BRIEF REPORT

# Sequential Therapy with Crizotinib and Alectinib in *ALK*-Rearranged Non-Small Cell Lung Cancer—A Multicenter Retrospective Study

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## ABSTRACT

**Introduction:** Alectinib and crizotinib have been approved for the therapy of NSCLC caused by anaplastic lymphoma kinase gene (*ALK*) rearrangement. The effect of alectinib or crizotinib on overall survival (OS) in patients with *ALK*-rearranged NSCLC remains unknown.

**Methods:** A multicenter retrospective study was conducted to compare OS between patients receiving alectinib and crizotinib and between patients treated with alectinib and those treated sequentially with crizotinib and then alectinib after crizotinib failure. The time to treatment failure (TTF), progression-free survival (PFS), and OS were compared.

**Results:** Sixty-one patients with *ALK*-rearranged NSCLC were enrolled. Forty-six patients were treated with anaplastic lymphoma kinase (ALK) inhibitors (31 with crizotinib, 28 with alectinib, and 13 with both ALK inhibitors). The response rate was 66.7% for the crizotinib-treated group and 80.8% for the alectinib-treated group. Among all patients, TTF and PFS were significantly prolonged in the alectinib-treated group compared with in the crizotinib-treated group. Subgroup analyses revealed significantly prolonged TTF for alectinib compared with crizotinib therapy in the ALK inhibitor–naive population. OS was significantly longer in the alectinib-treated group than in the crizotinib-treated group. The TTF and OS of patients treated sequentially with crizotinib and then with alectinib after crizotinib failure tended to be longer than those of patients treated with alectinib alone.

**Conclusions:** Therapy with alectinib alone was significantly superior to therapy with crizotinib alone in terms of TTF, PFS, and OS, and sequential therapy with crizotinib and alectinib after crizotinib failure tended to provide a better OS benefit than did therapy with alectinib alone in patients with *ALK*-positive NSCLC. However, large-scale prospective studies are needed to confirm these observations.

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*Keywords:* Non–small cell lung cancer; Anaplastic lymphoma kinase inhibitor; Crizotinib; Alectinib; Sequential therapy; Overall survival

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## Introduction

Anaplastic lymphoma kinase gene (*ALK*) gene rearrangement is detected in approximately 4% of NSCLC.[1] Anaplastic lymphoma kinase (ALK) inhibitors, including crizotinib, ceritinib, and alectinib, are currently available for treatment of NSCLC. Crizotinib showed longer progression-free survival (PFS) than standard chemotherapy in phase III clinical trials, and thus it is currently the first-line therapy for tumors with *ALK* rearrangement.[2–4] However, despite the strong antitumor activity of crizotinib, most patients receiving crizotinib therapy show a progressive clinical course within 1 year.[5,6] Ceritinib and alectinib have been demonstrated to be very effective in crizotinib-resistant populations.[7,8] Alectinib has also shown high clinical efficacy in Japanese crizotinib-naive patients with *ALK*-positive NSCLC.[9] On the basis of these results, a prospective phase III clinical trial comparing the efficacy of crizotinib and alectinib is currently ongoing. Although an interim analysis suggested a better PFS for the alectinib-treated group than for the crizotinib group, the result of an overall survival (OS) analysis is required to draw any conclusion about which of these two ALK inhibitors is superior. Consequently, to date whether administration of alectinib alone, administration of crizotinib alone, or their sequential administration differentially affects the OS of patients with *ALK*-rearranged NSCLC remains unknown.

The final conclusion as to the differential effects of crizotinib and alectinib on OS from ongoing prospective studies will still require time; thus, here we conducted a multicenter retrospective study to compare OS between patients treated with alectinib alone and those treated with crizotinib alone and between patients treated with alectinib alone and those treated sequentially with crizotinib and then with alectinib after crizotinib failure.

