Clinical characteristics and risk factors of drug-induced lung injury by ALK tyrosine kinase inhibitors: A single center retrospective analysis

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Keywords
Alectinib; anaplastic lymphoma kinase; ceritinib; crizotinib; drug-related side effects and adverse reactions.

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Abstract
Background: If anaplastic lymphoma kinase (ALK) gene rearrangement in lung cancer is identified, ALK-tyrosine kinase inhibitors (ALK-TKIs) can be an effective treatment. However, the details of drug-induced lung injury (DILI) caused by ALK-TKI, which can be a serious side effect of ALK-TKIs, remains unclear. This study aimed to investigate the clinical features and the onset risk factors of DILI by ALK-TKIs in clinical practice.

Methods: The clinical features of 56 consecutive patients who received crizotinib, alectinib, and/or ceritinib at our hospital from 2012 to 2018 were retrospectively examined. Among these, patients diagnosed with DILI due to ALK-TKIs were evaluated in terms of clinical features and parameters. Each clinical parameter before the administration of ALK-TKIs was compared between the DILI onset group and the non-onset group.

Results: A total of seven cases were diagnosed with DILI due to ALK-TKIs; no DILI-related deaths were observed. Chest computed tomography (CT) scan findings identified six patients with the organizing pneumonia (OP) pattern and one with the hypersensitivity pneumonia pattern. The onset of DILI was significantly different in patients age ≥ 64 years and with a creatinine clearance <80 mL/minute.

Conclusions: Extra caution for DILI due to ALK-TKIs may be needed when recommending ALK-TKIs for patients over 64 years of age, or with decreased renal function. CT images of the majority of patients with DILI by ALK-TKIs show an OP pattern.

Key points
- Significant findings of the study: Extra caution is needed when recommending ALK-TKIs for patients over 64 years of age or those with decreased renal function. Computed tomography images of the majority of patients with DILI by ALK-TKIs show an OP pattern.
- What this study adds: The same or a different ALK-TKI may be considered as a treatment option after the onset of DILI, based on careful judgment.
Introduction

Anaplastic lymphoma kinase (ALK) gene rearrangements are found in approximately 2.4%–5.6% of patients with non-small cell lung cancer (NSCLC) who show a distinct clinical course with substantial antitumor response to oral tyrosine kinase inhibitors targeting ALK.1,2 Since tyrosine kinase activity is present in the ALK protein, the effect is obtained by inhibiting this activity.3 To date, four different ALK-tyrosine kinase inhibitors (ALK-TKIs), crizotinib, alectinib, ceritinib and lorlatinib have been used in clinical practice for the treatment of advanced ALK positive lung cancer in Japan. However, ALK-TKIs are known to potentially cause serious adverse events (SAEs), including lung injury.

ALK-TKI-induced lung injury was first reported in Japanese patients treated with crizotinib for metastatic NSCLC.4 Subsequently, sporadic cases were reported5,6 indicating that ALK inhibitor-induced pneumonitis can be clinically problematic in some patients. Although re-administration of another ALK-TKI after ALK-TKI-induced interstitial lung disease seems possible and has been reported in previous studies,7,8 there have been few reports regarding the detailed clinical course after drug-induced lung injury (DILI), or readministration of ALK-TKIs. According to the results of all case surveys by pharmaceutical companies, the incidence rate of lung injury was 2.6%–5.9%, and the mortality rate was 0%–19% for the three ALK-TKIs.9,10 On the other hand, a recent systematic review and meta-analysis of the incidence of ALK inhibitor-related pneumonitis in patients with advanced NSCLC indicated a slightly lower global incident rate (2.1%). This report also suggested a higher incidence of ALK inhibitor-induced pneumonitis in cohorts from Japan (6.3%) when compared to cohorts from other countries (1.1%).11 However, the information of ALK-TKI-induced lung injury in the clinical practice remains limited.

The purpose of this study was to investigate the clinical features, risk factors, and the safety of readministration of ALK-TKIs after ALK-TKI-induced lung injury.

