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A prospective, phase II, open-label study (JO22903) of first-line erlotinib in Japanese patients with epidermal growth factor receptor (*EGFR*) mutation-positive advanced non-small-cell lung cancer (NSCLC)

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ABSTRACT

Introduction: The epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor erlotinib is associated with survival benefits in patients with *EGFR* mutation-positive non-small-cell lung cancer (NSCLC). This phase II, single-arm study examined the efficacy and safety of first-line erlotinib in Japanese patients with *EGFR* mutation-positive NSCLC.
Methods: Eligible patients received erlotinib 150 mg/day until disease progression or unacceptable toxicity. The primary endpoints were progression-free survival (PFS) and safety.
Results: A high degree of concordance was observed between different mutation testing methodologies, suggesting feasibility of early, rapid detection of *EGFR* mutations. Median PFS was 11.8 months (95% confidence interval [CI]: 9.7–15.3) at data cut-off (1 June 2012) ($n = 102$). Exon 19 deletions seemed to be associated with longer PFS compared with L858R mutations; T790M mutations were tentatively linked with shorter PFS. The safety profile was as expected: rash (any grade; 83%) and diarrhea (any grade; 81%) were most common. Six interstitial lung disease (ILD)-like cases were reported, and 5 were confirmed as ILD-like events by the extramural committee. Two patients died of treatment-related pneumonitis (JAPIC Clinical Trials Information number: Japic CTI-101085).
Conclusion: Erlotinib should be considered for first-line treatment in this subset of Japanese patients, with close monitoring for ILD-like events.

1. Introduction

Non-small-cell lung cancer (NSCLC) remains a significant global health burden, with high mortality and poor prognosis for patients diagnosed at an advanced stage. Erlotinib is an epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor (TKI), which has been approved for the treatment of advanced NSCLC. Originally approved as second- or third-line treatment in patients refractory to chemotherapy, erlotinib showed overall survival (OS) and progression-free survival (PFS) improvements compared with

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placebo in a large phase III trial (OS: 6.7 vs. 4.7 months, respectively, hazard ratio [HR] = 0.7, 95% confidence interval [CI]: 0.58–0.85, $p < 0.001$; PFS: 2.2 vs. 1.8 months, respectively, HR = 0.61, 95% CI: 0.51–0.74, $p < 0.001$) [1]. Further trials have expanded its use to maintenance therapy (SATURN) [2] and to first-line treatment of *EGFR* mutation-positive disease (OPTIMAL and EURTAC) [3,4]. The latter 2 studies reported significant PFS benefits with erlotinib as first-line treatment for *EGFR* mutation-positive NSCLC compared with chemotherapy in Chinese and European populations (OPTIMAL: 13.1 vs. 4.6 months, respectively, HR = 0.16, 95% CI: 0.10–0.26, $p < 0.0001$; EURTAC: 9.7 vs. 5.2 months, respectively, HR = 0.37, 95% CI: 0.25–0.54, $p < 0.0001$).

Until now, erlotinib has not been prospectively evaluated in Japanese patients with *EGFR* mutation-positive NSCLC. This prospective, phase II, open-label study (JO22903) was initiated to obtain confirmatory efficacy and safety data in the first-line setting for Japanese patients with *EGFR* mutation-positive NSCLC, in order to corroborate data from Chinese and Caucasian populations.

2. Materials and methods

2.1. Study design and patients

JO22903 was a phase II, multicenter, open-label, non-randomized study conducted at 25 centers in Japan. Eligible patients were aged ≥20 years with advanced, untreated, metastatic (stage IIIB/IV), or relapsed NSCLC, with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 and tumors harboring confirmed activating mutations of *EGFR* (exon 19 deletion or L858R point mutation in exon 21), with at least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0. Staging was assessed by TNM classification (7th edition). The study was carried out in accordance with the Declaration of Helsinki and Japanese Good Clinical Practice guidelines. The protocol was approved by ethics committees and all patients gave informed consent for study participation.

