Phase II Study of Erlotinib in Japanese Patients with Advanced Non-small Cell Lung Cancer

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Abstract. *The aim of this study was to evaluate the efficacy and safety of erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor, in Japanese patients with relapsed or recurrent advanced non-small cell lung cancer (NSCLC). Patients and Methods: This was a multicentre, open-label phase II study of erlotinib (150 mg/day) in patients with stage IIIB or IV NSCLC. The primary endpoint was the objective tumour response rate. Results: Of the 46 patients, 13 were assessed to have a partial response and 9 had stable disease. The median duration of response was 449 days and time to progression was 75 days. Median overall survival (OS) was 13.5 months and the 1-year survival rate was 56.5%. The most common adverse events were dermal or gastrointestinal, and were mainly grade 2 or less. An exploratory analysis suggested a link between rash severity and OS. Conclusion: Erlotinib has promising antitumour activity and is generally well tolerated in Japanese patients with previously treated NSCLC.*

Lung cancer is the most common cancer worldwide, with almost 1.5 million new cases diagnosed every year, and it is also the leading cause of cancer-related death (1-3). Non-small cell lung cancer (NSCLC) is the most common form of lung cancer (accounting for approximately 85% of cases) and because early-stage NSCLC is often asymptomatic, close to 70% of patients present with advanced (stage IIIB or IV) disease (3). The prognosis for patients with NSCLC remains poor, with 5-year survival rates of 5-10% and median survival times of 12-15 months (3, 4).

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Treatment approaches in NSCLC vary according to the extent of the disease (5). Surgery offers the chance of a cure in early disease, and combining surgery with chemotherapy can improve outcomes (6). However, advanced NSCLC cannot be resected and is therefore generally incurable. As a result, the major treatment goals in advanced NSCLC are to delay tumour progression (thereby increasing survival), delay worsening of symptoms, and to maintain or improve quality of life. Standard first-line treatment for metastatic NSCLC is platinum-based chemotherapy with the addition of third-generation agents (*e.g.* paclitaxel, gemcitabine, vinorelbine or irinotecan) (7, 8). However, it is generally accepted that a plateau in efficacy has been reached in NSCLC for traditional chemotherapy regimens (3).

Erlotinib (Tarceva®) is a highly potent, orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). Erlotinib has proven efficacy in Japanese patients with advanced NSCLC (9), and was approved in Japan for the treatment of relapsed NSCLC in October 2007. The pivotal BR.21 study showed that erlotinib has a beneficial effect on survival in a wide range of patients with NSCLC, irrespective of biomarker status (10). However, in this trial, patients of Asian ethnicity were found to have a significantly higher response rate than other patient groups combined (18.9% *vs.* 7.5%; p=0.02). One possible explanation is that Asian patients have a higher rate of tumors with *EGFR* mutations, and are more likely to respond to EGFR-TKI therapy. Recent studies indicate that response to EGFR-TKIs may be predicted by the presence of *EGFR* gene mutations (11-13), suggesting a role for biomarker-based tailored therapy.

Dermal toxicities, such as rash, pruritis and dry skin are major treatment-related adverse events (AEs) of erlotinib. The occurrence and severity of rash has been linked to the clinical efficacy of erlotinib in patients with NSCLC (14-16), suggesting that rash may be a surrogate marker for improved response to therapy.

This paper reports the findings of a phase II study of the efficacy and safety of erlotinib in Japanese patients with relapsed or recurrent advanced NSCLC. The study also examined the possible correlation between rash and survival time in patients receiving erlotinib, and a biomarker analysis was conducted.

Patients and Methods

This multicentre, open-label phase II study recruited patients at 11 sites in Japan. The primary endpoint was the objective tumour response rate (ORR), measured in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (17). An external confirmation of antitumour efficacy was conducted by an independent response evaluation committee. Secondary endpoints were the disease control rate (DCR), duration of response, time to progression (TTP), overall survival (OS), 1-year survival rate, quality of life (QoL) and safety.

