Clinical Significance of Erlotinib Monotherapy for Gefitinib-resistant Non-small Cell Lung Cancer with *EGFR* Mutations

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Abstract. *Background: The efficacy of the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) erlotinib is difficult to be accurately assessed in patients with non-small cell lung cancer (NSCLC) because it is commonly employed after failure of another EGFR-TKI, gefitinib. Patients and Methods: Medical records from 104 patients with NSCLC treated with erlotinib were retrospectively reviewed. Results: There were no significant differences in erlotinib efficacy between EGFR-mutated NSCLC with gefitinib resistance and NSCLC with wild-type EGFR. A therapeutic response of disease control (DC) and the onset of skin rash prolonged the progression-free survival (PFS), whereas the onset of interstitial lung disease shortened both PFS and overall survival (OS). The DC group also experienced prolonged OS. Conclusion: Erlotinib may be a therapeutic option for EGFR-mutated NSCLC with gefitinib resistance, as well as for NSCLC with wild-type EGFR. Therapeutic response of DC and the onset of the described adverse events may be practical predictors of survival in erlotinib treatment.*

Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI), which include gefitinib and erlotinib, comprise an important group of antitumor drugs for non-small lung cancer (NSCLC). These inhibitors bind to the ATP-binding domain of EGFR in which activating gene mutations often occur, and selectively inhibit EGFR signaling. In 2004, it was reported that the responsiveness of NSCLC cells to gefitinib is associated with the presence of mutant EGFR (1, 2), and recent phase III trials have confirmed that gefitinib provides clinical benefits to patients with NSCLC that harbors *EGFR* mutations (3-5).

In contrast, the efficacy of EGFR-TKIs in NSCLC with wild-type *EGFR*, or in NSCLC unselected by *EGFR* mutations, remains controversial because gefitinib and erlotinib have different efficacies in such populations. Gefitinib did not prolong survival in unselected patients with NSCLC compared to placebo administration (6), whereas erlotinib did (7). Therefore, gefitinib therapy is not currently recommended for patients with NSCLC with wild-type *EGFR*. Erlotinib may also provide therapeutic benefits to patients with NSCLC with acquired resistance to gefitinib, and the antitumor mechanisms of erlotinib may be different from those of gefitinib (8-10). If this is indeed the case, then differential use of gefitinib and erlotinib needs to be considered in the treatment of NSCLC. Until fairly recently in Japan, erlotinib treatment was approved exclusively for patients with NSCLC who failed the preceding treatment with antitumor drugs. Evidence for therapeutic efficacy against NSCLC harboring *EGFR* mutations is therefore more solid for gefitinib than for any other anti-NSCLC drug, and gefitinib is preferentially administered to these patients earlier than other drugs in the course of NSCLC treatment. These situations demonstrate that the therapeutic efficacy of erlotinib in clinical practice should be evaluated according to actual usage conditions. The important issues in this context are to determine whether erlotinib is actually effective against NSCLC that harbors *EGFR* mutations but has acquired resistance to gefitinib, and whether predictive factors for erlotinib efficacy, including *EGFR* mutation status, can be defined in clinical practice.

To attempt answering these questions, we retrospectively investigated patients with NSCLC with mutant *EGFR* given erlotinib after gefitinib failure and with wild-type *EGFR* given erlotinib as a first EGFR-TKI therapy.

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Key Words: Non-small lung cancer, epidermal growth factor receptor, erlotinib, gefitinib, acquired resistance to gefitinib, adverse events.

Table I. *Patients' characteristics (n=104).*

	Value/n (%)
Age, Median (range), years	63 (35-85)
≤70	85 (82)
>71	19 (18)
Gender	
Male	56 (54)
Female	48 (46)
Smoking status	
Never smoker	54 (52)
Light smoker (pack years <20)	7 (7)
Heavy smoker (pack years ≥20)	43 (41)
Clinical stage	
IIIB	8 (8)
IV	96 (92)
Performance status (ECOG)	
0	42 (40)
1	25 (24)
2	23 (22)
3	11 (11)
4	3 (3)
Histology	
Adenocarcinoma	90 (86)
Squamous cell carcinoma	6 (6)
Diagnosed only as NSCLC	8 (8)
EGFR mutation status	
Positive	54 (52)
Exon 18 (G719A)	2 (3)
Exon 19 deletion	22 (41)
Exon 21 (L858R)	22 (41)
Others	8 (15)
Negative	50 (48)

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor.