2.2. Procedures

Eligible patients received oral erlotinib 150 mg/day until disease progression (PD) or unacceptable toxicity (Fig. 1). Dose reductions (in 50-mg decrements) and/or interruptions (of up to 2 weeks) were permitted to manage adverse events (AEs) related to erlotinib treatment. Treatment was interrupted if interstitial lung disease (ILD) was suspected; for patients with confirmed ILD diagnosis, erlotinib was discontinued immediately. In cases of gastrointestinal perforation or any grade 4 AE, erlotinib was discontinued.

Patients were screened for *EGFR* mutations in a local or central laboratory. In the central laboratory, *EGFR* mutation status was determined using Scorpion ARMS [5]. For exploratory analyses, tumor samples were obtained from hospital archives for patients who were screened in their local laboratory to confirm the concordance between several local methods and Scorpion ARMS. In addition, serum samples were collected at screening from all patients who provided informed consent to participate in the exploratory research ($n = 95$). DNA was isolated from serum with the QIAmp MinElute Virus Spin kit (Qiagen, Hilden, Germany). Scorpion ARMS was used for *EGFR* mutation testing for circulating DNA in the serum.

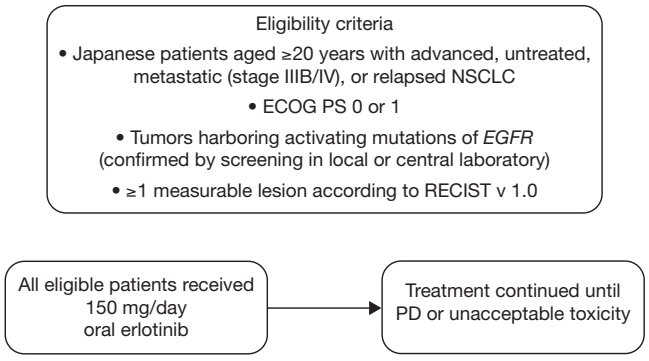

Fig. 1. Study design and eligibility criteria.

Tumor response was assessed by an independent review committee (IRC) using RECIST version 1.0. Tumor response evaluation was scheduled every 6 weeks. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTC AE) version 4.0.

At baseline mandatory lung and abdominal scans (CT/MRI), brain scans (CT/MRI) and bone scans (bone scintigraphy, PET, CT and MRI) were performed. During treatment until disease progression, lung and abdominal scans were mandatory. Brain scans were required for those patients who revealed brain metastases at baseline. When confirming complete or partial tumor response, bone scans were required for patients with bone metastases at baseline.

2.3. Study endpoints

Primary endpoints were PFS, as assessed by an IRC, and safety profile. Secondary endpoints included overall response rate (ORR), disease control rate (DCR), and OS. Exploratory analyses examined concordance between different *EGFR* mutation testing methodologies, and concordance between serum and tumor tissue at screening. *EGFR* mutation status alterations in serum before and after treatment were observed.

2.4. Statistical analyses

The statistical plan assumed a median PFS of 7 months in the historical control group and 11 months in the erlotinib treatment group. The primary analysis was planned for 11 months after the last patient was enrolled to confirm superiority of erlotinib over the historical control.

Given an expected median PFS of 11 months, 93 patients were necessary to provide statistical power of 80% to confirm the superiority of the lower confidence boundary of the observed median PFS compared with the threshold median PFS of 7 months. The target sample size was 100 patients, taking into consideration patients who would prove to be ineligible for the study. For PFS (the primary efficacy endpoint), OS, and duration of response, median and 95% CIs were estimated using Kaplan–Meier survival methodology. CI limits were calculated according to the Greenwood method. Response rate and DCR were summarized by presenting the rate and 95% CIs according to Pearson–Clopper.

The analysis of safety parameters (co-primary endpoint) was descriptive: all AEs were converted to MedDRA preferred terms and summary tables were produced. For laboratory parameters, descriptive summary tables or graphs of change over time were produced.

According to the statistical analysis plan, all patients who received at least 1 dose of study treatment would be included in the safety population. The modified intention-to-treat (ITT) population for the efficacy analysis excluded all patients with major protocol violations.

3. Results

3.1. Patient population

Between 8 April 2010 and 6 October 2010, 103 patients with confirmed *EGFR* mutations were enrolled and received erlotinib,

Table 1
Baseline characteristics for the safety population ($n = 103$).

