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Real Clinical Practice in ALK-rearranged NSCLC Patients: A Retrospective Observational Study

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Abstract. *Background/Aim: To describe real clinical outcomes when using systemic therapy to treat non-small cell lung cancer (NSCLC) patients who have anaplastic lymphoma kinase (ALK) fusion gene mutation. Patients and Methods: We performed a retrospective chart review from April 2008 to March 2019 sourced from 16 medical institutes that cover a population of three million people. Results: There were 129 ALK rearranged NSCLC patients. Among them, 103 patients including 40 recurrent disease cases received ALK-tyrosine kinase inhibitors (TKI) and chemotherapy. Our treatment results were comparable to previously reported clinical trials and clinical practice studies. First-line alectinib, treatment sequence of ALK-TKI followed by another ALK-TKI, and pemetrexed-containing chemotherapy contributed to the outcome of treatment. Conclusion: By arrangement of treatment such as treatment sequence of ALK-TKI and chemotherapy regimen, it might be possible to obtain a treatment outcome almost equivalent to those of clinical trials even in real clinical practice.*

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Key Words: Clinical practice, alectinib, non-small cell lung cancer, anaplastic lymphoma kinase fusion gene mutation, chemotherapy.

In non-small cell lung cancer (NSCLC), there may be significant benefits for patients when specific driver mutations and specific treatment drugs for the driver gene exist, and therefore a long-term survival of patients can be

expected (1). Examination of driver mutations is routinely performed when a histological diagnosis is obtained. Anaplastic lymphoma kinase (ALK) fusion gene mutation is one of such driver genes, but its frequency is very rare. ALK fusion gene is found in around 5% of NSCLC (2), but it may be slightly lower in NSCLC patients treated in actual clinical practice. Since crizotinib treatment has become possible, several new-generation ALK-TKIs, such as alectinib, ceritinib, and brigatinib, are now available (1). Prolonged overall survival (OS) in clinical trials is remarkable. Two recent reports based on clinical practice from United States and France also showed prolongation of OS (3, 4). Despite prolongation of OS, almost all patients ultimately develop resistance to ALK-TKIs. Even if ALK-TKI is chosen for first-line treatment, it is not clear what sequence treatments will provide maximum effectiveness. There have been few reports about the significance of pemetrexed-containing chemotherapy in the treatment of patients with ALK rearranged NSCLC (3, 5). Because of the rarity of ALK rearranged NSCLC, it is important to collect and evaluate clinical data in addition to the results of clinical trials.

Until now, we accumulated and published actual clinical data on lung cancer treatment collected by multiple medical Institutions covering the residents of the prefecture with a population of 3 million (6-9). This time, considering the background of scarce information on treatment in real clinical practice for ALK rearranged NSCLC patients, we assembled clinical information for the purpose of sharing information. We were particularly interested in treatment sequence of ALK-TKI and contribution of pemetrexed-containing chemotherapy on OS in ALK rearranged NSCLC patients. Since it was possible to investigate information on a certain number of ALK-rearranged NSCLC patients over a hundred patients, we would like to share our medical information in real clinical practice.

Patients and Methods

Patients. Sixteen Institutions located in the Ibaraki prefecture (area, 6,095 km^2; population, ~3 million) participated in the present retrospective study. We included patients who were diagnosed as having ALK-rearranged NSCLC between April, 2008 and March, 2019. Patients, who had started treatment before crizotinib was approved in Japan in May 2012 and were diagnosed as having ALK-rearranged NSCLC during the study period, were included in the study. All the patients demonstrated histological or cytological evidence of NSCLC. Histopathological diagnoses were defined according to the World Health Organization (WHO) classification system and the patients were staged according to the Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) staging system. Metastatic sites were evaluated as bone, lung, brain, liver, extrathoracic lymph nodes, adrenal glands, and other uncommon sites. Tumor responses were classified as complete response (CR), partial response (PR), stable disease (SD), progressive disease, or not evaluable, according to the response evaluation criteria in solid tumors (RECIST), version 1.1. The patient characteristics, efficacy, safety, progressive-free survival (PFS) and OS were evaluated using patient data extracted from the database of each Institution. Patient survival time was calculated from the date of initiation of first-line therapeutic drug to the date of death or latest follow-up contact of the patient. The present observational study conformed to the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labor and Welfare of Japan. In this subset analysis, patients were divided into two groups: those aged ≥65 years and those aged <65 years. In order to evaluate treatment sequence between ALK-TKI followed by another ALK-TKI and chemotherapy followed by ALK-TKI, we compared combined PFS (sum of PFSs) (10) of two sequential treatment sets: combined PFS of ALK-TKI followed by another ALK-TKI and combined PFS of chemotherapy followed by ALK-TKI. This study was approved by the Institutional Review Board of the Mito Kyodo General Hospital (NO. 18-15) or independent ethics committees associated with each study institute.

