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Second-line erlotinib in patients with advanced non-small-cell lung cancer: Subgroup analyses from the TRUST study

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ABSTRACT

Erlotinib is a highly potent inhibitor of epidermal growth factor receptor tyrosine-kinase activity that significantly prolongs overall survival in patients with non-small-cell lung cancer (NSCLC), and improves symptom control and quality of life compared with placebo. The safety and efficacy of erlotinib has been investigated in a large, international, phase IV, open-label study (TRUST) in patients ($n = 6665$) with advanced stage IIIB/IV NSCLC. An analysis of efficacy and safety outcomes is reported for patients receiving erlotinib as second-line therapy in TRUST ($n = 3224$). Best response data were available for all 3224 patients. Complete response, partial response and stable disease were achieved in 25 (<1%), 368 (14%) and 1444 (54%) patients, respectively, for a disease control rate of 68%. Median progression-free and overall survivals were 13.6 weeks and 8.6 months, respectively; 1-year survival was 39.4%. Safety data were available for all patients. Of these, 389 patients (12%) had an erlotinib-related adverse event (AE) other than pre-specified AEs defined in the protocol; only 96 patients (3%) had an erlotinib-related AE ≥grade 3. Of 1376 patients (43%) with serious AEs (SAEs), only 122 (4%) had treatment-related SAEs and most were gastrointestinal disorders (mainly diarrhoea and nausea). No treatment-related SAE occurred in ≥1% of patients. Data on the incidence of erlotinib-related rash were collected for all patients, 2302 (71%) of whom experienced rash. Of these rash events, 83% were of grade 1/2. These data confirm the good efficacy and tolerability of second-line erlotinib in a broad range of patients with NSCLC.

Clinical trial number: NCT00949910.

1. Introduction

Recent analyses of cancer incidence and mortality demonstrate that lung cancer is the leading cause of cancer mortality in both Europe [1] and the USA [2], accounting for 27% and 11% of cancer deaths in men and women in Europe, respectively, and 31% and 26% of cancer deaths in men and women in the USA, respectively. The high mortality rate is reflected in the extremely low 5-year survival rates (3%) for patients with advanced or metastatic disease [3], which highlights the need for more effective therapeutic interventions. Platinum-based doublet chemotherapy regimens for the first-line treatment of patients with advanced non-small-cell lung cancer (NSCLC) have achieved 1-year survival rates of approximately 34% [4]. The anti-angiogenic agent bevacizumab, combined with platinum-based doublets has further improved outcomes for patients in the first-line setting [5,6], achieving a 1-year survival rate of 51% in one phase III study [5]. Second-line chemotherapy regimens for advanced NSCLC include single-agent docetaxel or pemetrexed, which have achieved 1-year survival rates of 29–32% [7–9].

Erlotinib is a potent, orally active, reversible inhibitor of epidermal growth factor receptor (EGFR) tyrosine-kinase activity and is approved in more than 80 countries for the treatment of advanced NSCLC following the failure of at least one chemotherapy regimen. In a large, randomised, placebo-controlled, phase III trial (BR.21) in patients with advanced NSCLC who had previously received at least one line of chemotherapy ($n = 731$), erlotinib monotherapy significantly prolonged survival compared with placebo [10]. The 1-year survival rate was 31.2% with erlotinib, representing a 45% improvement compared with placebo (21.5%). The survival benefit was observed across a broad range of patient subtypes. Erlotinib was well tolerated, with rash and diarrhoea being the most com-

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mon adverse events (AEs) (generally mild or moderate in severity). The development of rash as an AE may be regarded as a surrogate marker of efficacy for EGFR inhibitors such as erlotinib [11–13]. Erlotinib treatment was also associated with improved symptom control and quality of life compared with placebo [10,14]. In order to make erlotinib available to patients with advanced NSCLC before the drug was licensed in their country, a large, international, phase IV, open-label study (TRUST) was initiated. A total of 6665 patients from 51 countries participated in the TRUST study and received erlotinib as first-, second- or third-line therapy; in each country, recruitment continued until erlotinib was granted a license. The overall disease control rate (the rate of complete responses [CRs] or partial responses [PRs] and stable disease [SD]) with erlotinib was 69% [15]. The benefits of erlotinib were particularly notable in Asian patients, with a disease control rate of 78% [16]. This analysis of the TRUST study was restricted to those patients receiving erlotinib as second-line therapy.