Patients and Methods

Patients. The present study included 104 patients with NSCLC treated with erlotinib at the Saitama Medical University International Medical Center from 2008 to 2010. The clinicopathological characteristics of the patients were extracted from medical records after approval of the Institutional Review Board (No. 12-003).

Treatment schedules, EGFR mutation analysis, and assessment of therapeutic effect. All patients received 100-150 mg/day of erlotinib after failure of more than one treatment regimen. *EGFR* mutation status was examined using the peptide nucleic acid-locked nucleic acid polymerase chain reaction clamp method (11). Maximal effect on tumor size was defined as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), according to the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (12). Additionally, CR plus PR was defined as the objective response (OR) and OR plus SD was defined as the disease control (DC). The therapeutic effect was evaluated based on the objective response rate (ORR; the rate of OR), the disease control rate (DCR; the rate of DC), the time from the initiation of erlotinib therapy to the confirmation of disease progression (progression-free survival; PFS) and the time from the initiation of erlotinib therapy to the death of the patient (overall survival; OS).

Adverse events. Adverse events associated with erlotinib therapy were confirmed by medical record reviewing and evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Table II. *Treatment regimens immediately before and after erlotinib monotherapy.*

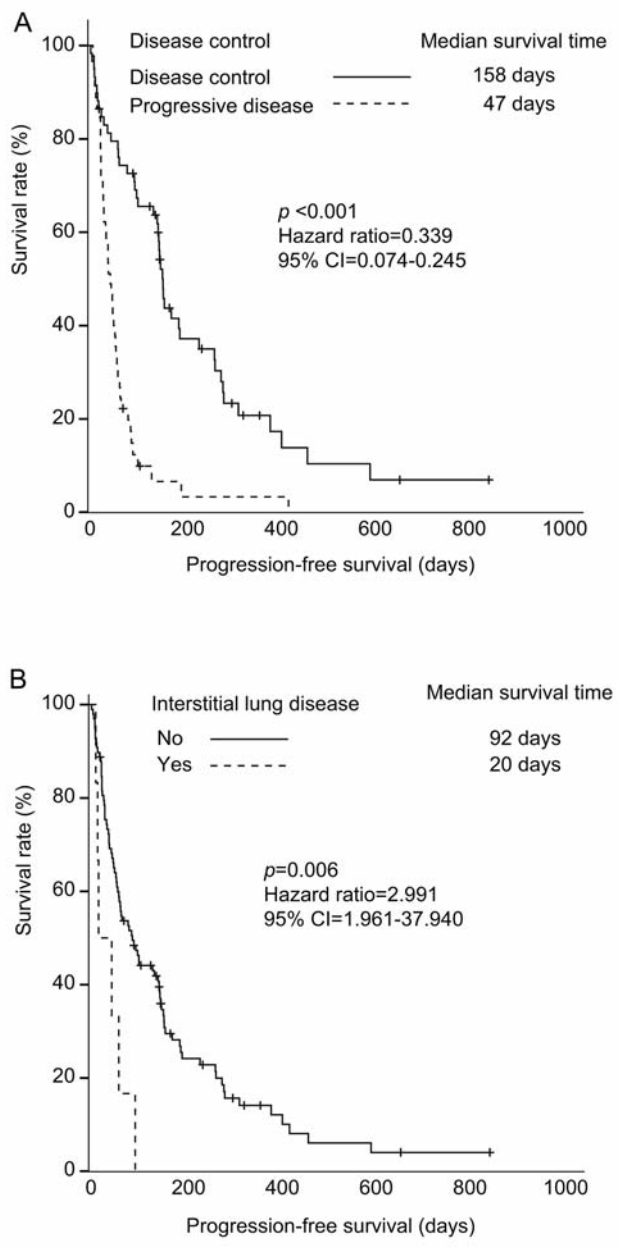
Treatment regimen	Treatment before erlotinib, n=104	Treatment after erlotinib, n=47
Carboplatin/docetaxel	3	1
Carboplatin/pemetrexed	6	2
Carboplatin/paclitaxel	16	2
Cisplatin/irinotecan	1	1
Cisplatin/pemetrexed	5	2
Cisplatin/vinorelbine	3	0
Irinotecan	1	0
Irinotecan/S1	1	0
Docetaxel	23	4
Docetaxel/gemcitabine	1	0
Docetaxel/S1	7	3
Gefitinib	9	2
Gemcitabine	3	4
Gemcitabine/vinorelbine	8	2
Pemetrexed	14	18
S1	2	5
Vinorelbine	1	0
Tegafur/uracil	0	1

S1, Tegafur/gimeracil/oteracil.