Measurement of ALK fusion gene. ALK fusion gene mutation analysis was performed by the assay method normally used by each institution, such as fluorescence *in situ* hybridization (FISH), real time-reverse transcription polymerase chain reaction, and immunohistochemistry, using biopsy specimens, cytology specimens, and plasma specimens.

Table I. *Demographic and clinical characteristics of 129 patients rearranged NSCLC at the time of primary diagnosis of ALK.*

	Number of patients
Age (median, range), years	63, 26-84
Gender	M 45, F 84
Smoking status	
Never	80
Former and current smoker	46
Unknown	3
Histology	
Adenocarcinoma	124
NSCLC	3
LCNEC	1
Squamous cell carcinoma	1
ALK testing	
FISH	75
IHC	30
FISH and IHC	22
Clinical stage	
Localized (1A-2B)	35
Locally advanced (3A-3C)	27
Metastatic (4A-4B)	67
Maximum size of primary lesion (mm)	
<20	41
20-30	26
>30	57
Unknown	5
Performance status	
0-1	111
2-4	18

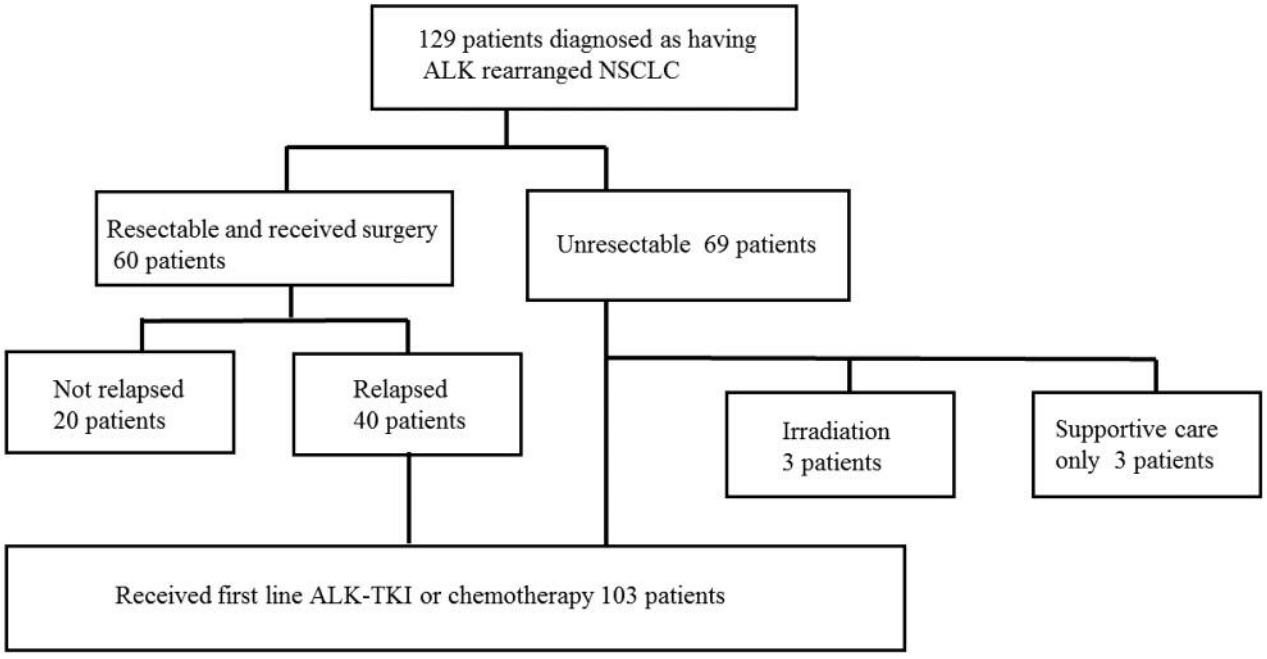

Figure 1. *Study flow chart*.