**Table 1.** Baseline Characteristics of All Patients (N = 61)

| Characteristic | n | % |
|---|---|---|
| Median age (range), y | 64 (28-89) | — |
| Sex | | |
| Male | 26 | 42.6 |
| Female | 35 | 57.4 |
| Smoking history | | |
| Never | 36 | 59.0 |
| Former/current | 21 | 34.4 |
| NA | 4 | 6.60 |
| Clinical stage | | |
| I | 7 | 11.5 |
| II | 4 | 6.60 |
| IIIA | 7 | 11.5 |
| IIIB | 3 | 4.90 |
| IV | 39 | 63.9 |
| NA | 1 | 1.60 |
| Histologic subtype | | |
| Adenocarcinoma | 53 | 86.9 |
| Large cell carcinoma | 4 | 6.60 |
| Squamous cell carcinoma | 1 | 1.60 |
| NSCLC | 2 | 3.30 |
| Others | 1 | 1.60 |
| ALK testing | | |
| IHC analysis-positive | 36 | 59.0 |
| FISH positive | 55 | 90.2 |
| IHC analysis-positive and FISH positive | 32 | 52.5 |
| RT-PCR-positive | 2 | 3.30 |

NA, not available; ALK, anaplastic lymphoma kinase; IHC, immunohistochemical; FISH, fluorescence in situ hybridization; RT-PCR, reverse transcriptase polymerase chain reaction.

## Materials and Methods

### Study Design and Patients

Sixty-one patients with *ALK*-rearranged NSCLC treated with an ALK tyrosine kinase inhibitor (TKI) at six institutions from May 2012 through December 2015 were enrolled in the present study. Performance status (PS) was assessed as described.[10] The objective response rate (ORR), time to treatment failure (TTF), PFS, and OS were calculated. All patients with positive results by sensitive immunohistochemistry, fluorescence in situ hybridization, or reverse-transcriptase polymerase chain reaction were defined as ALK positive.

The dose of crizotinib was 250 mg twice daily and that of alectinib was 300 mg twice daily following recommendations of the Japanese Cancer Therapy Guidelines. All patients receiving at least one dose of crizotinib or alectinib were categorized as belonging to the crizotinib-alone or alectinib-alone group. Patients who received both crizotinib and alectinib were enrolled in both groups. For OS analysis, the patients were categorized into the following groups: (1) crizotinib alone, (2) alectinib alone, and (3) alectinib after crizotinib failure.

Tumor response was determined according to the Response Evaluation Criteria for Solid Tumors, version 1.1.[11] The study was approved by the institutional ethical committees for clinical investigation from all six institutions (approval numbers: 150807-2-1, 1549, 28-2, 20160005, 2015-7, and 150).

### Statistical Analysis

Survival curves were estimated using the Kaplan-Meier method, and significant differences were calculated by the log-rank test. Comparison between groups was performed using the unpaired *t* test, chi-square test, and Fisher's exact test. We calculated hazard ratios (95% confidence intervals) by multivariate Cox proportional hazards analysis. All tests were two sided, and a *p* value less than 0.05 was considered significant. Statistical