Table III. *Association of response to erlotinib with epidermal growth factor receptor mutation and response to prior gefitinib.*

	Response to erlotinib				
	CR	PR	SD	PD	Total
EGFR mutation status (n=104)					
Negative	1	4	20	25	50
Positive	0	4	30	20	54
Response to gefitinib (n=54)					
CR	0	0	3	1	4
PR	0	2	18	12	32
SD	0	1	9	3	13
PD	0	1	0	4	5

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease.



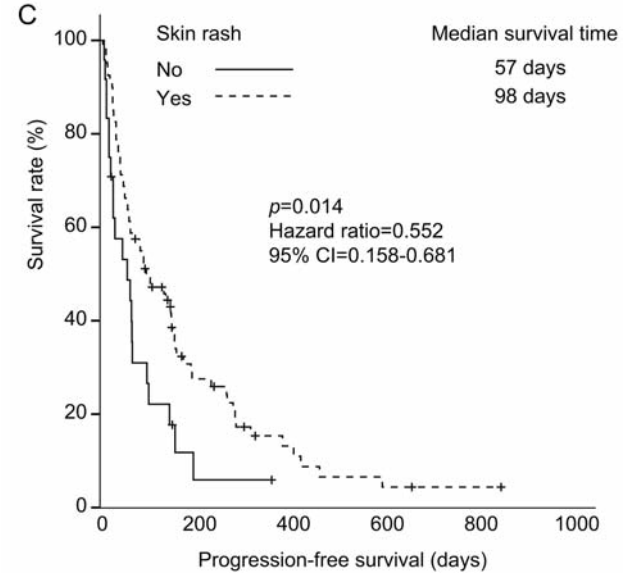


Figure 1. *Kaplan-Meier survival curves with log-rank tests for progression-free survival for patients with non-small cell lung cancer treated with erlotinib. Therapeutic response of disease control (DC) (A) and the onsets of interstitial lung disease (B) and skin rash (C) were independently-associated with progression-free survival using the multivariate Cox proportional hazards model. CI: Confidence interval.*

Statistical analysis. The relationship between the response to erlotinib therapy and the one to prior gefitinib therapy in patients with mutant *EGFR* was tested using Spearman's rank correlation coefficient. PFS and OS were calculated using the Kaplan-Meier method and survival curves were compared using the log-rank test. Variables contributing to PFS and OS were assessed using the multivariate Cox proportional hazards model. A p-value <0.05 was considered significant.

Results

Patients' characteristics. The clinicopathological features of the patients are shown in Table I. Most of the patients had adenocarcinoma. Prior to erlotinib therapy, 54 patients with *EGFR* mutations had all experienced gefitinib failure, whereas 50 patients with wild-type *EGFR* were all EGFR-TKI-naïve.

Table IV. *Adverse events related to erlotinib (n=104 patients).*

		CTC Grade			
Adverse event	n (%)	1	2	3	4
Diarrhea	34 (32.7)	30	4	0	0
Dry skin	15 (14.4)	14	1	0	0
Hepatotoxicity	16 (15.4)	15	1	0	0
High γGTP	7 (6.7)	6	1	0	0
Hyperbilirubinemia	14 (13.5)	13	1	0	0
Interstitial lung disease	6 (5.8)	2	2	2	0
Nephrotoxicity	11 (10.6)	11	0	0	0
Paronychia	16 (15.4)	10	6	0	0
Skin rash	80 (76.9)	54	16	10	0
Stomatitis	12 (11.5)	10	1	1	0

CTC, Common toxicity criteria; γGTP, Gamma-glutamyl transpeptidase.