2. Methods

2.1. Inclusion and exclusion criteria

Patients with histologically or cytologically confirmed, unresectable, stage IIIB/IV NSCLC who had received at least one course of standard systemic chemotherapy or radiotherapy (or were ineligible to receive chemotherapy or radiotherapy), and who were unsuitable for other erlotinib trials, were eligible to participate. Other eligibility criteria included: age ≥18 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–3; adequate hematologic, renal, and hepatic function; estimated life expectancy of ≥12 weeks. Prior treatments should have been completed at least 3 weeks before enrolment and patients must have fully recovered from any toxicity associated with prior therapy. Patients who had fully recovered from surgery less than 4 weeks previously could also be considered, while women of child-bearing potential were required to have a negative pregnancy test.

Key exclusion criteria included: any evidence of unstable systemic disease; prior treatment with anti-EGFR agents (including small molecules or monoclonal antibodies); any previous malignancies within the last 5 years (other than cervical carcinoma *in situ* or skin cancer that underwent successful treatment); untreated brain metastases (newly diagnosed or pre-existing) or spinal cord compression; and any significant ophthalmological abnormalities.

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 centres by appropriate ethics committees.

2.2. Study treatment

Oral erlotinib (F. Hoffmann-La Roche, Basel, Switzerland) was administered once daily at a dose of 150 mg to all patients, until unacceptable toxicity, disease progression or death. Dose interruption or reduction (in 50 mg/day steps) was permitted in the event of treatment-related AEs.

2.3. Clinical assessments

Outcomes included best response as per investigator assessment; progression-free survival (PFS) and overall survival (OS) analysis, and safety. Clinical and laboratory assessments were conducted at baseline, then every 4 weeks throughout the study. Tumor response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) [17], at least every 2 months. For patients classed as responders, a confirmatory evaluation was carried out 4 weeks after the initial determination of response. Safety and tolerability evaluations, including incidence and grade of erlotinib-related rash, serious adverse events (SAEs) and treatment-related SAEs, and AEs leading to treatment withdrawal were assessed and graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. Other treatment-related AEs were reported if they were not included on a list of prespecified AEs defined in the study protocol (rash, pruritus, dry skin, diarrhoea, nausea, vomiting, stomatitis, abdominal pain, fatigue, dyspnoea, cough, anorexia, infection, conjunctivitis, and keratoconjunctivitis sicca).

2.4. Statistical analysis

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 erlotinib initiation until the date of death from any cause. Differences in OS and PFS according to clinical or disease characteristics were analyzed using the log-rank test. A multivariate analysis was performed for PFS and OS using the Cox regression model. Baseline characteristics investigated in the models were: gender (male/female); age (<65 years/≥65 years); ethnicity (oriental/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 (never-smoker/former or current smoker). The same analysis method was also used to test the predictive value of treatment line (second line/third line) for the overall population ($n = 6586$). Patients with a missing value for any of the baseline characteristics were excluded from the multivariate analysis. For both PFS and OS analysis, 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.

3. Results

3.1. Patients

The population included in this analysis ($n = 3224$) comprised all patients who had received at least one dose of erlotinib as second-line treatment and for whom clinical data (from submitted case report forms) had been entered in the study database by the cut-off date of April 17, 2009. At the time of data cut-off, 3125 patients had discontinued study treatment and 99 patients (3.1%) were still ongoing (non-progressive) in the study. Baseline patient and disease characteristics are summarised in Table 1. The majority of patients had stage IV NSCLC (78%) and an ECOG PS of 0 or 1 (78%). The most common NSCLC histologies were adenocarcinoma (56%) or squamous-cell carcinoma (22%).

3.2. Response and survival

Best response data were available for all 3224 patients. A CR was achieved in 25 patients (<1%), while PR was achieved in 368 patients (14%) and SD was achieved in 1444 patients (54%) for an overall disease control rate of 68%. For PFS and OS analysis, data were available for 3224 patients, with PFS censored for 8.0% of patients and OS censored for 20.2% of patients. Median PFS was 13.6 weeks (95% confidence interval [CI], 12.9–14.9) (Fig. 1A) and median OS was 8.6 months (95% CI, 8.2–9.2) (Fig. 1B). The 1-year survival rate was 39.4% (95% CI, 37.6–41.1).