**Table 2.** Clinicopathological Characteristics of Patients Treated with Single or Sequential Therapy

| | TTF and PFS Analysis Group | | | OS Analysis Group | | |
|---|---|---|---|---|---|---|
| Characteristic | Crizotinib (n = 31) | Alectinib (n = 28) | *p* Values | Alectinib Alone (n =15) | Alectinib after Crizotinib Failure (n = 13) | *p* Values |
| Median age (range), y | 63 (28-89) | 58.5 (29-80) | 0.254 | 55 (37-75) | 62 (28-80) | 0.379 |
| Sex | | | | | | |
| Male | 13 | 13 | | 8 | 5 | |
| Female | 18 | 15 | 0.728 | 7 | 8 | 0.431 |
| Smoking history | | | | | | |
| Never | 18 | 16 | | 9 | 8 | |
| Former/current | 10 | 12 | 0.584 | 6 | 5 | 0.934 |
| NA | 3 | 0 | | 0 | 0 | |
| Clinical stage | | | | | | |
| I | 0 | 0 | | 0 | 0 | |
| II | 1 | 1 | | 0 | 1 | |
| IIIA | 3 | 3 | 0.843 | 2 | 1 | 0.600 |
| IIIB | 2 | 2 | | 1 | 1 | |
| IV | 24 | 20 | | 10 | 10 | |
| Recurrent | 1 | 2 | | 2 | 0 | |
| ECOG PS | (at induction with TKI) | (at induction with TKI) | | | (at induction with CRZ) | |
| 0-1 | 21 | 22 | | 14 | 7 | |
| 2-4 | 10 | 6 | 0.350 | 1 | 6 | 0.722 |
| Histologic subtype | | | | | | |
| Adenocarcinoma | 28 | 25 | | 12 | 13 | 0.139 |
| Nonadenocarcinoma | 3 | 3 | 0.614 | 3 | 0 | |
| Previous treatment | | | | | | |
| 1-2 | 24 | 21 | | 13 | 7 | |
| 3 | 7 | 7 | 0.827 | 3 | 6 | 0.023 |
| ALK inhibitors-naive, n (%) | 31 (100) | 15 (53.6) | <0.0001 | 15 (100) | 13 (100) | — |
| ALK testing | | | | | | |
| IHC analysis positive | 18 | 19 | 0.187 | 12 | 9 | 0.476 |
| FISH positive | 30 | 20 | 0.267 | 12 | 12 | 0.156 |
| IHC analysis positive and FISH positive | 18 | 15 | 0.473 | 8 | 9 | 0.331 |
| RT-PCR positive | 1 | 1 | — | 0 | 1 | — |
| Objective response, N | | | | | (response to alectinib) | |
| CR | 0 | 0 | | 0 | 0 | |
| PR | 18 | 21 | | 10 | 11 | |
| Stable disease | 3 | 2 | | 1 | 1 | |
| PD | 6 | 3 | | 2 | 1 | |
| NE | 4 | 2 | | 2 | 0 | |
| Response rate, % (95%CI) | 66.7 (47.7-85.7) | 80.8 (64.5-97.0) | 0.244 | 76.9 (50.4-103.4) | 84.6 (61.9-107.3) | 0.500 |

TTF, time to treatment failure; PFS, progression-free survival; OS, overall survival; NA, not available; ECOG PS, Eastern Cooperative Oncology Group performance status; TKI, tyrosine kinase inhibitor; CRZ, crizotinib; ALK, anaplastic lymphoma kinase; IHC, immunohistochemical; FISH, fluorescence in situ hybridization; RT-PCR, reverse-transcriptase polymerase chain reaction; CR, complete response; PR, partial response; PD, progressive disease; NE, not evaluable.

analyses were performed using the SPSS software version 23.0 (IBM Corp., Armonk, NY).

## Results

### *Characteristics of the Patients*

The characteristics of the patients are described in Table 1. In all, 46 patients were treated with *ALK* inhibitors, and of these 31 were treated with crizotinib, 28 with alectinib, and 13 with both *ALK* inhibitors. Fifteen patients received no *ALK* inhibitor because of very poor PS, surgical procedure, or ongoing best supportive care.

There was significant difference between the crizotinib and alectinib groups by previous treatment but no statistically significant difference was found between them in terms of sex, age, smoking history, clinical stage, PS, specimen type, or *ALK* gene testing (Table 2).