Treatment regimens immediately before and after erlotinib monotherapy. Treatment regimens administered immediately before erlotinib therapy are shown in Table II. Docetaxel (n=23), carboplatin/paclitaxel (n=16), and pemetrexed (n=14) were predominantly employed immediately before erlotinib

Table V. *Multivariate Cox proportional hazards model.*

	p-Value	Hazard ratio	95% Confidence interval
Parameters associated with progression free survival			
Clinicopathological characteristic			
Gender (male *vs.* female)	0.740	1.084	0.674 to 1.742
Objective response	0.905	0.950	0.387 to 2.318
Disease control	<0.001	0.266	0.160 to 0.444
Adverse event			
Interstitial lung disease	<0.001	5.675	2.236 to 14.400
Skin rash	0.040	0.571	0.334 to 0.975
Treatment before erlotinib			
Surgery experience	0.076	0.614	0.358 to 1.052
Parameters associated with overall survival			
Clinicopathological characteristic			
Performance status (0-2 vs. 3-4)	<0.001	0.195	0.090 to 0.420
Treatment lines (2-3 *vs.* >3)	0.690	1.169	0.543 to 2.520
Disease control	0.001	0.318	0.165 to 0.613
Adverse event			
Hepatotoxicity	0.088	1.946	0.912 to 3.735
Interstitial lung disease	<0.001	12.399	3.842 to 40.014

therapy, whereas pemetrexed (n=18) was most frequently employed directly after erlotinib therapy.

Responses to erlotinib and EGFR mutation status. We investigated the association of responses to erlotinib with *EGFR* mutation status and prior gefitinib therapy (Table III). The ORR and DCR in prior gefitinib therapy were 66.7% and 90.7%, respectively. In the present study, patients with mutant *EGFR* corresponded completely with those who had already failed gefitinib therapy prior to erlotinib therapy, and consequently, the ORR and DCR in these 54 patients were 7.4% (four PRs) and 63.0% (four PRs and 30 SDs), respectively. There were no significant differences between the response to erlotinib to the one prior to gefitinib therapy (p=0.750) in patients with mutant *EGFR*.

Adverse events. To evaluate the safety of erlotinib therapy in clinical practice, we investigated the adverse events ascribed to erlotinib as shown in Table IV. The most frequent toxicity was skin rash (76.9%), and the morbidity of interstitial lung disease (ILD) (5.8%) was similar to that of a previous report (7, 13), whereas no fatal adverse events occurred. This suggests that erlotinib is well-tolerated in clinical practice.

Parameters correlating with PFS and OS in erlotinib monotherapy. We evaluated parameters associated with PFS and OS in erlotinib therapy using Kaplan-Meier survival curves compared by a log-rank test. The median PFS and OS in patients overall, were 79 and 212 days, respectively (data not shown). For parameters that showed statistical significance in this analysis, we further applied the multivariate Cox proportional hazards model to identify for parameters that were independently associated with PFS and OS (Table V). Figures 1 and 2 show the Kaplan-Meier survival curves compared by a log-rank test for the parameters that were independently associated with PFS or OS in the multivariate Cox proportional hazards model. The DC group, which predominantly consisted of patients with SD, experienced prolonged PFS (median PFS=158 *versus* 47 days; p<0.001; hazard ratio=0.339). A shortened PFS was observed due to the onset of ILD, a serious adverse event leading to discontinuation of treatment (median PFS=20 *vs.* 92 days; p=0.006; hazard ratio=2.991) (Figure 1). Similar to the previous reports, the onset of skin rash as a dermatological toxicity was observed in association with prolonged PFS (median PFS=98 *versus* 57 days; p=0.014; hazard ratio=0.552) (Figure 1) (14, 15). DC (median OS=677 *versus* 314 days; p=0.005, hazard ratio=0.436) and the onset of ILD (median OS=111 *versus* 509 days; p<0.001; hazard ratio=6.150) were positively and negatively associated with OS, respectively (Figure 2). Prolonged OS was observed in patients with good performance status (median OS=538 *versus* 157 days; p<0.001; hazard ratio=0.269) (Figure 2). There were no significant differences in PFS (p=0.550; hazard ratio=0.877) and OS (p=0.526; hazard ratio=1.210) for erlotinib-treated patients with NSCLC with mutant *EGFR* after gefitinib failure (median PFS=135 days; median OS=333 days) and those with wild-type *EGFR* (median PFS=63 days; median OS=509 days) (Figure 3). No treatment regimens employed directly before or after erlotinib therapy led to significant differences in PFS or OS (data not shown).