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Table 1
Demographic and clinical characteristics of patients in the TRUST study receiving erlotinib as second-line therapy ($n = 3224$).

Characteristic	
Median age, years (range)	62 (19 – 90)
Gender, *n* (%)	
Male	1919 (60)
Female	1305 (40)
Ethnic origin, *n* (%)	
Caucasian/white	2365 (73)
Oriental	751 (23)
Black	18 (<1)
Other	90 (3)
ECOG PS, *n* (%)	
0	774 (24)
1	1744 (54)
2	544 (17)
3	158 (5)
No data	4 (<1)
Stage, *n* (%)	
IIIB	719 (22)
IV	2499 (78)
Other	6 (<1)
Histology, *n* (%)	
Adenocarcinoma	1818 (56)
Bronchoalveolar carcinoma	161 (5)
Large cell carcinoma	201 (6)
Squamous-cell carcinoma	719 (22)
Other	322 (10)
No data	3 (<1)
Smoking history, *n* (%)	
Never-smoker	1022 (32)
Former or current smoker	2196 (68)
No data	6 (<1)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status.

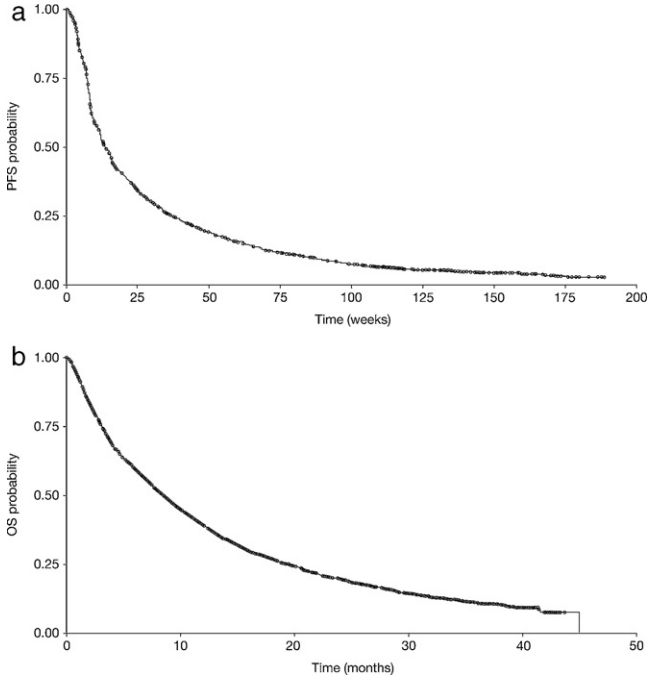

Fig. 1. Kaplan–Meier survival plots of patients in the TRUST study receiving erlotinib as second-line therapy ($n = 3224$): (A) progression-free survival and (B) overall survival.

3.3. Subgroup analyses

Subgroup analyses demonstrated that PFS and OS were significantly longer in women versus men, in oriental patients versus other ethnic groups, in patients with adenocarcinoma or bronchoalveolar carcinoma versus those with squamous-cell carcinoma, and in never-smokers versus former or current smokers (Table 2). PFS and OS were also significantly longer in patients with ECOG PS of 0 or 1 versus those with PS of 2 or 3 (Table 2 and Fig. 2) and in patients who developed erlotinib-related rash compared to those with no rash (Table 2 and Fig. 3). A multivariate analysis was performed for PFS and OS using the Cox regression model, with all 3224 patients providing information. An optimal model for prognosis of PFS and OS includes the factors: smoking status, baseline ECOG PS, ethnicity, stage of disease, gender and histology. The Cox regression multivariate analysis showed that smoking,

Table 2
Progression-free and overall survival according to patient or disease characteristics in patients in the TRUST study receiving erlotinib as second-line therapy.