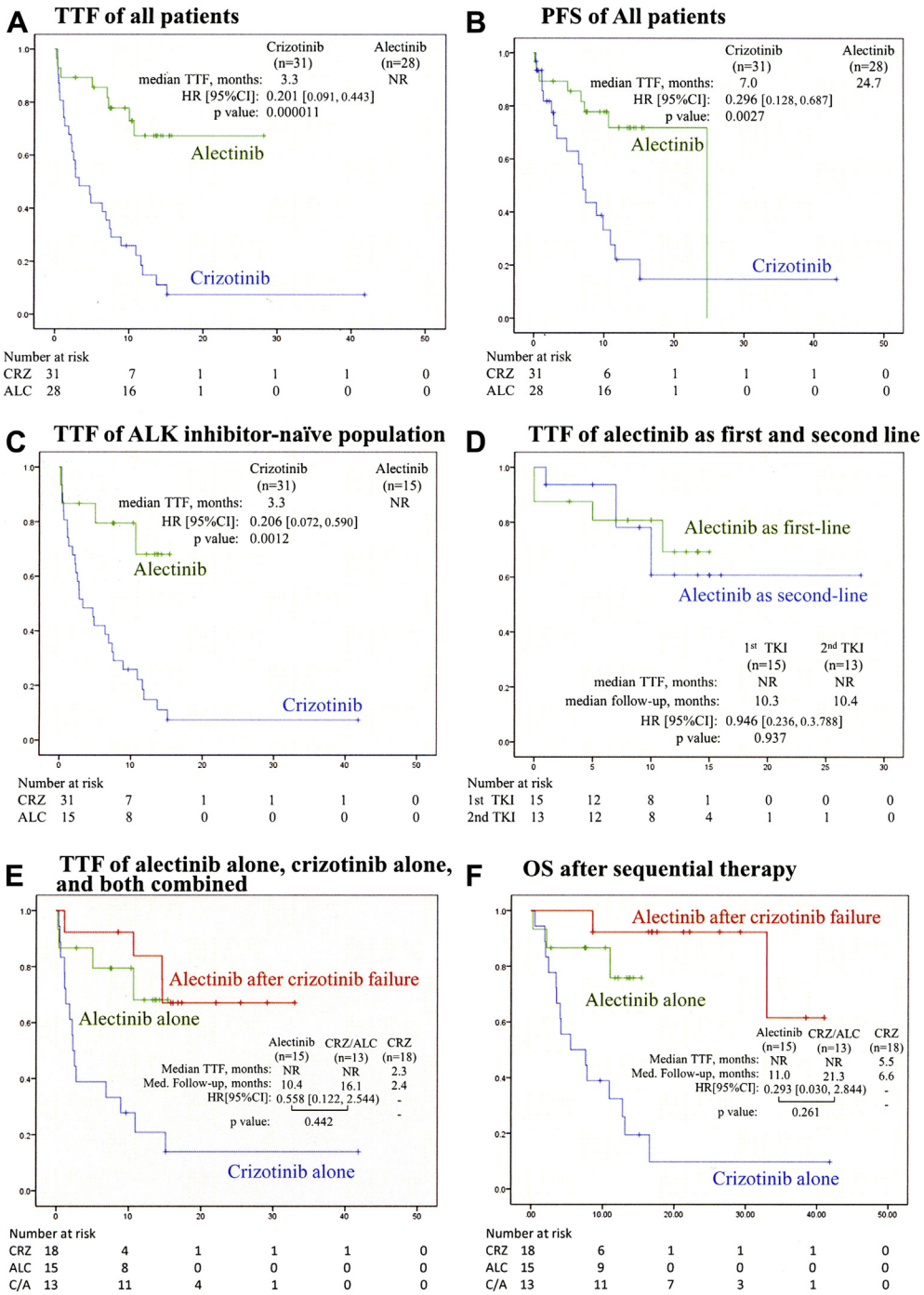


**Figure 1.** Kaplan-Meier curves of all patients and subgroups. Time to treatment failure (TTF) (*A*) and progression-free survival (PFS) (*B*) were significantly different between crizotinib (CRZ) alone-treated and alectinib (ALC) alone-treated patients. In the subgroup analysis, TTF was significantly different between the CRZ alone- and ALC alone-treated patients within the anaplastic lymphoma kinase (ALK) inhibitor-naive population (*C*). The TTF Kaplan-Meier curves were also calculated in patients treated with ALC as a first-line tyrosine kinase inhibitor (TKI) and in those treated with alectinib as a second-line TKI (*D*), but no difference was observed. Comparative analysis of the TTF and OS Kaplan-Meier curves between CRZ-alone and ALC-alone groups showed significant difference but both TTF and OS of the ALC-after-CRZ-failure group tended to be longer than those of the ALC alone-treated group (*E* and *F*). NR, not reached; HR, hazard ratio; CI, confidence interval; C/A, alectinib after crizotinib failure.