Characteristics	n (%)
Median age, years (range)	65.0 (36–86)
Gender	
Female	70 (68)
Male	33 (32)
ECOG PS	
0	49 (48)
1	54 (52)
Smoking status	
Current smoker	7 (7)
Former smoker	37 (36)
Never smoker	59 (57)
Median Brinkman index (range) ($n = 44$)	580.0 (3–1720)
Type of *EGFR* mutation	
Exon 19 deletion	50 (49)
L858R mutation	51 (50)
L858R mutation + T790M	2 (2)
EGFR mutation in serum ($n = 95$)	
EGFR mutation detected	25 (26)
EGFR mutation not detected	70 (74)
Histology	
Adenocarcinoma	102 (99)
Other	1 (1)
Stage	
IIIB	4 (4)
IV	74 (72)
Post-operative recurrence	25 (24)
Previous treatment	
Surgery	
Yes	25 (24)
No	78 (76)
Induction or adjuvant chemotherapy[a]	
Yes	12 (12)
No	91 (88)
Radiation	
Yes	17 (17)
No	86 (84)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor.

[a] Patients may have had prior therapy providing the following conditions were met: platinum-based chemotherapy: wash-out period of 6 months; non-platinum-based chemotherapy: wash-out period of 4 weeks.

comprising the safety population. The majority of patients (95/103; 92%) had their samples screened in local practice, while the remaining 8 (8%) had their samples screened at a central laboratory. One patient was excluded from the modified ITT population as they had a major protocol violation after enrollment. The baseline characteristics for the safety population are shown in Table 1. At the time of data cut-off for the primary analysis (1 September 2011), 44 patients remained in the study, either on treatment or in follow-up.

3.2. Efficacy analyses

At the primary analysis (data cut-off 1 September 2011), median PFS with first-line erlotinib was 11.8 months (95% CI: 9.7 to not reached). The 1-year event-free survival rate was 49% (95% CI: 39–59). Eighty patients had a complete or partial response with erlotinib, giving an ORR of 78% (complete response: 4 patients; partial response: 76 patients); a further 17 patients had stable disease, giving a DCR of 95%.

In the follow-up analysis (data cut-off 1 June 2012), the median PFS was 11.8 months (95% CI: 9.7–15.3) (Fig. 2) and had not changed after a longer follow-up. The 1-year event-free survival rate was 50% (95% CI: 40–60). The median duration of response was 11.1 months (95% CI: 9.7–13.9). Full response data also did not change with a follow-up analysis by IRC.

Subgroup analyses of baseline characteristics and PFS are summarized in Fig. 3. All patient subgroups showed favorable PFS regardless of gender, age, smoking status, disease stage, or type of *EGFR* mutation.

Examining the PFS results by *EGFR* mutation type, i.e., exon 19 deletions vs. L858R point mutations, demonstrated that exon 19 deletions seemed to be associated with longer PFS (Fig. 4a). Median PFS with exon 19 deletions ($n = 50$) was 12.5 months (95% CI: 10.3–16.6), while with L858R mutations ($n = 50$) it was 11.0 months (95% CI: 6.9–15.2). Two patients whose tumors harbored the T790M mutation with L858R had poor outcomes, with PFS of 2.9 and 4.6 months, respectively. It should be noted that it is impossible to distinguish between prognostic or predictive effects of different mutations without a control arm. In this study, however, the 4 patients with complete response to erlotinib all had tumors with exon 19 deletions (Fig. 4b). Response rate with exon 19 deletions ($n = 50$) was 84%, while with L858R mutations ($n = 50$) it was 76%.

Examining PFS by grade of skin rash determined that higher grades (grade ≥ 2) of rash were associated with longer PFS with erlotinib (Supplementary data, Fig. S1).

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2013.07.003.

By the second cut-off date, 28 of 102 patients had died. The median survival time could not be calculated.