Methods

In accordance with the amended Declaration of Helsinki, we conducted a single-center, retrospective study for ALK-TKI-induced lung injury. All procedures involving human participants were approved by the Human Ethics Committee of the Graduate School of Medicine of Chiba University (approval number 2265). Approval for the opt-out consent method was given by the Chiba University Hospital.

Patients

The records of 56 consecutive patients with ALK positive lung cancer who were treated with crizotinib, alectinib, and/or ceritinib from August 2012 to August 2018 at our hospital were retrospectively examined. Crizotinib, alectinib, and ceritinib were administered to 23, 25, and eight patients, respectively. Patients treated with lorlatinib were not included as lorlatinib was not available at the time of the present study in Japan. Among the 56 patients, cases diagnosed with DILI due to ALK-TKIs were evaluated with regard to their clinical features, risk factors, and recurrence after treatment of DILI with ALK-TKIs. Each clinical parameter before administration of an ALK-TKI was also compared between the DILI onset group and the non-onset group (Figure S1). Patients for whom multiple ALK-TKIs had been used were included as different cases according to the type of ALK-TKI they received. A total of 11 patients who switched to alectinib from crizotinib, seven patients who switched to ceritinib from alectinib, two patients who switched to crizotinib from alectinib, and one patient who switched to ceritinib from crizotinib due to the disease progression or side effects were included in the total of 56 patients. There were no patients who had a prior history of having received radiotherapy.

Diagnosis of ALK-TKI-induced lung injury

Drug-induced lung injury was diagnosed using the following diagnostic criteria:12 (i) patients with a treatment history of ALK-TKI; (ii) clinical manifestations reported to be induced by the corresponding drug; (iii) exclusion of other causes of clinical manifestations; (iv) improvement after drug discontinuation; and (v) exacerbation by re-administration. Two physicians individually confirmed the final diagnosis of DILI.

Evaluation of parameters and clinical progression

Data regarding clinical progression, blood test findings, and chest computed tomography (CT) scan findings for the 56 patients were retrieved from their medical records. We analyzed the presence of pulmonary metastasis, history and comorbidity of interstitial pneumonia, histologic lung cancer type, and smoking history. We evaluated laboratory data included the estimated creatinine clearance (Ccr), lactate dehydrogenase (LDH) levels, white blood cell (WBC) and eosinophil counts, Krebs von den Lungen-6 (KL-6; normal range, <500 U/mL) protein levels, brain natriuretic peptide (BNP; normal range, <18.4 pg/mL) levels, percentage of predicted vital capacity, and forced expired volume in one second/forced vital capacity. Clinical course after
ALK-TKI discontinuation. The number of risk factors and their relation to the frequency of DILI onset are summarized in Figure 1. The number of risk factors was significantly associated with DILI onset; DILI onset was not seen in patients with no patient-related risk factors, while 26.3% of patients who had both risk factors experienced DILI onset. The progress to DILI onset according to the number of risk factors is significantly different between patients with no risk factors and patients with one or two risk factors (Fig 1).

**Characteristics of cases at DILI onset**

The characteristics of patients at DILI onset are shown in Table 3. Five cases were diagnosed with DILI at the time of routine follow-up chest CT, and two cases were diagnosed with DILI using CT to evaluate the appearance of shadows on chest radiographs after dyspnea and/or slight fever. The CT images of each patient were separately evaluated by two physicians. Bronchoscopy was performed in three patients and the results were all consistent with DILI: the finding of interstitial pneumonia in pathological diagnosis (Case A); the finding of epithelioid granulomas in pathological diagnosis (Case C); the finding of organizing pneumonia in pathological diagnosis; and a high percentage of lymphocytes in bronchoalveolar lavage (Case D). The median time from the start of ALK-TKI administration to the onset of DILI was 97 days (range: 9–531 days). We observed one case of grade 2 pneumonitis due to DILI with crizotinib. For alectinib, we observed one case of grade 1, three cases of grade 2, and one case of grade 4 pneumonitis due to DILI. Only one case of grade 2 pneumonitis was observed due to DILI with ceritinib. Each ALK-TKI type usually resulted in a grade 2 pneumonitis.