**Table 3.** Univariate and Multivariate Analysis for TTF

| | Univariate Analysis | | Multivariate Analysis | |
|---|---|---|---|---|
| Variables | HR (95% CI) | *p* Value | HR (95% CI) | *p* Value |
| Institution | 0.918 (0.794-1.062) | 0.221 | – | – |
| Age (<65 y) | 0.776 (0.401-1.504) | 0.452 | – | – |
| Sex (male) | 1.275 (0.662-2.456) | 0.466 | – | – |
| Smoking history (current/ex-smoker) | 1.046 (0.523-2.094) | 0.898 | – | – |
| ECOG PS (0-1) | 0.709 (0.348-1.442) | 0.339 | – | – |
| Histologic type (adenocarcinoma) | 0.257 (0.104-0.632) | 0.001 | 0.253 (0.056-1.136) | 0.073 |
| Clinical stage (<III) | 0.905 (0.396-2.070) | 0.813 | – | – |
| Brain metastasis (yes) | 2.212 (0.853-5.739) | 0.094 | 0.950 (0.288-3.139) | 0.933 |
| ALK naive (yes) | 0.304 (0.107-0.863) | 0.018 | 1.353 (0.287-6.390) | 0.702 |
| IHC analysis (positive) | 0.76 (0.021-0.276) | <0.001 | 0.167 (0.032-0.870) | 0.034 |
| FISH (>15%) | 0.720 (0.219-2.367) | 0.586 | – | – |
| ALK inhibitors (alectinib) | 0.201 (0.091-0.443) | 0.000011 | 0.235 (0.067-0.820) | 0.023 |

TTF, time to treatment failure; HR, hazard ratio; CI, confidence interval; y, year(s); ECOG PS, Eastern Cooperative Oncology Group performance status; ALK, anaplastic lymphoma kinase; IHC, immunohistochemical; FISH, fluorescence in situ hybridization.

### *ORR, TTF, and PFS in All Patients and in the ALK Inhibitor-Naive Population*

Among all patients, the ORR rate was 66.7% in the crizotinib group and 80.8% in the alectinib group (see Table 2). TTF in the alectinib group was significantly longer than in the crizotinib group (Fig. 1*A*). Alectinib therapy and the results of immunohistochemical analysis were significantly associated with prolonged TTF in the multivariate analysis (Table 3). PFS was significantly longer in the alectinib group than in the crizotinib group (Fig. 1*B*).

In the ALK inhibitor–naive population, 31 patients were treated with crizotinib and 15 with alectinib as a first-line ALK inhibitor. ORR was not different between the crizotinib and alectinib groups. The TTF of the alectinib group was significantly longer than that of the crizotinib group (Fig. 1*C*).

### *ORR, TTF, and OS in the Alectinib-after-Crizotinib-Failure Population*

Thirteen patients were treated with alectinib after crizotinib failure; among 13 patients, 11 showed partial response to alectinib after crizotinib failure. Comparative analysis of the TTF Kaplan-Meier curves of the group treated with alectinib as a first-line ALK TKI with those of the group treated with alectinib as a second-line ALK TKI revealed no significant difference (Fig. 1*D*). The TTF Kaplan-Meier curve of the alectinib-after-crizotinib-failure group tended to be prolonged compared with that of the alectinib-alone group (Fig. 1*E*). The OS also tended to be much more prolonged in the alectinib-after-crizotinib-failure group than in the group treated with alectinib alone (Fig. 1*F*). The OS of patients treated with alectinib alone was significantly prolonged compared with that of patients treated with crizotinib alone ($p = 0.0067$) (Fig. 1*F*); The OS of patients from the alectinib-after-crizotinib-failure group was significantly longer than that of the crizotinib-alone group ($p < 0.0001$) (Fig. 1*F*). Swimmer plots showed that patients receiving alectinib therapy continued receiving their therapy with good therapeutic response irrespective of whether alectinib was used as a first-line or second-line TKI (Fig. 2).