Statistical analysis. The survival rate was analyzed by the Kaplan-Meier method and comparisons were performed using the log-rank test. The effects of clinicopathological factors on survival were analyzed using the Cox proportional hazards model. $p<0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. During the study period, 129 patients were diagnosed as having ALK rearranged NSCLC. Table I presents the characteristics of these patients. There were 45 (34.9%) males and 84 females. The median age was 63 (range=26-84) years, and 59 (45.7%) patients were ≥65 years old. FISH was the most common procedure to confirm ALK rearrangement. There were 111 (86.0%) patients with a good performance status (PS) (Eastern Cooperative Oncology Group 0-1). Eighty (62.0%) of them were no smokers. One hundred twenty-four (96.1%) had adenocarcinoma. There were 16 patients who had started treatment before crizotinib was approved in our country and were diagnosed as having ALK rearranged NSCLC during the study period. Median maximum diameter of the primary lesion was 26 mm (range=7-130 mm). At the time of initial diagnosis of NSCLC, 27 (20.9%) and 67 (52.9%) patients were diagnosed as stage IIIA-C and IVA-B, respectively. Among the patients, 28 (21.7%), 21 (16.3%), 16 (12.4%), 12 (9.3%), 7 (5.4%), 4 (5.4%) and 23 (17.8%) had bone, lung, brain, liver, extrathoracic lymph node, adrenal gland, other uncommon sites metastases, respectively, whereas 36 (27.9%) patients presented with pleural fluid. Figure 1 shows the study flow chart. Among the 129 patients, 69 patients were evaluated as unresectable and 60 patients received surgical resection. Forty of the 60 patients who received surgical resection relapsed during the study period. Among 109 patients with unresectable and relapsed disease, 103 patients received systemic therapy with ALK-TKI and chemotherapy, 3 had chest irradiation, and 3 had supportive care. Figure 2 shows individual swimmer plots in the overall study population. As the first-line therapy, 55 (53.4%), 33 (32.0%), 11 (10.7%), and 4 (3.9%) of the 103 patients received chemotherapy, alectinib, crizotinib, and others, respectively.

PFS and combined PFS of two sequential treatments. We first compared PFS in patients treated with alectinib to that in patients treated with crizotinib as the first-line therapy. The median PFS for alectinib and crizotinib was 31 months (95%CI=30-56 months) and 16 months (95%CI=7-33 months), respectively. There was a statistically significant difference in PFS between them ($p=0.0271$). In second or later treatment lines, 42 patients received alectinib and 31 patients had crizotinib. The median PFS for each treatment was 16 months (95%CI=7-25 months) and 4 months (95%CI=3-11 months), respectively. In these treatment lines, PFS in patients treated with alectinib was longer than that in patients treated with crizotinib ($p=0.0001$). We next focused on cytotoxic chemotherapy with or without pemetrexed (PEM). There was a statistically significant difference in PFS between 70

treatments with PEM (median=6, months=95%CI: 3-9 months) and 57 without PEM (median PFS=3 months, 95%CI=2-4monts) (p=0.0001). Lastly, we examined combined PFS (10) of two sequential treatments. The median combined PFS in 19 patients who received ALK-TKI flowed by another ALK-TKI was 27 months (95%CI=11-43 months) and that in 29 patients who received chemotherapy followed by ALK-TKI was 10 months (95%CI=7-13 months). There was a significant difference between them (p=0.0087).

Overall survival (OS). Median follow-up in the 103 patients treated with systemic therapy was 123 months (95%CI=98-153 months). Median OS from the start of treatment was 64 months (95%CI=36-69 months) in patients treated with first-line crizotinib, and not reached (95%CI=166-200 months) in those with first-line alectinib. Median OS was 52 months (95%CI=25-87 months) in patients treated with first-line chemotherapy.

Discontinuation and adverse events in ALK-TKI. On all the lines of ALK-TKI therapy, alectinib, crizotinib, ceritinib, and lorlatinib were administered in 75, 42, 9, and 5 patients, respectively. The number of patients discontinued from alectinib and crizotinib treatment was observed in 3 (3.7%) and 11 (26.2%) patients, respectively. Table II shows all grades and grade 3 or more severe adverse events (AEs). With regards to Grade 3 or higher AEs were as follows: crizotinib (4 pulmonary, 3 liver, 3 appetite loss, 1 skin, and 1 QT prolongation), alectinib (2 pulmonary, 1 liver, and 1 skin).