Characteristic	Progression-free survival			Overall survival		
	Median (weeks)	Hazard ratio (95% CI)	*p*-value	Median (months)	Hazard ratio (95% CI)	*p*-value
Gender						
Female ($n = 1305$)	17.00	0.75 (0.70 – 0.81)	<0.0001	11.17	0.68 (0.63 – 0.74)	<0.0001
Male ($n = 1919$)	12.14			7.10		
Ethnic origin						
Oriental ($n = 751$)	24.14	0.68 (0.63 – 0.75)	<0.0001	14.91	0.59 (0.53 – 0.65)	<0.0001
Other ($n = 2473$)	12.14			7.19		
ECOG PS						
0/1 ($n = 2518$)	15.71	0.68 (0.62–0.74)	<0.0001	10.32	0.48 (0.44 – 0.53)	<0.0001
2/3 ($n = 702$)	8.57			3.35		
Histology						
Adenocarcinoma/bronchoalveolar carcinoma ($n = 1979$)	15.86	0.76 (0.69 – 0.83)	<0.0001	10.38	0.67 (0.61 – 0.74)	<0.0001
Squamous-cell carcinoma ($n = 719$)	12.29			6.64		
Smoking status						
Never smoker ($n = 1022$)	26.00	0.56 (0.52 – 0.61)	<0.0001	15.24	0.52 (0.47 – 0.56)	<0.0001
Former/current smoker ($n = 2196$)	11.43			6.60		
Skin toxicity						
Rash ($n = 2299$)	18.00	0.52 (0.48 – 0.57)	<0.0001	11.24	0.50 (0.45 – 0.55)	<0.0001
No rash ($n = 684$)	8.14			4.11		
Disease stage						
IIIB ($n = 719$)	16.86	0.98 (0.97 – 0.99)	0.0004	9.99	0.98 (0.97 – 0.99)	0.0021
IV ($n = 2499$)	12.71			8.11		

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

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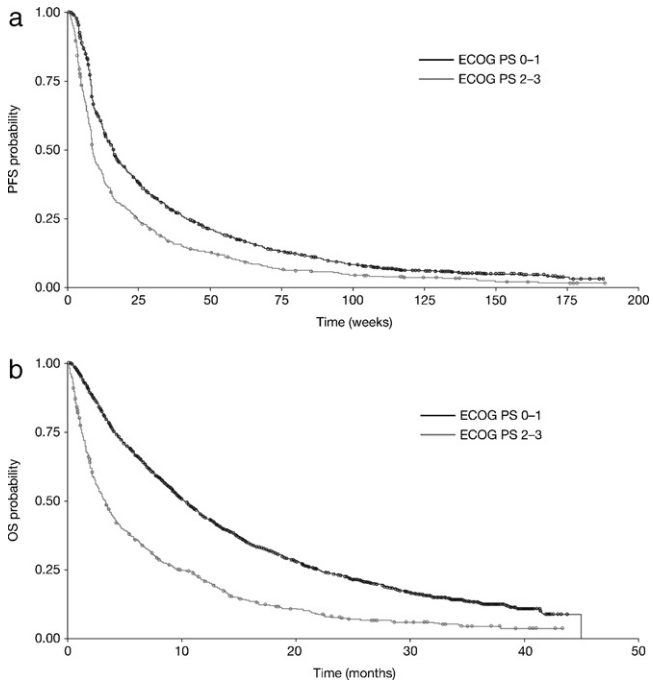

Fig. 2. Kaplan–Meier survival plots according to ECOG PS at baseline of patients in the TRUST study receiving erlotinib as second-line therapy: (A) progression-free survival and (B) overall survival.

squamous-cell carcinoma histology, poor PS, non-oriental ethnicity, male gender and stage IV disease were all predictive of early disease progression and poor survival (Table 2). The line of treatment (second or third line) was not found to be a prognostic factor for efficacy in the same analysis for the overall population.