### *Safety and Tolerability Assessment*

Therapy was discontinued for adverse events in 12 patients treated with crizotinib and in one treated with alectinib during the follow-up period (Supplementary Table 1). The rate of withdrawal for adverse events was 42.9% in the crizotinib-treated group and 12.5% in the alectinib-treated group. The median period between the initial induction therapy with crizotinib and the appearance of any adverse event was 61.5 days. Only age ($p = 0.015$), and not sex, smoking history, PS, or clinical stage, was significantly different between cases in which crizotinib was discontinued for side effects and cases with no crizotinib withdrawal because of adverse events.

## Discussion

Crizotinib, the first ALK inhibitor developed, has been shown to be very effective for the treatment of NSCLC with *ALK* rearrangement, with statistically significant improvement in ORR and PFS compared with those with standard chemotherapy.[4,12] Within 1 year of therapy, however, most patients showed resistance to crizotinib leading to disease recurrence and systemic dissemination, particularly in the central nervous system.[5,6] To overcome resistance to crizotinib new ALK inhibitors, including ceritinib and alectinib, have been developed. Therapy with these new *ALK* inhibitors has been well tolerated and has shown efficacy in crizotinib-resistant

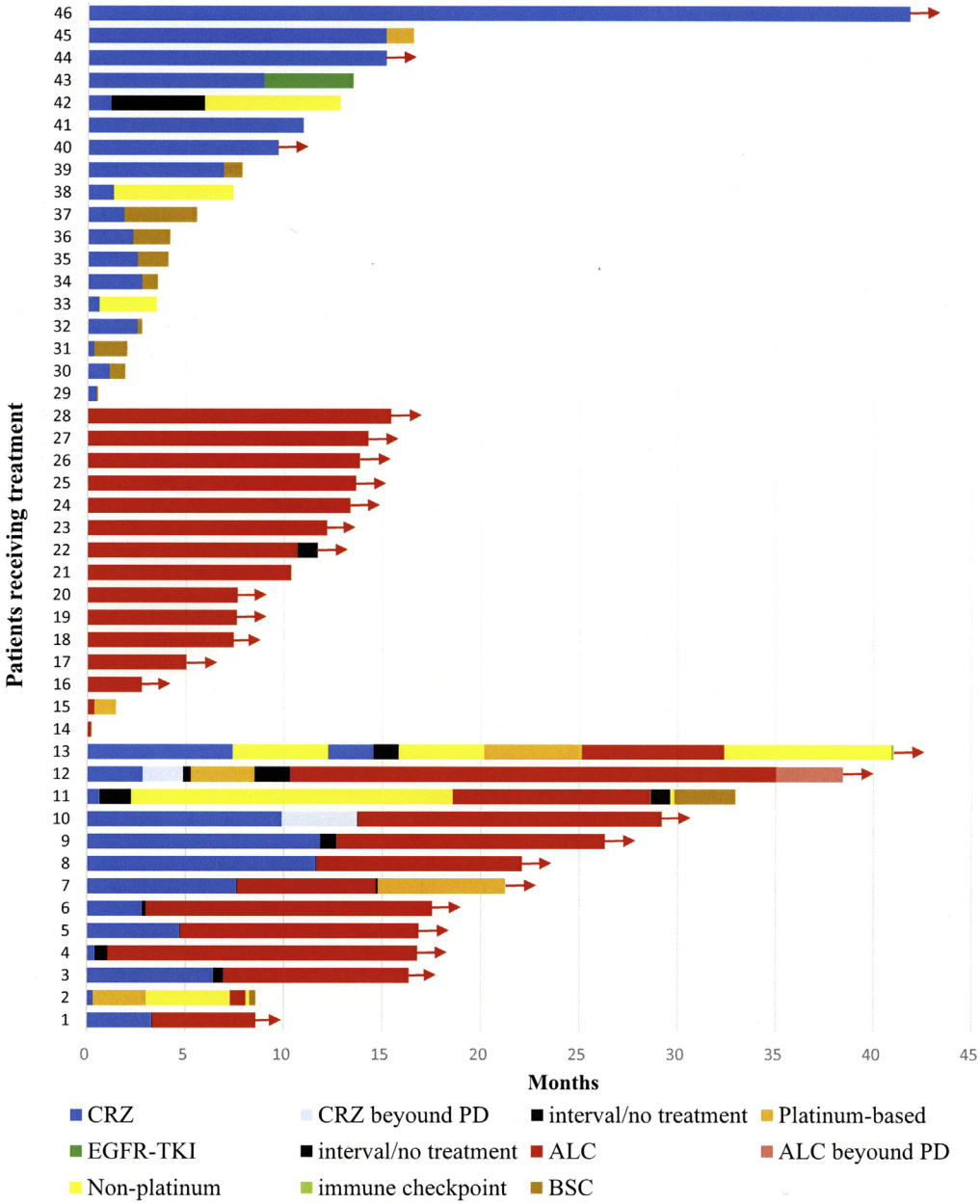


**Figure 2.** Individual swimmer plots for all patients receiving anaplastic lymphoma kinase (ALK) inhibitors. Patients 1 to 13 received alectinib (ALC) after crizotinib (CRZ) failure, patients 14 to 28 received ALC as first ALK inhibitor, and patients 29 to 46 received CRZ as first ALK inhibitor without ALC. The duration of treatment with CRZ is shown in blue and that with ALC in red. Arrows indicates patients who remained alive at the time of data cutoff. PD, progressive disease; TKI, tyrosine kinase inhibitor; BSC, best supportive care.

*ALK*-rearranged lung tumors in terms of ORR and PFS.[8,13] High antitumor activity has been also reported for alectinib in crizotinib-naive *ALK*-positive NSCLC.[9] A question not yet addressed is whether a single-arm of alectinib is better than a single-arm of crizotinib. Chugai Pharmaceutical from Japan has undertaken a prospective phase III clinical trial to address this question, and the interim results showed significantly longer PFS in alectinib-treated patients than in those treated with crizotinib alone. Because comparative analysis of OS in prospective studies require many years, here we conducted a retrospective study to compare OS between patients receiving single therapy with alectinib or crizotinib. Our present study showed that patients treated with alectinib alone have significantly prolonged PFS, TTF, and OS compared with those of patients receiving crizotinib alone, suggesting the superiority of alectinib alone over crizotinib alone.