Prognostic factors. Table III presents the results of uni- and multi-variate analysis of prognostic factors in 109 patients treated with systemic therapy. In univariate analysis, smoking habit, poor PS (PS 0-1), presence of adrenal gland metastasis, and presence of metastasis in uncommon sites were unfavorable prognostic factors. In multivariate, all these factors were confirmed as unfavorable prognostic factors.

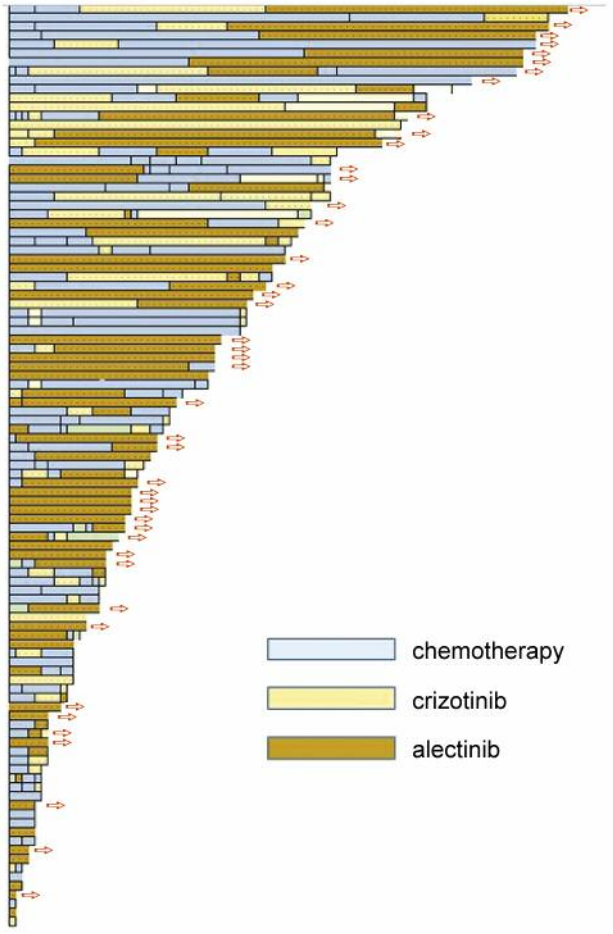

Figure 2. *Individual swimmer plots for each patient in 103 patients treated with ALK-TKI and chemotherapy. Arrows indicate patients who remained alive at the time of data cut-off.*

Discussion

ALK-rearranged NSCLC is a rare disease (2). Unlike other clinical trials in NSCLC patients, phase III randomized controlled trials in ALK rearranged NSCLC patients included up to 350 patients (11, 12). In these clinical trials, the majority of patients were young, females, and without a smoking habit (2). In most recent retrospective clinical practice studies, the number of patients evaluated was around 100 (3, 10, 17-21), and the proportion of men, elderly patients, and smokers seemed to be higher than those in clinical trials (3, 4, 10, 13-23). In our present study, we confirmed that these proportions were almost the same as previous clinical practice studies. These data are also summarized in Table IV.

With regard to treatment for ALK-rearranged NSCLC patients, at present, not only crizotinib, but also next-generation TKIs, such as alectinib, can be administered (24). These ALK-TKIs are specific drugs, therefore, how to use ALK-TKIs will be most important in order to prolong survival in ALK-rearranged NSCLC patients. In addition, it is still important to effectively use cytotoxic anticancer drugs (3, 5), since ALK-TKI will eventually become resistant. Some clinical trials suggested that next generation TKIs contributed not only to PFS, but also to OS, and recent comparative studies revealed clinical superiority of next-generation TKIs (12, 25). Our first question is whether prolongation of PFS could be observed also in real clinical practice in the era of next-generation ALK-TKIs. In recent clinical practice studies, median PFS in first-line crizotinib was 7.8-23 months (10, 16, 18-20, 22, 23) and that in first-line alectinib was 24.7 months (17). On the other hand, in