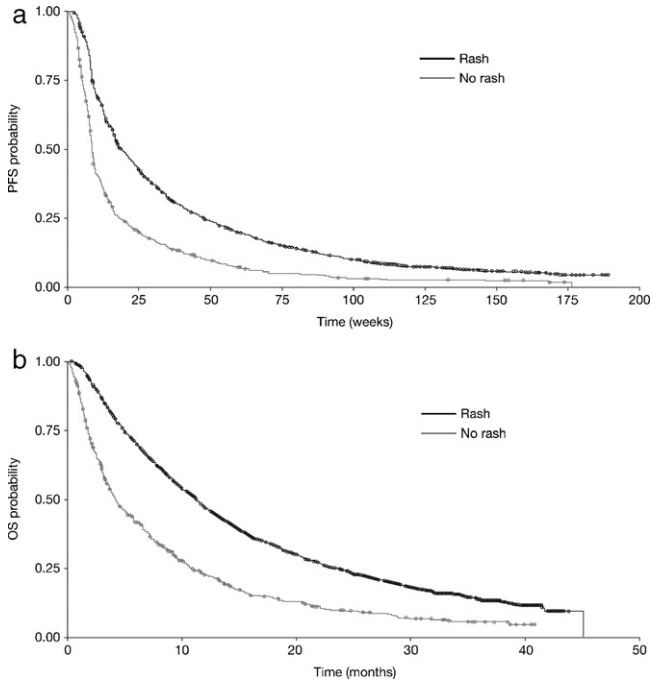

Fig. 3. Kaplan–Meier survival plots according to development of erlotinib-related rash of patients in the TRUST study receiving erlotinib as second-line therapy: (A) progression-free survival and (B) overall survival.

Table 3
Treatment-related adverse events and serious adverse events[a] (other than the pre-specified events defined in the protocol) occurring in patients in the TRUST study receiving erlotinib as second-line therapy ($n = 3224$) with the two most common listed for each class.

Event	Any, *n* (%)	Grade 3 – 5, *n* (%)
Total patients with any treatment-related AE	389 (12)	96 (3)
Eye disorders	35 (1)	4 (<1)
Dry eye	9 (<1)	0 (0)
Trichomegaly	4 (<1)	0 (0)
Blurred vision	4 (<1)	0 (0)
Gastrointestinal disorders	61 (2)	9 (<1)
Mouth ulceration	13 (<1)	0 (0)
Dry mouth	10 (<1)	0 (0)
Infections and infestations	86 (3)	13 (<1)
Paronychia	72 (2)	4 (<1)
Pneumonia	3 (<1)	3 (<1)
Laboratory parameters	66 (2)	11 (<1)
Abnormal blood bilirubin	22 (<1)	1 (<1)
Abnormal alanine transferase	17 (<1)	4 (<1)
Nervous system disorders	46 (1)	7 (<1)
Dysgeusia	16 (<1)	0 (0)
Headache	8 (<1)	2 (<1)
Respiratory, thoracic and mediastinal disorders	38 (1)	12 (<1)
Epistaxis	11 (<1)	0 (0)
Pneumonitis/interstitial lung disease	7 (<1)	6 (<1)
Skin and subcutaneous tissue disorders	71 (2)	9 (<1)
Alopecia	37 (1)	0 (0)
Nail disorder	8 (<1)	2 (<1)
Total patients with any treatment-related SAE	122 (4)	94 (3)
Gastrointestinal disorders	53 (2)	39 (1)
Diarrhoea	27 (<1)	19 (<1)
Nausea	13 (<1)	5 (<1)

Abbreviations: AE, adverse event; SAE, serious adverse event.
[a] Observed in ≥1% of all patients.

3.4. Toxicity

Safety data were available for 3224 patients, 1676 (52%) of whom had at least one AE. Of these, 389 patients (12%) had an erlotinib-related AE (other than the pre-specified AEs defined in the protocol) (Table 3). Of 389 patients, 292 (9% of the safety population) experienced an erlotinib-related AE of grade 1–2. Only 96 patients (3% of the safety population) had an erlotinib-related AE of grade 3 or greater severity (less than 1% were grade 4–5). Seven patients (<1%) had pneumonitis or interstitial lung disease (ILD). The most common classes of treatment-related AEs, occurring in ≥2% of patients (65 or more patients), were infections and infestations and skin and subcutaneous tissue disorders. SAEs were reported in 1376 (43%) of patients; however, only in 122 patients (4%) were these considered to be treatment related. The most common SAEs were gastrointestinal disorders, predominantly diarrhoea (28 patients) and nausea (12 patients). No treatment-related SAE occurred in ≥1% of patients.