**CT pattern of cases at DILI onset**

The CT patterns of patients at DILI onset are shown in Table 3. Six (85.7%) patients exhibited the OP pattern, one (14.3%) exhibited the HP pattern, and one (14.3%) exhibited the NSIP pattern. Figures 2 and 3 show the plain CT images of the seven patients.
A total of 56 patients were diagnosed with DILI, and the median time from ALK-TKI administration to DILI onset was 97 days (range: 9–531 days). Suh et al. conducted a systematic review and meta-analysis which reported that the global incident rate of ALK inhibitor-related pneumonitis in patients with advanced NSCLC was 2.1%. We considered that the higher incidence rate in this study (7/56, Table 1) may be due to risk factors such as age ≥64 years and Ccr < 80 mL/min at baseline.

### Discussion

In the present study, we investigated the clinical characteristics of ALK-TKI-induced lung injury and found that age ≥ 64 years and Ccr < 80 mL/min at baseline may be risk factors. In most cases with ALK-TKI-induced lung injury, an OP pattern on chest CT scan was observed at DILI onset; the therapeutic response to corticosteroid therapy was then relatively good.

Patients age ≥ 64 years was a significantly different factor between the DILI group and non-DILI group; in addition, Ccr < 80 mL/min before ALK-TKI administration was also significantly different. The post-marketing survey of crizotinib has suggested that the risk factors for DILI include old age, performance status of Eastern Cooperative Oncology Group ≥ 2, existing interstitial pneumonia, or history of interstitial pneumonia, existing pleural effusion, and a history of smoking. In a previous retrospective review of interstitial lung disease (ILD) associated with crizotinib therapy, a greater percentage of ex-smokers were shown in the patients with crizotinib-related ILD. One of the ways in which this study was different from the previous literature might be that the present study targeted multiple ALK-TKI drugs and not just a single one (eg, crizotinib).

A total of 12.5% patients (7 of 56 patients) in the present study were diagnosed with DILI, and the median time from ALK-TKI administration to DILI onset was 97 days (range: 9–531 days). Suh et al. conducted a systematic review and meta-analysis which reported that the global incident rate of ALK inhibitor-related pneumonitis in patients with advanced NSCLC was 2.1%. We considered that the higher incidence rate in this study (7/56, Table 1) may be due to risk factors such as age ≥64 years and Ccr < 80 mL/min at baseline.

### Table 1 Baseline characteristics of total patients

| Age (years) | 59.5 ± 12.9 | 71.2 ± 5.8 | 57.8 ± 12.8 |
| Male/female | 26/30 | 2/5 | 24/25 |
| Smoking history, n (%) | 23 (41.0%) | 2 (28.5%) | 1 (2.0%) |

**Histologic type**

| Type | Total (n = 56) | DILI group (n = 7) | Non-DILI group (n = 49) |
|------|---------------|-------------------|------------------------|
| Adenocarcinoma, n (%) | 54 (96.4%) | 7 (100%) | 46 (95.9%) |
| Squamous cell carcinoma, n (%) | 1 (1.7%) | 0 (0%) | 0 (0%) |
| Other, n (%) | 1 (1.7%) | 0 (0%) | 1 (2.0%) |
| Lung metastasis, n (%) | 43 (76.7%) | 6 (85.7%) | 37 (75.5%) |