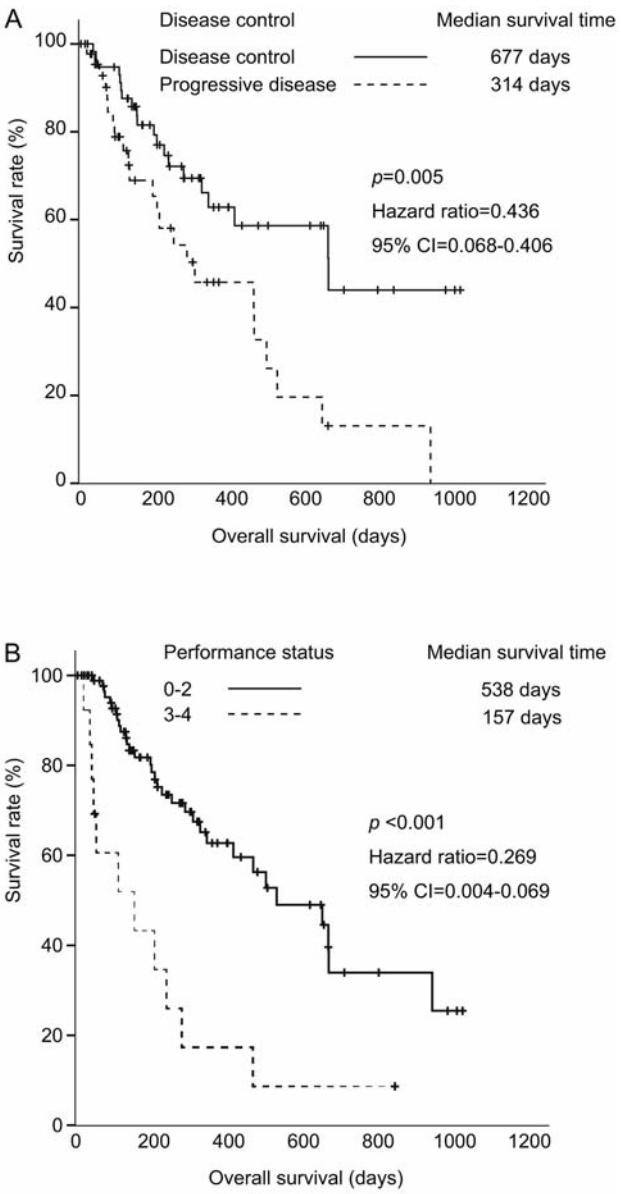


Figure 2. *Kaplan-Meier survival curves with log-rank tests for overall survival for patients with non-small cell lung cancer treated with erlotinib. Therapeutic response of disease control (DC) (A), good performance status (B), and the onset of interstitial lung disease (C) were independently associated with overall survival using the multivariate Cox proportional hazards model. CI: Confidence interval.*

Discussion

The aim of this study was to evaluate the significance of erlotinib therapy against NSCLC and find a predictive factor regarding treatment outcomes in clinical practice. In the present study, in which all patients with mutant *EGFR* received erlotinib monotherapy after gefitinib treatment had already failed, erlotinib was similarly efficacious for NSCLC to wild-type *EGFR* and *EGFR*-mutated NSCLC that had acquired resistance to gefitinib. Even when used as a second-line or further treatment, erlotinib conferred longer PFS and OS, as well as favorable therapeutic responses, in view of the results of other trials (7, 13, 14, 16-18). These findings suggest that erlotinib may be a therapeutic option for patients with *EGFR*-mutated NSCLC with acquired resistance to gefitinib, as well as for patients with NSCLC with wild-type *EGFR*.

The present study also showed that erlotinib therapy resulted in similar ORR and higher DCR in *EGFR*-mutated cases after gefitinib failure in view of previous reports (18-20) and that the response of DC in erlotinib therapy was independently-associated with both PFS and OS. EGFR-TKI treatment often results in the attainment of SD for a long period of time, which is one of the benefits EGFR-TKIs bring to patients (21, 22). A hallmark of responses to erlotinib compared to responses to prior gefitinib therapy was the predominance of patients with SD. This suggests that the response of SD may contribute to erlotinib efficacy in *EGFR*-mutated NSCLC with acquired resistance to gefitinib. Furthermore, this study, based on common practice, demonstrated that the onset of skin rash was associated with a longer PFS, similarly to previous clinical trials (14, 15). The response of SD and the onset of skin rash may be positive predictors for a survival benefit of erlotinib therapy in clinical practice. Although a good performance status was also associated with better OS, this retrospective study has difficulty in its definitive evaluation because further treatments after erlotinib failure might have been preferred for patients with a good performance status.