Patients. Patients (aged 20-74 years) with histologically or cytologically documented stage IIIB or IV NSCLC that was recurrent or refractory to treatment, and who had received at least one prior chemotherapy regimen, were enrolled in the study. Eligibility criteria included: measurable lesions (by RECIST) not curable by surgery or radiotherapy; an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0-2, and adequate bone marrow function, hepatic function (aspartate aminotransferase [AST], alanine aminotransferase [ALT] levels ≤2.5 times and total bilirubin ≤1.5 times the upper limit of normal [ULN]), renal function (serum creatinine ≤1.5 times ULN) and pulmonary function (arterial oxygen pressure [PaO_2] ≥70 Torr). Patients had to complete their last cycle of chemotherapy at least 4 weeks prior to the study, and their last course of thoracic radiotherapy had to have been at least 12 weeks previously. Patients were excluded from the study if they had a history or complications of interstitial lung disease (ILD) (scarred radiation pneumonitis limited to the field of radiation was permitted) or current ophthalmological abnormalities (dry eye syndrome including Sjögren's syndrome, severe dry keratoconjunctivitis, keratitis). Written informed consent was obtained from all patients.

Study design and treatment. All patients received 150 mg erlotinib once daily before breakfast, until the occurrence of progressive disease (PD) or unacceptable toxicity. In the event of treatment-related toxicity, two dose reductions were permitted per patient (first reduction to 100 mg/day, second reduction to 50 mg/day), and dosing could be interrupted for up to 14 days. No dose escalations were permitted. For grade 3 or intolerable grade 2 rash or stomatitis, treatment was discontinued until improvement to grade 2 or less, and then a lower dose of erlotinib was started. For any other grade 3 treatment-related toxicities, treatment was interrupted until improvement to grade 1 or less and then the same dose was re-started. For ILD of any grade or grade 4 toxicity, treatment was permanently discontinued.

Efficacy evaluation. Tumour assessments were evaluated in accordance with RECIST (17) and were performed at baseline and every 4 weeks until week 16, then every 8 weeks thereafter. Confirmation of complete or partial responses (CR or PR) was obtained by a second assessment conducted ≥28 days after the initial assessment. Stable disease (SD) was defined as disease control (absence of progression) maintained for at least 6 weeks. An independent response evaluation committee, consisting of two oncologists and a radiologist, reviewed images of patients with CR, PR and SD. Individual survival times were calculated during the study period and at the post-study follow-up survey, and OS was defined as time from first erlotinib administration to death.

Safety evaluation. Baseline assessments included a full patient history, physical examination, standard laboratory tests, electrocardiography, chest radiography and ophthalmology tests (visual acuity test, slit-lamp examination). Vital signs and ECOG PS were monitored and blood samples were taken every week until week 8, and every 2 weeks thereafter. In addition, a radiograph to assess pulmonary toxicity was conducted weekly until week 4, and every subsequent 2 weeks, and ophthalmological tests were repeated at week 8 and at the end of the study. AEs were monitored throughout the study and graded using National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0. For ILD-like events, the data safety monitoring board (which consisted of oncologists and pneumologists) reviewed the clinical data and

Table I. *Summary of patient baseline characteristics and demographics.*

Characteristic	Number of patients (%) (n=46)
Median age (range), years	60.0 (38-74)
Gender	
Male	27 (59)
Female	19 (41)
Performance status	
0	24 (52)
1	22 (48)
Histology	
Adenocarcinoma	40 (87)
Squamous cell	4 (9)
Large cell	1 (2)
Adenosquamous carcinoma	1 (2)
Stage	
IIIB	3 (7)
IV	31 (67)
Recurrent	12 (26)
Smoking history	
Never	22 (48)
Former	21 (46)
Current	3 (7)
Median time since initial diagnosis, days (range)	280.5 (3-3452)
Prior chemotherapy regimens	
1	23 (50)
2	12 (26)
≥3	11 (24)
Prior taxane treatment	
No	14 (30)
Yes	32 (70)
Median time since last regimen, days (range)	62.0 (29-939)

images: the images were also examined by a review committee of radiologists with expertise in drug-induced pulmonary disorders.

QoL evaluation. QoL was assessed using the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire (version 4-A) (18). The full FACT-L questionnaire was administered at baseline and every 28 days, and the Lung Cancer Subscale (LCS), an independently validated component of FACT-L, was administered weekly during the treatment period except for the extension study period. Symptomatic improvement in LCS was defined as an increase of two or more points from baseline, sustained for at least 4 weeks and best responses were analysed for all patients with a baseline score of 24 or less (out of a possible 28).