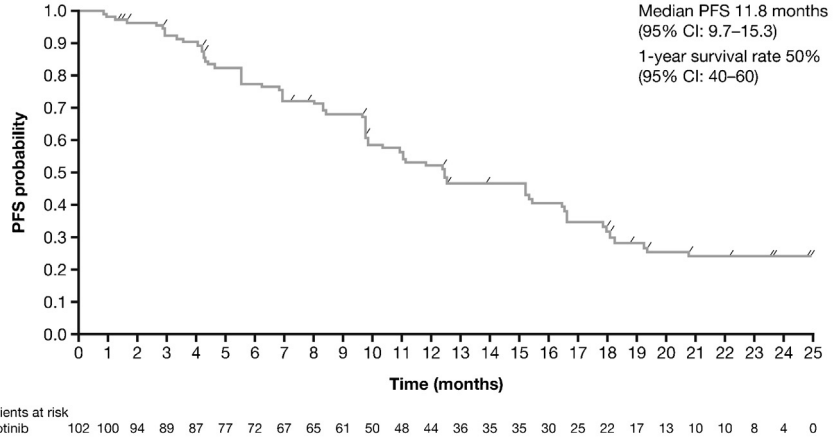

Fig. 2. PFS in the modified ITT population by the follow-up analysis (1 June 2012 data cut-off). PFS = progression-free survival; ITT = intention-to-treat; CI = confidence interval.

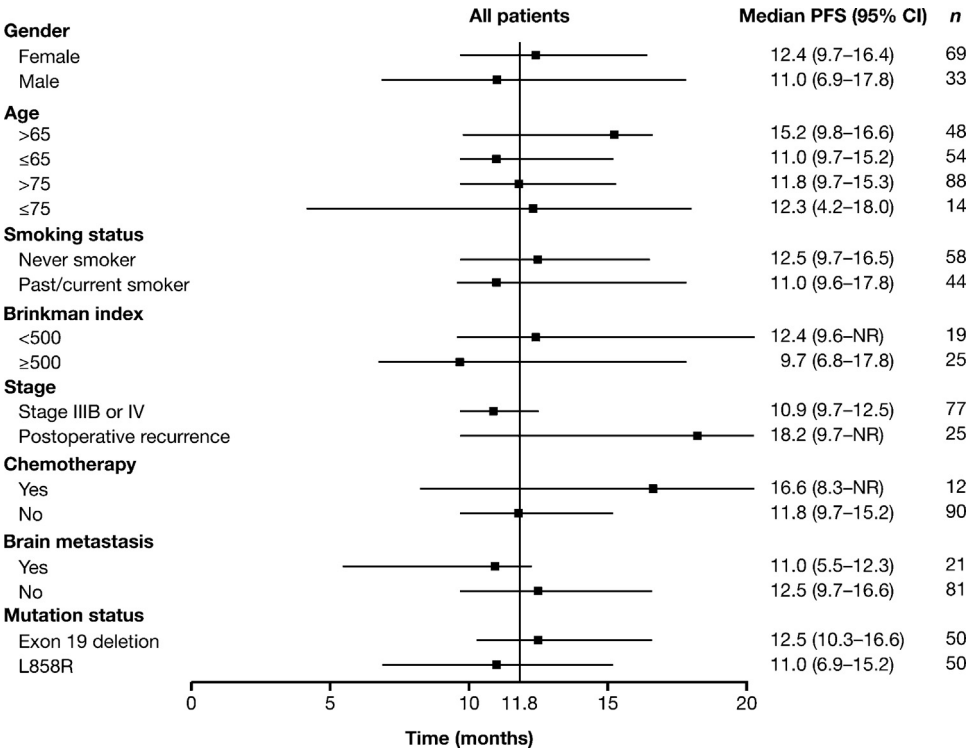

Fig. 3. Forest plot of subgroup analyses for PFS (1 June 2012 data cut-off). PFS = progression-free survival; CI = confidence interval.

3.3. Safety analyses

AEs reported in more than 20% of patients in the safety population are presented in Table 2. Two patients died of treatment-related pneumonitis; in both cases, simultaneous PD was reported by the investigators. A total of 43 patients required dose modification due to AEs of grade ≥2, the majority of which were skin toxicities ($n = 22$). Ten patients (10%) discontinued erlotinib due to AEs: ILD or ILD-like events ($n = 6$), abnormal liver function or liver enzyme levels ($n = 3$), and skin rash ($n = 1$).