Data on the incidence of erlotinib-related rash were collected for 3224 patients, 2302 (71%) of whom experienced rash. Among the reports of rash, 83% were grade 1 or 2 and 17% were grade 3 or 4. A total of 169 patients (5%) withdrew from treatment due to a treatment-related AE, most commonly rash (59 patients; 2%) or diarrhoea (30 patients; <1%). Erlotinib dose reductions were reported in 532 of 3224 patients (17%), of whom 96% received a reduced dose of 100 mg/day and 12% a dose reduction to 50 mg/day. Most dose reductions (95%) were implemented owing to an erlotinib-related AE, predominantly rash (>70% of dose reductions), diarrhoea (10% of dose reductions) or both (4% of dose reductions).

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4. Discussion

This analysis of the TRUST study in more than 3000 patients receiving second-line erlotinib is consistent with findings from the overall TRUST population [15]. The current analysis provides robust data on the efficacy and tolerability of erlotinib as second-line therapy in a broad patient population. The TRUST study was conducted in a large patient population, with broad inclusion and exclusion criteria, across a number of countries with differences in clinical practice. As such, conclusions regarding efficacy are tempered by the limitations of any open-label, non-comparative study. However, indirect comparison between TRUST and BR.21 provides further evidence that erlotinib can provide active disease control and prolong both PFS and OS in patients with previously treated advanced NSCLC [10]. Due to differences in trial design and study population (inclusion of third-line patients in BR.21; different male/female ratios; differences in patient histology, ethnicity and smoking status), the findings of the TRUST study cannot be directly compared with the BR.21 overall population but it is appropriate to assess the clinical relevance of the TRUST data in relation to data from the BR.21 second-line population [Roche data on file]. The disease control rate of 68% for the second-line population achieved in the TRUST study in a broad patient population is higher than that observed in the second-line population of BR.21 (44%). The TRUST study also shows an increase in median PFS (13.6 weeks versus 9.7 weeks) and OS (8.6 months vs 6.7 months) compared with the BR.21 second-line population. There were no unexpected safety findings in this analysis and no individual treatment-related AE of any grade occurred in more than 2% of patients; the pre-specified AEs defined in the protocol were not monitored. Diarrhoea and rash were the most common reasons for treatment withdrawal or erlotinib dose reductions. The statistically significantly prolonged survival achieved with erlotinib therapy in patients who develop rash versus those with no rash ($p < 0.0001$) provides further evidence that this event may be predictive of greater clinical response [13].

Second-line treatment options for patients with advanced NSCLC include conventional chemotherapy with docetaxel or pemetrexed, or targeted therapy with erlotinib. Alternatively, patients could elect to receive best supportive care or to participate in a clinical trial. This raises the critical question of how to select the most appropriate therapy for a particular patient. Certain factors should be taken into consideration when selecting therapy, including efficacy, toxicity, likelihood of response, patient acceptability and resource implications. The findings of TRUST, together with those of BR.21, indicate that erlotinib is as effective as conventional chemotherapy in terms of disease control and survival advantage in patients with advanced NSCLC who had previously failed chemotherapy. Of note, median OS for different subgroups (other than poor PS and patients without rash) (Table 2) are within the 6.6–15.24 months range and higher than previously reported for erlotinib [10]. The 1-year survival rate of 39.4% achieved in the TRUST population is comparable with 1-year survival rates observed in phase III studies with docetaxel (30 – 37%) [7–9] or pemetrexed (30%) [9]. Previous studies have also shown that the median duration of response of 7.9 months achieved with erlotinib [10] compares favourably with those observed with docetaxel (5.3–6.0 months) [7–9] or pemetrexed (4.6 months) [9].

Within the second-line patient population (3224 patients), 138 patients had known *EGFR* mutation status and only 18 of those had disease with an *EGFR* activating mutation, thus indicating that the results seen here are not *EGFR* activating mutation dependent and confirming erlotinib efficacy in broad patient populations (those with and without *EGFR* activating mutations and those whose *EGFR* mutation status is unknown). This is in accordance with previously reported data from the SATURN and TITAN trials, both of which found erlotinib to be active in patients with *EGFR* wild-type disease [18,19].

Efficacy results from a randomised phase III trial by the Hellenic Oncology Research Group (HORG) that compared pemetrexed with erlotinib in second-line NSCLC patients with PS 0–2 and unknown EGFR status found the two agents to be comparable in terms of OS ($p = 0.934$). Similar data were obtained from the TITAN trial (HR = 0.96 and 0.85 for OS in patients with unknown EGFR status and EGFR wild type, respectively) further supporting the findings from TRUST that erlotinib is similar to chemotherapy in terms of efficacy [19,20].