Biomarker analysis. Tumour samples were obtained for biomarker analysis as formalin-fixed and paraffin-embedded blocks, or as thinly sliced tissue sections mounted on glass slides (at least five slides were examined). *EGFR* gene mutations were assessed at first diagnosis or surgery, when tumour specimens were available. These assessments were only carried out with separate written consent. The tumour tissue was laser microdissected at Targos Molecular Pathology GmBH (Kassel, Germany) and direct sequencing was then carried out at the Roche Centre of Medical Genomics (Basel, Switzerland) using a nested polymerase chain reaction (PCR) to amplify exons 18-21.

Table II. *Response to erlotinib (core study period).*

	Number of patients (%)
Partial response	13 (28.3)
Stable disease	9 (19.6)
Progressive disease	20 (43.5)
Not evaluable	4 (8.7)
Response rate (%) (95% CI)	28.3 (16.0-43.5)
Disease control rate (%) (95% CI)	47.8 (32.9-63.1)
Median time to progression (days)* (95% CI)	75 (56-**)

*Kaplan-Meier analysis; **not estimated.

Pharmacokinetics. The pharmacokinetic profiles of erlotinib and its *O*-desmethylated metabolite OSI-420 were analysed at baseline, and weeks 2, 4 and 8. Plasma concentrations of erlotinib and OSI-420 were measured by reverse-phase liquid chromatography-tandem mass spectrometry (LC-MS/MS) (19).

Statistical analysis. Given an expected overall response rate (ORR) of 25%, a Fisher's exact test was performed (two-sided α=5.0%). Based on 40 patients, the power to test the null hypothesis (ORR=5%) was 95.67%. In the event that the true ORR was proven to be 20%, the power to test the null hypothesis (ORR=5%) would be 83.87%. The target sample size of 45 patients was chosen on the expectation that a proportion of patients would prove to be ineligible for the study. Efficacy analyses were conducted on the full analysis set, which was produced by omitting ineligible patients. The 95% confidence intervals (CIs) for ORR, DCR, and symptom improvement were calculated using the Clopper-Pearson method. Time-to-event variables were estimated using Kaplan-Meier method. Cox proportional hazards regression analysis of OS was conducted to evaluate the effects of 11 factors related to patient characteristics and treatment history.

Results

Patient characteristics. A total of 46 patients were recruited and participated in the study period between January 2005 and January 2006 (Table I). Fifteen patients who maintained a response or SD to erlotinib at January 2006 were able to continue with treatment. Efficacy and safety were continuously assessed for these patients in an extension study until January 2008. All 46 patients were evaluable for safety and efficacy. Patients had a median age of 60 years (38-74 years) and 27 (59%) were male. Forty (87%) patients had adenocarcinoma and 22 (48%) were never smokers. Erlotinib administered in the current study was second-line treatment for half of the 46 patients recruited and the proportion of patients who were to receive erlotinib as third- or fourth (or greater) -line was similar (26% and 24%, respectively).

Efficacy. Overall, 13 patients were assessed as having a PR and nine as having SD (Table II). Objective response could not be confirmed in four patients: three patients discontinued erlotinib early after the first administration because of AST, ALT

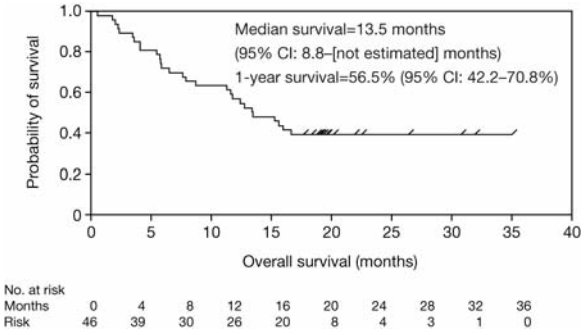

Figure 1. *Kaplan-Meier plot of overall survival (including extension study period).*