Six ILD-like cases were reported, and 5 cases were confirmed as ILD-like events according to the extramural committee. Three cases were grade 1/2, 2 were grade 5, and the 1 unconfirmed ILD case was grade 1. One fatal ILD case that occurred 9 months after treatment initiation showed co-existence of aspiration pneumonia. The extramural committee suggested the possibility that ILD developed as a secondary complication following the aspiration pneumonia. By the second cut-off date (1 June 2012), no further ILD or ILD-like events had been observed.

Table 2
AEs occurring in >20% of the safety population ($n = 103$).

	Any grade		Grade 1		Grade 2		Grade ≥3	
	n	%	*n*	%	*n*	%	*n*	%
Rash	85	83	27	26	44	43	14	14
Diarrhea	83	81	58	56	24	23	1	1
Dry skin	79	77	45	44	29	28	5	5
Paronychia	68	66	17	17	50	49	1	1
Pruritus	66	64	36	35	27	26	3	3
Stomatitis	65	63	45	44	19	18	1	1
Decreased appetite	36	35	20	19	13	13	3	3
Nasopharyngitis	34	33	25	24	9	9	–	–
ALT increased	34	33	21	20	5	5	8	8
Alopecia	28	27	27	26	1	1	–	–
AST increased	27	26	19	18	5	5	3	3
T-Bil increased	26	25	11	11	15	15	–	–

Abbreviations: AEs = adverse events; ALT = alanine aminotransferase; AST = aspartate aminotransferase; T-Bil = total bilirubin. No patient counted here had a grade 4/5 adverse event.

3.4. Exploratory analyses

This study offered an opportunity to assess concordance across different methodologies. Forty archive samples from local testing were assessed at a central laboratory; for 38 of the samples (95%), the central laboratory testing produced identical results to the original local laboratory testing. Baseline serum samples were available from 95 patients, and *EGFR* mutations were detected in 25 patients (centrally by Scorpion ARMS), which showed the same mutation type as the tumor (Supplementary data, Tables S1–S3 and Fig. S1). No patients showed T790 M mutation in serum at baseline. In the serum samples obtained from the 2 patients whose tumors showed T790 M at baseline, no mutation at baseline was observed in the serum sample.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2013.07.003.

4. Discussion

JO22903 is the first prospective study to investigate erlotinib for the first-line treatment of *EGFR* mutation-positive NSCLC in Japanese patients. In this study, the lower boundary of the 95% CI was 9.7 months, which was longer than the 7 months threshold value, and the median PFS reached 11.8 months in this patient population.

The median PFS of 11.8 months is similar to that reported for Chinese patients with *EGFR* mutation-positive disease in the phase III OPTIMAL study, which was 13.1 months [3]. The PFS of both the present study and OPTIMAL were slightly higher than the PFS in European patients with *EGFR* mutation-positive NSCLC (9.7 months) [4]. Gefitinib has also been evaluated as a first-line treatment for NSCLC in Asian patients. According to a retrospective