Table II. *Adverse events in ALK TKIs*

	Alectinib (75 therapies)		Crizotinib (42 therapies)		Ceritinib (9 therapies)		Lorlatinib (5 therapies)	
	All grades	Grade 3 or more	All grades	Grade 3 or more	All grades	Grade 3 or more	All grades	Grade 3 or more
Adverse event								
General fatigue	2	0	0	0	1	0	0	0
Edema	1	0	2	0	0	0	1	0
Pulmonary toxicity	7	2	5	4	0	0	0	0
Liver toxicity	2	1	11	3	2	0	0	0
Diarrhea	1	0	5	0	2	0	0	0
Constipation	1	0	0	0	0	0	0	0
Appetite loss	0	0	4	3	1	0	0	0
Nausea and vomiting	0	0	3	0	0	0	0	0
Anemia	1	0	0	0	0	0	0	0
Leukocytopenia	1	0	0	0	0	0	0	0
Thrombocytopenia	1	0	6	0	0	0	0	0
Skin toxicity	5	1	6	1	1	0	0	0
CPK elevation	2	0	0	0	0	0	0	0
QT prolongation	0	0	6	3	0	0	0	0
Visual disturbance	0	0	8	0	1	0	0	0
Real cyst	0	0	1	0	0	0	0	0
Renal toxicity	0	0	3	0	1	0	0	0
Neural toxicity	0	0	1	0	0	0	0	0
Mental	0	0	0	0	0	0	1	1
Hyperlipidemia	0	0	0	0	0	0	1	1

Table III. *Uni- and multivariate analysis of prognostic factors*.

	Univariate analysis	Multivariate analysis		
Factor	*p*-Value	Odds ratio (OR)	95% Confidence interval	*p*-Value
Age (65 years or more)	0.70			
Male gender	0.09			
Smoker	<0.01	1.02	1.01-1.03	<0.01
Performance status 2or more	<0.01	2.18	1.37-3.48	<0.01
Present metastasis				
Lung	0.56			
Bone	0.12			
Brain	0.17			
Liver	0.70			
Adrenal gland	<0.01	6.44	1.67-24.88	<0.01
Extra-regional lymph nodes	0.48			
Other sites	0.02	3.83	1.54-9.55	<0.01

the most recent clinical trials, median PFS of first-line crizotinib and alectinib was 10.9 months and 34.8 months, respectively (25). In our study, median PFS was 16 months and 31 months, respectively. These results in clinical trials and recent clinical practice studies, including ours, suggested that PFS of crizotinib and alectinib in clinical practice could be prolonged almost the same as that in clinical trials (11, 12). Our second question was whether prolongation of OS could be also observed in real clinical practice. Several clinical practice studies in first-line crizotinib treatment showed that the median OS was between 23.4 and 49.4 months (4, 10, 14, 18, 19, 22, 23). Two recent prominent studies in first-line next-generation ALK-TKIs showed a median OS more than 80 months (3, 4). One of them included patients registered in clinical trial subjects (3), and the other study included patients with localized disease (4).

Table IV. *Comparison between previous studies and ours in clinical practice.*

First author	Country	Publication year	Median age	Non-smoker %	Females %	No. of patients	TKI	PFS (months)	OS (months)	Ref. No.
Gainor	USA	2015	55	73.7	57.9	73	C, Ce	Crizo 8.2, ceri 7.8	49.4	10
Duruissseaux	France	2017	58.3	55.8	49.4	318	C, Ce	Not described	Crizo 16.6, 2nd generation 89.6	4
Kayaniyil	Canada	2016	53.2	67.3	53.1	97	C	7.8	31.6 (III 61.4, IV 23.7)	18
Ito	Japan	2017	64	59	57.4	61	A, C	C 7, A 24.7	A>C not reached	17
Pacheco	USA	2019	53	83	50%	110	C	Not described	81	3
Tsimafeyeu	Russia	2019	53	79	59	149	C	Not described	31	13
Reynolds	USA	2018	60.2	54.8	51.2	199	C	8.5	33.8	14
DiBonaventura	USA	2018	60.1	70	56	207	A	Not described	Not described	15
Davis	US, Canada	2018	58.9	32.1	31.1	212	C	9.5	23.4	16
Martin	Argentina	2018	58		60.6	73	C	7.07		19
Bedas	Israel	2019				53	C, Ce	23	29.8	20
Descourt	France	2019	56.6	61.5	60.6	104	B	6.7 (2nd line)	17.2 (from 2nd line therapy)	21
Gobbini	Italy	2019	59	59	52.8	290	C, N	C 9.4, N 11.1	39	22
Yang	China	2019	50	69.1	52.8	201	C	13.2	50.5	23
Okauchi	Japan	2019	63	62	65.1	129	C, A	C 16, A 31	C 64, A not reached	