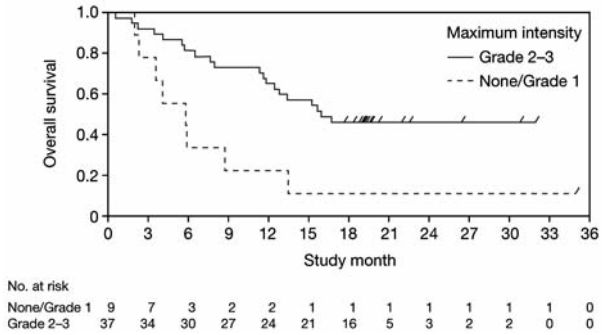

Figure 2. *Kaplan-Meier plot showing the relationship between rash and overall survival (including extension study period).*

elevation, withdrawal of informed consent or patient's refusal, and the fourth patient was not evaluable due to lack of baseline assessment for non-target lesions. The ORR was 28.3% (95% CI: 16.0-43.5%) and the DCR was 47.8% (95% CI: 32.9-63.1%). The symptom improvement rate, measured using the LCS, was 35.7% (15/42, 95% CI: 21.6-52.0%).

The median duration of response, TTP and OS were also evaluated, including data from the extension study period up to January 2008. The median duration of response was 449 days (95% CI: 295 days-[not estimated]) and TTP was 75 days (95% CI: 56-263 days). Median OS was 13.5 months (95% CI: 8.8 months-[not estimated]) and the 1-year survival rate was 56.5% (95% CI: 42.2-70.8%) (Figure 1).

A Cox regression analysis of OS showed that only gender was a significant predictor for OS (Table III).

Pharmacokinetics. Pharmacokinetic parameters were evaluated in 40 patients; however, mean trough concentration data at steady-state ($C_{ss,min}$) were available for only 36 patients as baseline sampling was not performed in 4 patients. The results showed that $C_{ss,min}$ of erlotinib did not vary significantly over time, with stable levels reached by around day 15 and maintained until day 57. The mean $C_{ss,min}$ values (±standard deviation) of erlotinib on days 15, 29 and 57 were 1085.8±660.9 ng/ml, 1001.5±727.2 ng/ml and 981.3±528.5 ng/ml, respectively (average 1063.8±657.0 ng/ml). The corresponding mean values for OSI-420 were 92.4±81.2 ng/ml, 83.6±84.5 ng/ml and 81.9±61.8 ng/ml, respectively (average 88.5±75.1 ng/ml). There was no statistically significant difference in $C_{ss,min}$ based on patient characteristics (age, gender, tumour histology or smoking status) or major AEs.

Biomarker analysis. Paraffin-embedded tissue samples were available for 15/46 patients and there was sufficient tumour tissue lysate to carry out DNA sequencing to determine *EGFR* mutation status in six of these samples. All six patients for whom *EGFR* mutation analysis was carried out had adenocarcinoma (Table IV): three were never smokers and three were former smokers. *EGFR* mutations were identified in three patients, two of whom experienced PR (both have exon 19 deletions) and one who had PD (exon 19 point mutation).

Safety. All 46 patients who received erlotinib were assessed for safety, and treatment-related AEs were observed in all patients (treatment-related AEs with ≥20% incidence are shown in Table V). The most common events were rash, experienced by 45/46 (97.8%) patients, of which 91.3% cases were grade 1 or 2, diarrhoea (31/46 [67.4%] patients, 52.2% grade 1), pruritis (30/46 [65.2%] patients, 50.0% grade 1) and dry skin (28/46 [60.9%] patients, 54.3% grade 1). All events with an incidence >30% were gastrointestinal or skin disorders.

AEs led to discontinuation of erlotinib in 4 patients. One patient (aged 60 years) developed interstitial pneumonia on day 8, and this resulted in death. A computed tomography scan showed that this patient exhibited the characteristic features of ILD, and the ILD review committee judged that the event may possibly have been related to erlotinib. The remaining three patients who discontinued erlotinib did so because of ALT elevation, ALT and AST elevation, and fever, respectively. The case of fever was later found not to be directly related to study treatment. Twenty patients (43.5%) required dose interruption. The main reasons for the dose interruptions were rash (9/46 [19.6%]), ALT elevation (5/46 [4.2%]) and AST elevation (4/46 [8.7%]). Ten patients (21.7%) had dose reduction due to AEs, mostly due to rash (6/46 [13.0%]). Furthermore, there were no intolerable clinical episodes during the extension study

Dose intensity and duration of treatment. To assess the feasibility of treatment, we evaluated compliance with treatment for patients experiencing PR and SD (22 patients). The treatment duration of patients with PR or SD was a mean of 375.4 days (median=317 [43-1066]) days. The mean and median relative dose intensity of responders and patients with SD was 88.6% and 96.9%, respectively. Among these patients, 13 did not require a dose reduction and one patient was treated with erlotinib for 1066 days without dose reduction.