**Laboratory findings**

| Test | Total (n = 56) | DILI group (n = 7) | Non-DILI group (n = 49) |
|------|---------------|-------------------|------------------------|
| LDH (IU/L) | 265.9 ± 150.9 | 336.1 ± 292.0 | 255.8 ± 120.9 |
| Ccr (mL/min) | 82.9 ± 31.5 | 60.4 ± 21.5 | 86.1 ± 31.6 |
| KL-6 (U/mL) | 979 ± 1004 | 1038 ± 1215 | 966 ± 993 |
| BNP (pg/mL) | 25.5 ± 21.3 | 26.5 ± 8.5 | 25.2 ± 23.5 |
| WBC (μL) | 7141 ± 3336 | 9228 ± 6349 | 6842 ± 2644 |
| Eosinophils/WBC (%) | 2.4 ± 1.8 | 2.1 ± 2.3 | 2.4 ± 1.8 |

**Spirometry**

| Test | Total (n = 56) | DILI group (n = 7) | Non-DILI group (n = 49) |
|------|---------------|-------------------|------------------------|
| %VC | 81.7 ± 17.7 | 89.9 ± 23.7 | 80.0 ± 16.5 |
| FEV1/FVC | 76.7 ± 7.5 | 73.1 ± 7.7 | 77.4 ± 7.1 |

Data are expressed as mean ± standard deviation. %VC, percent vital capacity; BNP, brain natriuretic peptide; Ccr, creatinine clearance; DILI, drug-induced lung injury; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; WBC, white blood cells.

progression of lung cancer. An ALK-TKI was re-administered in the five patients after improvement of DILI, of which three had no relapse of DILI. Cases A and B were the cases where different ALK-TKIs had been used in the same patient. The patient continued treatment with ALK-TKI after the onset of the DILI. With regard to the clinical course of the patient who had a DILI relapse (the first DILI was due to alectinib, the second DILI was due to ceritinib; Fig 2), the treatment of the patient with the first DILI due to alectinib was changed to treatment with ceritinib. Then, the second DILI was observed in chest CT scan 110 days after using ceritinib, but subsequently improved with corticosteroid therapy. The DILI resulted in discontinuation of ceritinib. Ceritinib was changed to a cytotoxic agent and no further DILI was observed. The two cases of DILI recurrence showed improvement with systemic corticosteroid treatment (Table S1).
12.5%) was attributed to the population difference (Japanese) and our study design (ie, a retrospective study for a small number of cases with various comorbidities and therapeutic course, and the readministration of ALK-TKI after the onset of DILI due to another ALK-TKI). In particular, the incidence of ILD by alectinib which was mainly administered in our study was differently reported in two phase III studies with a similar design comparing alectinib with crizotinib.16,17 The incidence of alectinib-induced ILD was 8% (n = 8/103) in J-ALEX conducted exclusively in Japan16 and 1% (n = 2/152) in ALEX study not including Japan.17 In the subanalysis in the systematic review and meta-analysis by Suh et al.,11 also suggested the incidence of ALK inhibitor-induced pneumonitis in cohorts from Japan were higher (6.3%) when compared to cohorts from other countries (1.1%).

Table 2 Risk factors associated with DILI onset due to ALK-TKIs

| Factors                        | DILI onset (n = 7) | Univariate analysis |
|--------------------------------|-------------------|---------------------|
| Sex                            |                   |                     |
| M                              | 2                 | 1                   |
| F                              | 5                 | 2.40 (0.47–17.89)   | 0.30 |
| Age                            |                   |                     |
| Continuous value               | 1                 |                     |
| <64                            | 1                 | 1.11 (1.03–1.22)    | 0.01 |
| ≥64                            | 6                 | 12.38 (1.90–244.18) | 0.01 |
| Smoking history                |                   |                     |
| Current + Ex                   | 2                 | 1                   |
| Non-smoker                     | 5                 | 1.88 (0.36–13.99)   | 0.46 |
| Lung metastasis                |                   |                     |
| Nonexistent                    | 1                 | 1                   |
| Existent                       | 6                 | 1.95 (0.29–38.66)   | 0.53 |
| Pre-existing ILD               |                   |                     |
| Existent                       | 1                 | 1                   |
| Nonexistent                    | 6                 | 1.35 (0.20–27.13)   | 0.79 |
| LDH (IU/L)                     |                   |                     |
| Continuous value               | 3                 | 1                   |
| <230                           | 3                 | 1.00 (1.00–1.01)    | 0.25 |
| ≥230                           | 4                 | 1.78 (0.36–9.84)    | 0.48 |
| Ccr (mL/min)                   |                   |                     |
| Continuous value               | 1                 | 0.96 (0.92–1.00)    | 0.02 |
| ≥80                            | 4                 | 1                   |
| <80                            | 6                 | 8.00 (1.24–157.11)  | 0.03 |
| KL-6 (U/mL)                    |                   |                     |
| Continuous value               | 2                 | 1                   |
| <500                           | 2                 | 1                   |
| ≥500                           | 2                 | 1.11 (0.11–10.91)   | 0.92 |
| BNP (pg/mL)                    |                   |                     |
| Continuous value               | 1                 |                      |
| <18.4                          | 3                 | 3.38 (0.35–76.18)   | 0.30 |