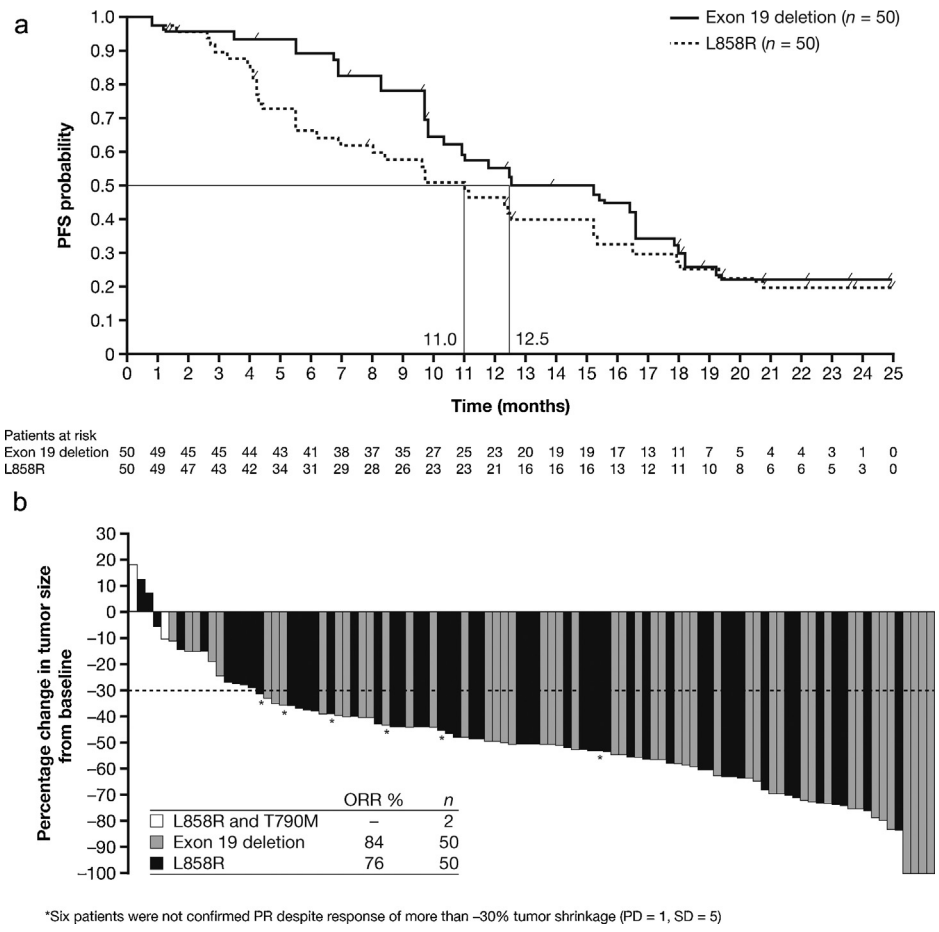

Fig. 4. (a) PFS according to type of *EGFR* mutation (1 June 2012 data cut-off). PFS = progression-free survival; EGFR = epidermal growth factor receptor. (b) Waterfall plot of tumor response by type of *EGFR* mutation. Negative values represent a decrease in tumor size from baseline and positive values represent an increase in tumor size from baseline. The dashed line represents partial response indicated by 30% tumor shrinkage. EGFR = epidermal growth factor receptor; ORR = overall response rate; PR = partial response; PD = progressive disease; SD = stable disease.

analysis of the IPASS study by *EGFR* mutation status, the subgroup of patients with *EGFR* mutation-positive NSCLC had a median PFS of 9.5 months [6]. In addition, 2 Japanese studies in patients with *EGFR* mutation-positive NSCLC showed median PFS of 9.2 and 10.8 months (WJTOG3405 and NEJ002, respectively) [7,8]. Again, these medians are similar to that achieved in the present study (Supplementary data, Table S4).

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.lungcan.2013.07.003.

According to an analysis of data from an online tumor registry examining first-line EGFR TKI treatment, all efficacy outcomes (ORR, time to progression, OS) were better in patients with exon 19 deletions compared with L858R mutations [9]. In the EURTAC study, a similar trend was observed. However, this association has not been observed in gefitinib studies (IPASS, NEJ002 and WJTOG3405) [6–8]. The present study also showed longer PFS in patients with exon 19 deletions rather than L858R mutations (median PFS of 12.5 and 11.0 months, respectively). This study suggests that the difference seen in efficacy outcomes between patients with exon 19 deletions mutations and those with L858R is specific to erlotinib, as also demonstrated in the EURTAC study [4].

The safety profile of erlotinib in this study was as expected, with rash and diarrhea being the most common AEs. Although patients in this study received treatment with erlotinib for a longer duration than patients treated in the second- and third-line Japanese studies, due to the longer PFS, the common AEs were similar to previous studies [10,11]. No long-term toxicity was observed.

Six out of the total 108 patients included in the erlotinib second-/third-line Japanese studies were confirmed to have *EGFR* mutations [10,11]. Common AEs were similar between patients with *EGFR* mutation-positive NSCLC receiving first-line or second-/third-line erlotinib.