Table III. *Cox regression analysis of survival (including extension study period).*

	Hazard ratio*	95% Confidence interval	*p*-Value
Univariate analysis			
Age (≥65 *vs*. ≤65 years)	0.94	0.41-2.14	0.883
Gender (female *vs*. male)	0.34	0.15-0.77	0.010
Histology (adenocarcinoma *vs*. non-adenocarcinoma)	0.28	0.11-0.76	0.012
Smoking history (never *vs*. current or former)	0.48	0.23-1.03	0.060
Performance status (0 *vs*. ≥1)	0.65	0.31-1.38	0.259
Prior regimens (≥2 *vs*. 1)	0.98	0.47-2.07	0.967
Baseline serum KL-6 (<median, 465 U/ml *vs*. ≥median)	0.79	0.37-1.69	0.540
Best response to previous chemotherapy (non-PR *vs*. PR)	0.68	0.29-1.60	0.373
Prior taxane therapy (no *vs*. yes)	0.61	0.26-1.44	0.259
Time since initial diagnosis (>12 months *vs*. ≤12 months)	0.68	0.30-1.54	0.678
Final model			
Gender (female *vs*. male)	0.34	0.15-0.77	0.010

*Left of '*vs*.' indicates reference group; KL-6, a mucinous glycoprotein expressed on type II pneumocytes; PR, partial response.

Table IV. *EGFR mutation analysis (including extension study period).*

Response	TTP (days)	Survival (days)	Gender	Histology	Smoking history	Mutation status	Exon	Type of mutation
PR	308	599+	F	Adenocarcinoma	Never	+	19	Del L747 - P753 ins S
PR	973+	973+	F	Adenocarcinoma	Never	+	19	Del L747 - P752 ins PL
SD	116	669+	F	Adenocarcinoma	Never	–	–	–
PD	28	559+	M	Adenocarcinoma	Former	–	–	–
PD	57	356	M	Adenocarcinoma	Former	+	19	I759T
PD	29	597+	M	Adenocarcinoma	Former	–	–	–

PR, Partial response; SD, stable disease; PD, progressive disease; TTP, time to progression; + censored.

Exploratory analysis of a relationship between rash and OS. An exploratory analysis suggested a link between rash severity and OS. Kaplan-Meier analysis showed an advantage in terms of survival time for patients with rash grade 2 or 3 compared with those exhibiting rash grade ≤1 (Figure 2). Patients with a maximum rash grade ≤1 had a median OS of 5.8 months compared with 16.0 months for those with rash grade 2 or 3.

Discussion

In the current study, erlotinib of 150 mg/day achieved an ORR of 28.3%, which is higher than that observed in phase II and phase III studies of erlotinib (second- or subsequent-line) in NSCLC conducted in the United States (12.3% (14); 18.9% (10) [Asian subpopulation]), but the same as that seen in a previous phase II study carried out in Japan (28.3% (9)). The characteristics of patients in this study were generally similar to those of NSCLC patients as a whole, in terms of their demographics and disease and treatment history, with the exception of a particularly high proportion of patients with adenocarcinoma (87%) and those never having smoked (48%). However, the possibility of enrolment bias on the basis of histological type cannot be ruled out, in part because enrolment coincided with some reports regarding the clinically predictive factor of EGFR-TKI therapy (20-22).

The median survival time with erlotinib was a promising 13.5 months, which is similar to that reported with erlotinib in a recent phase II study of Japanese patients with NSCLC (14.7 months) (9). One-year survival rates were the same in these two studies (56.5%), and the median TTP (75 days) was similar to that reported in previous studies of patients with advanced or recurrent NSCLC conducted in the United States and Japan (9, 10, 14). Together these data provide a convincing body of evidence supporting the efficacy of erlotinib in patients with advanced NSCLC.