ALK-TKI, anaplastic lymphoma kinase-tyrosine kinase inhibitor; BNP, brain natriuretic peptide; Ccr, creatinine clearance; DILI, drug-induced lung injury; ILD, interstitial lung disease; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase.

In general clinical practice, drugs suspected to cause DILI should not be re-administered. However, resuming ALK-TKIs after resolution of a lung injury might be a clinical option because ALK-TKIs have a potent antitumor effect. In fact, some studies have reported successful readministration of a different ALK-TKI after the occurrence of DILI.7,8 In the present study, ALK-TKIs were again successfully administered to three patients after the resolution of DILI. In addition, the relapse of ALK-TKI DILI after the initial resolution of DILI was improved in two patients with treatment (Cases A and G). In Case A, the first DILI due to alectinib was improved when corticosteroids and alectinib were discontinued. After the resolution of the first DILI due to alectinib, Case A was switched to ceritinib to treat their lung cancer. A DILI recurrence was subsequently recognized, but it was also improved by...
corticosteroid and ceritinib discontinuation. In Case G, the first DILI due to crizotinib was improved by corticosteroid and crizotinib discontinuation. After the resolution of the first DILI due to crizotinib, Case G again received crizotinib with a dose reduction, and under treatment with corticosteroid. The DILI recurrence was recognized, but it was improved after crizotinib discontinuation. With regard to the response to corticosteroid therapy in the present study, among the six patients with improved DILI, five improved with corticosteroid therapy and one was relieved only after the cessation of ALK-TKI.

In this study, the CT patterns of patients at the onset of DILI were mainly OP patterns. On the other hand, in a previous retrospective review of CT images in patients with EGFR-TKI-induced interstitial lung disease, the DAD pattern was most commonly observed. Approximately one third of cases of DILI as a result of EGFR-TKIs are fatal with DAD appearance on chest CT scan. For DILI-induced by ALK-TKIs in the present study, improvements were observed in almost all cases. When the same or a different ALK-TKI was administered after the improvement of the first DILI following administration of ALK-TKI, some patients did not show a recurrence of DILI, and some patients who showed a recurrence of DILI subsequently improved with corticosteroid therapy (Table S1). From these results, even if DILI is diagnosed, the prognosis of DILI after administration of ALK-TKIs may be better than that by EGFR-TKIs. One of the possible reasons might be

![Kaplan-Meier plot of time to DILI onset classified according to the number of risk factors. Solid, dotted, and dashed lines correspond to zero (in 26 patients), one (in 11 patients), and two (in 19 patients) risk factors. Categorical data analysis conducted using the Cochran-Armitage trend test.](image)

