Eur J Cancer* 2006;42:1031–9.
26. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004;304:1497–500.
27. Bryant A, Cerfolio RJ. Differences in epidemiology, histology, and survival between cigarette smokers and never-smokers who develop non-small cell lung cancer. *Chest* 2007;132:185–92.
28. Toh CK, Gao F, Lim WT, Leong SS, Fong KW, Yap SP, et al. Never-smokers with lung cancer: epidemiologic evidence of a distinct disease entity. *J Clin Oncol* 2006;24:2245–51.
29. Subramanian J, Govindan R. Molecular genetics of lung cancer in people who have never smoked. *Lancet Oncol* 2008;9:676–82.
30. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers—a different disease. *Nat Rev Cancer* 2007;7:778–90.
31. Chen G, Feng J, Zhou C, Wu YL, Liu XQ, Wang C, et al. Quality of life (QoL) analyses from OPTIMAL (CTONG-0802), a phase III, randomised, open-label study of first-line erlotinib versus chemotherapy in patients with advanced EGFR mutation-positive non-small-cell lung cancer (NSCLC). *Ann Oncol* 2013;24:1615–22.
32. Shi Y, Au JS, Thongprasert S, Srinivasan S, Tsai CM, Khoa MT, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). *J Thorac Oncol* 2014;9:154–62.