Therapeutic tolerability is an important consideration in the selection of treatment for patients with advanced lung cancer, where quality of life and toxicity of therapy are critical selection criteria. AEs and toxicities associated with targeted therapies such as erlotinib are notably different to those associated with conventional chemotherapy. Erlotinib side effects, most commonly diarrhoea and skin toxicity, are well-characterised, predictable, and manageable, with algorithms developed to help manage skin toxicity [21]. In contrast, the AEs associated with conventional regimens such as docetaxel and pemetrexed may more severely impact patient experience [7–9].

Using particular patient characteristics to select therapy has become an intriguing area of research; however, benefits of erlotinib therapy have been observed in most patient subgroups. While comparisons in the TRUST study indicate that clinical outcomes were notably better in some patient subgroups, including females, never-smokers and patients with non-squamous histology, conclusions about the efficacy of erlotinib in these particular patient populations cannot be drawn from this single-arm study, as it is likely that these characteristics are prognostic for NSCLC in general, rather than predictive of erlotinib effect. The prognostic nature of certain characteristics only emerges from placebo-controlled studies where comparison of data across arms is possible.

Characteristics such as gender can have strong prognostic value but no predictive value for likely patient benefit [22]. The BR.21 study demonstrated a survival benefit for erlotinib in almost all patient populations relative to placebo, with OS equivalent to chemotherapy [10]. Furthermore, the INTEREST study of gefitinib versus docetaxel in the second-line setting demonstrated that survival was substantially longer in never-smokers versus ever-smokers; females versus males; patients of Asian origin versus others; and patients with adenocarcinoma versus non-adenocarcinoma, regardless of the type of treatment received [23].

It has been suggested that agents such as erlotinib should be reserved for patients with poor PS, owing to their milder toxicity profile. However, this analysis of the TRUST study indicates that better outcomes are achieved in patients with good PS (0/1) than those with poor PS, although this is probably due to the prognostic effect of PS. Nevertheless patients with poor PS derived a similar benefit from erlotinib to patients with good PS in BR.21 (HR for survival 0.77 for ECOG PS 2/3 versus 0.73 for ECOG PS 0/1). This is consistent with findings for other treatments. Therefore, these data provide evidence to support the use of erlotinib therapy irrespective of a patient's PS. Furthermore, the effects of second-line erlotinib on survival in patients with PS 0/1 are equivalent to those of chemotherapy (9.4 – 10.32 months with erlotinib compared with 9.1 months with docetaxel and 9.4 months with pemetrexed) [24].

Taken together, these studies indicate that although erlotinib can benefit more than one subset of patients, it is possible that some subsets may receive more benefit than others. As yet, there is no simple method of patient selection for erlotinib therapy; however, the search for predictive markers is ongoing. In conclusion, the findings of this subanalysis of the TRUST study in patients receiving second-line erlotinib confirm that oral dosing with erlotinib

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offers patients a convenient therapeutic option with similar efficacy and reduced toxicity compared with conventional second-line chemotherapy.

Conflict of interest statement

David Heigener has received payment for consultancy from F. Hoffmann-La Roche Ltd. and Eli Lilly, and honoraria from F. Hoffmann-La Roche Ltd., Eli Lilly and AstraZeneca. Yi-Long Wu has received honoraria from F. Hoffmann-La Roche, Eli Lilly, AstraZeneca, Pfizer and Novartis. Nico van Zandwijk has received payment for consultancy and received honoraria from Eli Lilly, AstraZeneca, Merckserono and Pfizer and has patent applications/registrations pending for Agendia. Pekka Mali has received honoraria from F. Hoffmann-La Roche Ltd. for seminar presentations and has also been sponsored by F. Hoffmann-La Roche Ltd. to attend scientific meetings. Keith Horwood has received payment for attending a Roche advisory board. Martin Reck has received payment for consultancy on advisory boards from F. Hoffmann-La Roche Ltd., Merck, Eli Lilly, Pfizer, BMS and AstraZeneca as well as honoraria for lectures from F. Hoffmann-La Roche Ltd., Eli Lilly, Merck and AstraZeneca.

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