**Table 3** The characteristics of patients at DILI onset

| Case | ALK-TKI | Onset (day) | Previous treatment | History of DILI by ALK-TKI | Image pattern Grade | Treatment for DILI | Outcome |
|------|---------|-------------|-------------------|---------------------------|-------------------|-------------------|---------|
| A    | Alectinib | 531         | Crizotinib        | –                         | OP                | 2                 | Improvement |
| B    | Ceritinib | 97          | Alectinib + OP   | –                         | OP                | 2                 | Improvement |
| C    | Alectinib | 97          | Crizotinib        | –                         | HP                | 2                 | Improvement |
| D    | Alectinib | 246         | Crizotinib        | –                         | OP + NSIP         | 2                 | Improvement |
| E    | Alectinib | 254         | Crizotinib        | –                         | OP                | 1                 | Improvement |
| F    | Alectinib | 9           | No                | –                         | OP                | 4                 | No improvement (death from lung cancer) |
| G    | Crizotinib | 63          | No                | –                         | OP                | 2                 | Improvement |

DILI, drug-induced lung injury; ALK-TKI, anaplastic lymphoma kinase-tyrosine kinase inhibitor; OP, organizing pneumonia; PSL, prednisolone; HP, hypersensitivity pneumonia; NSIP, nonspecific interstitial pneumonia.

![Event free rate](image)

| Event free rate |
|-----------------|
| Group 0         |
| Group 1         |
| Group 2         |

| Log-rank test, p=0.032 |
|-----------------------|
| p=0.024 (0 vs 1)      |
| p=0.007 (0 vs 2)      |

Risk factor: age ≥ 64 y, Ccr < 80 mL/min
Group 0: no risk factor
Group 1: age ≥ 64 y or Ccr < 80 mL/min
Group 2: age ≥ 64 y and Ccr < 80 mL/min

![Figure 1](image)
that the DAD pattern in DILI by ALK-TKI is uncommon. Therefore, we considered that treatment continuation may be one of our options under careful observation or in future issues to be considered.

This study had several limitations. First, it was designed as a retrospective, single-center study. Second, the sample size was small, which was also why univariate and not multivariate logistic regression analysis was chosen. Third, DILI was primarily diagnosed based on conventional CT findings. DILI in asymptomatic patients could have been overlooked because the timing of CT was at the discretion of the physician, and we included not only HRCT but also conventional CT data in the study. Since ALK-TKI-induced lung injury is reportedly a relatively rare condition (2.1%–6.3%) and the number of ALK-TKI administered cases in this study were quite small, it is difficult to accurately describe the clinical implications. However, we believe that it is important to elucidate the underlying condition in order to accurately reflect a clinical outcome, even with a small number of cases, and assist in assembly of the total number of reported cases.

In conclusion, our results suggest that patients age ≥ 64 years and with Ccr < 80 mL/min at baseline may be at an increased risk of DILI by ALK-TKIs. Extra caution may be needed when recommending ALK-TKIs for patients who meet these criteria, although the treatment response appears to be good. The same or a different ALK-TKI may be considered as a treatment option after DILI.
onset, based on careful judgment because DILI might not recur, or the treatment response might be relatively good, even if it does recur. Readministration of ALK-TKI is one of the issues that requires resolution as it is currently not definitive and there are only a few reported cases in the literature.

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**Disclosure**

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**References**

1. Solomon B, Varella-Garcia M, Camidge DR. ALK gene rearrangements: A new therapeutic target in a molecularly defined subset of non-small cell lung cancer. *J Thorac Oncol* 2009; 4 (12): 1450–4.

2. Scagliotti G, Stahel RA, Rosell R, Thatcher N, Soria JC. ALK translocation and crizotinib in non-small cell lung cancer: An evolving paradigm in oncology drug development. *Eur J Cancer* 2012; 48 (7): 961–73.

3. Garber K. ALK, lung cancer, and personalized therapy: Portent of the future? *J Natl Cancer Inst* 2010; 102 (10): 672–5.

4. Tamiya A, Okamoto I, Miyazaki M, Shimizu S, Kitaichi M, Nakagawa K. Severe acute interstitial lung disease after crizotinib therapy in a patient with EML4-ALK-positive non-small-cell lung cancer. *J Clin Oncol* 2013; 31 (1): e15–7.