Another relevant question in clinical practice is whether the use of alectinib as a first-line therapy or as a second-line therapy after crizotinib failure is better for patients with ALK-positive NSCLC. To address this question, we compared the OS of patients treated with alectinib alone with those receiving a sequential therapy of crizotinib and then alectinib after crizotinib failure. Interestingly, the OS of the alectinib-after-crizotinib-failure group tended to be longer than that of the alectinib-alone group, potentially suggesting that sequential therapy with crizotinib as a first-line drug followed by alectinib as a second-line drug would be an optional therapeutic approach for patients with ALK-positive NSCLC. However, this conclusion has to be considered in light of the fact that it may be confounded by the fact that those who survive to receive next-line therapy will have a longer prognosis than those who do not. The results of previous multicenter studies showing therapeutic effectiveness of a second ALK inhibitor (mostly ceritinib) after failure of a first ALK inhibitor (mostly crizotinib) are consistent with our present findings and also support the sequential use of crizotinib followed by alectinib after crizotinib failure in patients with *ALK*-positive NSCLC.[14,15] However, because of the limitations of the present study, including its retrospective nature, the scarce number of patients and imbalance in pretreatment conditions, a definite conclusion on the superiority of sequential therapy over monotherapy cannot be drawn.

In summary, this retrospective study showed that despite the apparent superiority of alectinib alone over crizotinib alone in terms of TTF, PFS, or OS, sequential therapy with crizotinib followed by alectinib after crizotinib failure tends to provide a better OS benefit than alectinib alone for the management of patients with NSCLC with *ALK* rearrangement in real-world clinical practice. However, larges-scale and well-controlled prospective studies need to be carried out to confirm these observations.

## Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at http://dx.doi.org/10.1016/j.jtho.2016.07.022.

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