C: Crizotinib, A: alectinib, C: ceritinib, B: brigatinib, N: new generation

In the present study, median OS in patients treated with first-line alectinib was not yet achieved, but 95%CI of OS after first-line alectinib was 166-200 months. Median OS in patients treated with first-line crizotinib was 63 months. Recent clinical practice studies and ours suggested that prolongation of OS could be achieved with next-generation ALK-TKIs. At present, either first-line or next-generation ALK-TKI, many chest physicians consensus that ALK-TKI is the first line treatment for NSCLC patients with ALK rearranged mutations (26-29). However, the subsequent treatment order is unknown. That is, there is scarce data on whether we had better prescribe cytotoxic drugs or ALK-TKI followed by first line ALK-TKI (10, 17). Our third question is whether there is a better therapeutic sequence of ALK-TKI and chemotherapy, and whether pemetrexed-containing chemotherapy contributes to survival. Ito *et al*. reported that OS tended to be much more prolonged in the alectinib-after-crizotinib failure group than in the group treated with alectinib alone (17). According to a study by Gainor *et al*., the combined PFS for sequential treatment with crizotinib and ceritinib was longer (10). In the present study, we showed that the combined PFS with ALK-TKI followed by another ALK-TKI was longer than that with ALK-TKI followed by chemotherapy. We also showed that pemetrexed-containing chemotherapy contributed to the outcome of treatment. Information related to such treatments might be well worth considering.

With regard to AEs of ALK-TKIs, we confirmed specific AEs such as visual disturbance and renal cysts in crizotinib and neural toxicity in lorlatinib, that have been shown in clinical trials and clinical practice studies (21, 22). AEs in next-generation of ALK-TKIs seemed less toxic than those in crizotinib. In the present study, treatment-related death due to pulmonary toxicity was observed in a patient treated with crizotinib, but was not found in any treatment line with next-generation ALK-TKIs.

In the present study, we conducted a multivariate analysis of unfavorable factors. We included patients who had received chemotherapy before the diagnosis of the ALK fusion gene mutation, and those treated with various ALK-TKIs and chemotherapeutic drugs according to the idea of the attending physician. Considering these backgrounds, we evaluated that "ALK-TKI", "alectinib", and "pemetrexed-included chemotherapy" were not appropriate as prognostic factors and did not analyze them in this multivariate analysis of prognosis. As a result, poor PS, smoking habit, presence of adrenal gland metastasis, and presence of metastasis in uncommon sites were significant unfavorable prognostic factors. With regard to prognostic factors, there have been three reports in clinical practice in ALK-rearranged NSCLC patients (3, 4, 17). Pacheco *et al*. reported that distant metastasis including male gender, smoking history, and brain metastasis were poor prognostic factors in 110 ALK rearranged NSCLC patients (3). Ito *et al*. showed that alectinib and positive staining IHC were favorable prognostic factors in 61 patients (17). In a French study with a large number of patients, no brain metastasis, oligoprogression, and crizotinib beyond PD were good prognostic factors (4). The unfavorable prognostic factors obtained in our study were the usual ones reported so far. These differences

between previous studies and ours might be due to differences in patient background and the relatively small number of patients evaluated. Further research that integrates data from larger number of patients is required.

This population-based, multi-institutional study covering a single prefecture has several limitations. Firstly, it was a retrospective study with patients from miscellaneous backgrounds. Secondly, the methods for examining ALK-fusion gene mutation were not unified. Thirdly, the limited number of patients and the short period of investigation were also limitations. Fourthly, difference in timing of drug approval. In fact, alectinib became available 2 years after crizotinib in our country. Despite these limitations, we believe that our treatment information in ALK-rearranged NSCLC patients collected by multiple institutions covering the residents with a population of 3 million will provide clinically meaningful information.

ALK-rearranged NSCLC is a rare entity of NSCLC. Therefore, there may be "facts" regarding the treatment that cannot be grasped by clinical trials alone. In order to clarify these facts, it must be meaningful to accumulate, collect and publish clinical practice data. This study was conducted from this point of view. As the characteristics of patient background and prognostic factors obtained in this study, all information obtained in this study should be verified in large-scale trials and clinical practice studies.

Conflicts of Interest

The Authors have no conflicts of interest to disclose regarding this study.

Authors' Contributions

HS and NH designed the study. SO, TN, TN, HI, TS, KH, HY, TE, YI, TK, MK, YY, TT, KS, MI, YS, TS, IS, HI, KK, MS, KK, MK, NK, HN, KF, TK, KM, TY, SH, YF and AN collected the data. SO, TN, TT, YY, and HS analyzed the data and prepared the manuscript. All Authors approved the final version of the article.

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