5. Maka VV, Krishnaswamy UM, Anil Kumar N, Chitrapur R, Kilara N. Acute interstitial lung disease in a patient with anaplastic lymphoma kinase-positive non-small-cell lung cancer after crizotinib therapy. *Oxf Med Case Reports* 2014; 2014 (1): 11–2.

6. Watanabe N, Nakahara Y, Taniguchi H e a. Crizotinib-induced acute interstitial lung disease in a patient with EML4-ALK positive non-small cell lung cancer and chronic interstitial pneumonia. *Acta Oncol* 2014; 53 (1): 158–60.

7. Hwang A, Iskandar A, Dasanu CA. Successful re-introduction of alectinib after inducing interstitial lung disease in a patient with lung cancer. *J Oncol Pharm Pract* 2019; 25 (6): 1531–3.

8. Bender L, Meyer G, Quoix E, Mennecier B. Crizotinib-related interstitial lung disease improving after treatment cessation without recurrence under either crizotinib or brigatinib: A case report. *Ann Transl Med* 2019; 7 (5): 106.

9. Xalkori® (crizotinib): Proper usage information Vol. 5, Interim report of specific use result investigation. Pfizer Japan Inc.: 2017. Available from URL: https://www.pfizerjpn.co.jp/publication/infokixlinfo.pdf. 2018.

10. Zykdia® (ceritinib): pharmaceutical risk management plan. Novartis Pharmaceuticals Corporation; 2017. Available from URL: http://www.pmda.go.jp/RMP/www/300242/ac4a974b-fc2f-45a2-936e-e42d2f4b4c/300242_4291044M1021_002RMP.pdf.

11. Suh CH, Kim KW, Pyo J, Hatabu H, Nishino M. The incidence of ALK inhibitor-related pneumonitis in advanced non-small-cell lung cancer patients: A systematic review and meta-analysis. *Lung Cancer* 2019; 132: 79–86.

12. Camus P, Fannot A, Bonniaud P, Camus C, Foucher P. Interstitial lung disease induced by drugs and radiation. *Respiration* 2004; 71 (4): 301–26.

13. Travis WD, Costabel U, Hansell DM e a. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2013; 188 (6): 733–48.

14. The Japanese Respiratory Society. *The JRS Guidelines for the Management of Drug-Induced Lung Disease 2018*. The Japanese Respiratory Society, Tokyo 2018.

15. Yoneda KY, Scranton Jr, Cadogan MA e a. Interstitial lung disease associated with crizotinib in patients with advanced non-small cell lung cancer: Independent review of four PROFILE trials. *Clin Lung Cancer* 2017; 18 (5): 472–9.

16. Hida T, Nakihara H, Kono M e a. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): An open-label, randomised phase 3 trial. *Lancet* 2017; 390 (10089): 29–39.

17. Peters S, Camidge DR, Shaw AT e a. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med* 2017; 377 (9): 829–38.

18. Min JH, Lee HY, Lim H e a. Drug-induced interstitial lung disease in tyrosine kinase inhibitor therapy for non-small cell lung cancer: A review on current insight. *Cancer Chemother Pharmacol* 2011; 68 (5): 1099–109.

19. Yoneda KY, Hardin KA, Gandara DR, Shelton DK. Interstitial lung disease associated with epidermal growth factor receptor tyrosine kinase inhibitor therapy in non-small-cell lung carcinoma. *Clin Lung Cancer* 2006; 8 (Suppl 1): S31–5.

20. Yoneda KY, Shelton DK, Beckett LA, Gandara DR. Independent review of interstitial lung disease associated with death in TRIBUTE (paclitaxel and carboplatin with or without concurrent erlotinib) in advanced non-small cell lung cancer. *J Thorac Oncol* 2007; 2 (6): 537–43.

**Supporting Information**

Additional Supporting Information may be found in the online version of this article at the publisher’s website.