Pharmacokinetic analysis showed that steady-state concentrations of erlotinib were reached after 15 days, were maintained for the 2 months of analysis, and were not affected by patient characteristics such as gender or smoking history. This supports a previous analysis where no significant differences were seen between a phase I study of Japanese patients (23) and a phase I study in Western patients (24) in terms of the pharmacokinetic profile of erlotinib. In contrast to the present study, another previous study demonstrated that current smokers had significantly less erlotinib exposure than non-smokers (25). The reasons underlying this difference are

Table V. *Major treatment-related adverse events with an incidence ≥20% (including extension study period).*

Event*	Number of patients (%)	NCI-CTC grade			
		1	2	3	4
Rash	45 (97.8)	8	34	3	0
Diarrhoea	31 (67.4)	24	6	1	0
Pruritus	30 (65.2)	23	7	0	–
Dry skin	28 (60.9)	25	3	–	–
Stomatitis	21 (45.7)	16	4	1	0
Anorexia	16 (34.8)	11	2	3	0
Paronychia	15 (32.6)	11	4	0	0
T-Bil increased	13 (28.3)	6	7	0	0
ALT increased	12 (26.1)	5	3	3	1
C-Reactive protein increased	11 (23.9)	10	1	0	0
Fatigue	11 (23.9)	8	3	0	0
Nausea	10 (21.7)	9	1	0	–

NCI-CTC, National Cancer Institute Common Toxicity Criteria; T-Bil, total bilirubin; ALT, alanine aminotransferase. *Categorised by MedDra Ver.7.1 (the Medical Dictionary for Regulatory Activities Ver.7.1).

unclear; however, it is possible that the small numbers of current smokers enrolled in our study may have been a contributing factor.

As in previous studies of erlotinib in NSCLC, the observed AEs were predominantly dermal or gastrointestinal in nature and, although they occurred at frequencies of 50% or more, they were generally classified as grade 2 or lower. Although the frequency of these AEs was higher than that seen in patients receiving erlotinib in the pivotal BR.21 US phase III study (10), the frequency of severe toxicities (grade 3 or greater rash or diarrhoea) was not. These findings did not support the magnitude of the difference seen between the BR.21 and the Japanese phase II study populations, with the exception of ethnic difference. Further studies are needed to clarify the influence of ethnic difference on the frequency and severity of erlotinib-induced toxicities.

Notably, erlotinib is not associated with the haematological toxicities that are often seen with standard chemotherapy such as docetaxel, and there is no need for co-medications or routine monitoring. The main events associated with erlotinib, rash and diarrhoea, can be effectively managed using symptomatic treatment, dose reduction and/or suspension of administration. One patient died due to ILD in this study. As similar cases of ILD-related death have been reported in previous studies, we recommend that careful screening of patients for ILD risk factors (signs of pulmonary fibrosis or interstitial pneumonia) should be carried out before prescribing erlotinib.

The favourable tolerability profile of erlotinib enabled patients to remain on treatment for long periods: the median treatment duration was more than a year, and one patient received erlotinib for 1066 days. We also found that improved OS was correlated with the severity of rash in this study, as has been noted by other investigators (26). Therefore, active management of rash may be an important consideration for prolonged survival without QoL deterioration.

Mutations in the kinase region of the *EGFR* are thought to enhance sensitivity to EGFR TKIs such as erlotinib and gefitinib. A meta-analysis of 1170 patients has shown that more than 70% of patients with *EGFR* mutations respond to TKIs, whereas only 10% of patients without *EGFR* mutations responded (27). However, the link between *EGFR* mutational status and survival is not straightforward, and there may be some other factors influencing the efficacy of EGFR-TKIs, such as *EGFR* copy number, status of other members of the EGFR family, and somatic mutations of downstream molecules such as *KRAS* (13, 28, 29). *EGFR* mutation analysis was only possible for six patients in the current study, and two out of the three patients with *EGFR* mutations experienced a (partial) response. A significant amount of work is required to determine the relationship between such biomarkers and OS in Japanese patients receiving erlotinib.

In summary, erlotinib was found to have promising antitumour activity in this phase II study of Japanese patients with previously-treated NSCLC. Erlotinib of 150 mg/day was well tolerated by most patients and the AE profile was in line with that seen in previous studies with similar patient populations. There was some evidence to suggest a correlation between the severity of rash and improved survival. *EGFR* mutation analysis was only possible for six patients and therefore definitive conclusions on the predictive importance of this marker on the efficacy of erlotinib could not be made. Further studies are needed to clarify the markers that are predictive of erlotinib efficacy in Japanese patients, not only *EGFR* mutations, but also *KRAS* mutations and other as yet unidentified, biomarkers.

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