Six occurrences (6%) of treatment-related ILD or ILD-like events were reported by investigators, among which 5 (5%) were confirmed as ILD cases but 1 case was denied by an extramural committee. Two (2%) of these 5 were classified as severe and resulted in death. The WJTOG3405 and NEJ002 studies reported an ILD incidence of 2% (2/87, with 1 fatal case) and 5.3% (6/114 patients, with 1 fatal case), respectively [7,8]. According to a recent large-scale surveillance study of erlotinib in the second-/third-line treatment of Japanese NSCLC patients, the incidence of ILD was 4.5% and the mortality rate was 1.6% [12]. Thus, the incidence of ILD/ILD-like events in the JO22903 study was generally as expected. Close monitoring of Japanese patients for symptoms of ILD and immediate cessation of erlotinib therapy on diagnosis is recommended.

In this study, the incidence of grade 3 rash was 14%, compared with 2% in the WJTOG3405 study of gefitinib [7] and 5% in the NEJ002 study of gefitinib [8]. A higher incidence of grade 3 rash was observed in this study; however, with the exception of 1 patient, it was possible for patients to continue receiving erlotinib with dose modification and/or AE treatment.

The incidence of grade ≥3 alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevation was 8% and 3%, respectively. In addition, the incidence of grade ≥3 abnormal hepatic function or liver disorder was 4% in this study. Three patients were withdrawn from erlotinib treatment due to abnormal liver function or liver enzyme levels. Despite these 3 patients showing normal enzyme levels for AST and ALT at screening, they showed severe changes approximately 1 month after treatment initiation.

A total of 43 patients required dose modification due to AEs, and 10 patients (10%) discontinued erlotinib in this study. In the WJTOG3405 study, 14 of 87 patients (16%) discontinued gefitinib due to AEs. Although the safety profile of these 2 EGFR TKIs seem to be slightly different, this study suggests that erlotinib has similar tolerability to gefitinib in the first-line treatment of Japanese patients with *EGFR* mutation-positive NSCLC.

A final exploratory aspect of this study concerned the *EGFR* mutation assessment for circulating DNA in serum. Twenty five (26%) of 95 patients showed *EGFR* mutation-positive disease assessed by Scorpion ARMS. This 26% detection rate was lower than in the EURTAC study (58 [53%] of 109 serum samples) [4], and seemed to be insufficient for the screening test. However, although low detection rates were seen in serum samples, both studies showed high concordance (~100%) between serum and tumor samples at baseline. Thus, we cannot make definitive conclusions regarding the utility of serum samples as *EGFR* mutation assessment specimens.

5. Conclusions

This study indicates that early, local testing of *EGFR* mutation status is feasible and can reliably identify patients with *EGFR* mutation-positive NSCLC. The reported PFS in this study of Japanese NSCLC patients was 11.8 months with first-line erlotinib treatment, which is comparable to PFS outcomes seen with this agent in other *EGFR* mutation-positive populations, confirming that erlotinib can provide a good PFS benefit in this subgroup. Erlotinib was generally well tolerated, although 6 (of 103) patients reported ILD/ILD-like events and 5 were confirmed by an extramural committee, confirming that ILD remains a risk with EGFR TKI treatment in Japanese patients. Continued monitoring for symptoms of ILD and prompt action on diagnosis is recommended. Despite this, the efficacy and manageable safety profile demonstrated by erlotinib in this study confirms that erlotinib should be recommended for the first-line treatment of Japanese NSCLC patients with *EGFR* mutation-positive disease.

Role of the funding source

This trial was designed, funded by and monitored by Chugai Pharmaceuticals Ltd. Data were collected, analyzed and interpreted by Chugai with input from the authors and investigators. The initial draft of the manuscript was reviewed and commented on by all authors and by employees of Chugai. The corresponding author was provided data from Chugai and took full responsibility for the final decision to submit the paper.

Conflict of interest statement

K. Goto, M. Nishio, M. Maemondo, T. Seto, and T. Tamura have received lecture fees from Chugai Pharmaceutical Co. Ltd. N. Katakami has previously received payment from Chugai Pharmaceutical Co. Ltd. for writing or reviewing manuscripts. T. Fukuyama is an employee of Chugai Pharmaceutical Co. Ltd. All remaining authors have declared no conflicts of interest.

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