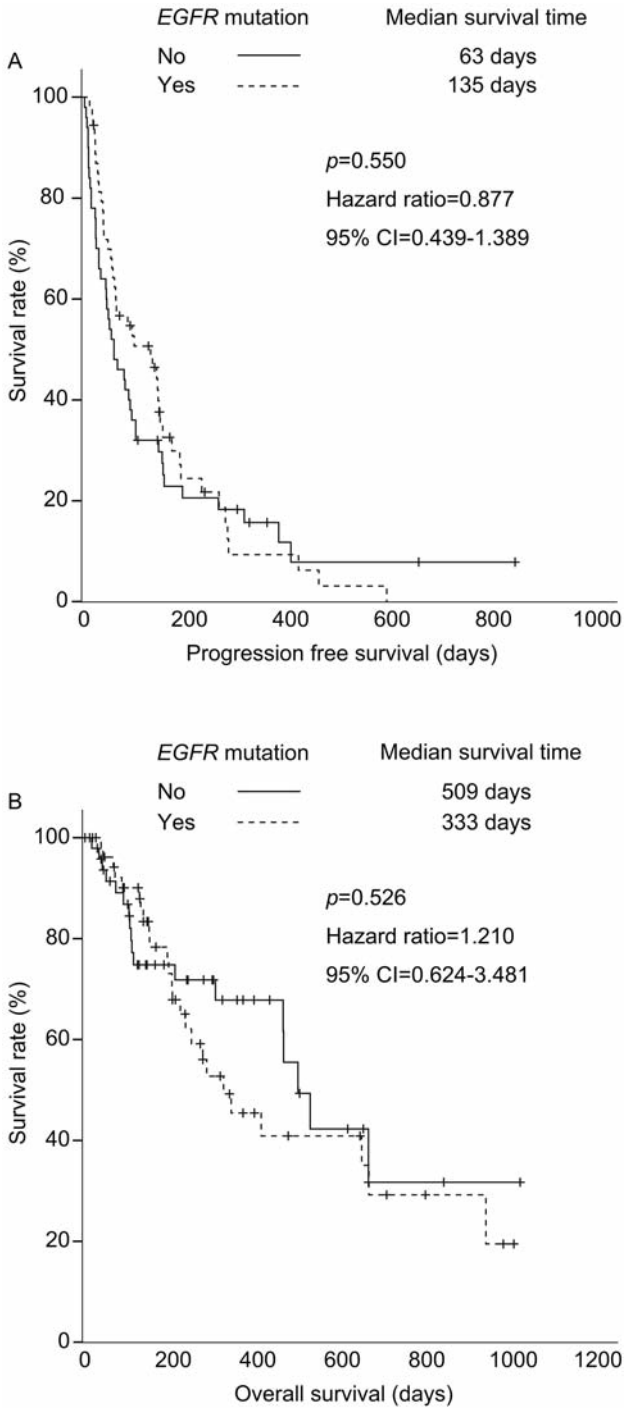


Figure 3. *Kaplan-Meier survival curves with log-rank tests for progression-free survival (A) and overall survival (B) for erlotinib-treated with patients with non-small cell lung cancer mutant EGFR after gefitinib failure and those with wild-type EGFR.*

Despite these clinical findings, this retrospective study has some limitations. Firstly, the study consisted of a heterogeneous patient population as patients received erlotinib therapy in different treatment lines. Secondly, there were differences in the number of patients for each factor analyzed. Although larger prospective studies would be of benefit in further evaluation, the present study advocates the therapeutic option of erlotinib after gefitinib failure and highlights potential predictive factors for patients with NSCLC treated with erlotinib.

In conclusion, following the development of resistance to gefitinib, erlotinib may be a therapeutic option for patients with NSCLC with mutant *EGFR*, as well as for those with wild-type *EGFR*. Furthermore, a therapeutic response of DC and the onset of the adverse events, skin rash and ILD, may be factors predictive of survival outcomes of erlotinib therapy in clinical practice.

Conflicts of Interest

Nobuyuki Koyama has received honoraria and/or lectures from Astrazeneca K.K., Boehringer Ingelheim Japan, Inc., Chugai Pharmaceutical Co., LtD., Eli Lilly Japan K.K., GlaxoSmithKline K.K., and Kyowa Hakko Kirin Co., LtD., and payment for the development of educational presentations from Pfizer Japan Inc. Yoshitaka Uchida declares no conflicts of interest.

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