Outcomes of switching from crizotinib to alectinib in patients with advanced non-small cell lung cancer with anaplastic lymphoma kinase fusion

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Background: Alectinib and crizotinib have been approved as first-line therapies for advanced non-small cell lung cancer (NSCLC) with anaplastic lymphoma kinase (ALK) gene fusion. However, the therapeutic efficacy and side effects are still largely unknown of patients who switched to next-generation ALK tyrosine kinase inhibitors (ALK-TKIs), such as alectinib, after experiencing no disease progression with initial crizotinib treatment.

Methods: This prospective real-world study enrolled patients who were treated with alectinib after experiencing no disease progression with initial crizotinib treatment. The patients’ baseline characteristics, objective response rate (ORR) of crizotinib and alectinib, size change of target tumor lesions, treatment regimen and adverse events (AEs) were collected and analyzed.

Results: The study included 53 patients, the majority of whom (96.2%) had non-squamous NSCLC. The median age was 51 (range, 31–80) years old. The ORR of first-line crizotinib was 54.7%. The ORR of sequential alectinib was 73.6%, and 90.5% of patients showed further tumor shrinkage after the alectinib treatment. The median progression-free survival was not reached, and 90.5% of patients were still enrolled in the study at the last follow-up. Among them, 34.0% of patients switched to alectinib treatment due to the toxicity. Crizotinib was associated with a higher frequency of AEs of grades 3 and 4 than alectinib (15.1% vs. 0%). Neither group had any AEs resulting in death.

Conclusions: Switching to alectinib might be an option for patients who do not experience disease progression with initial crizotinib treatment, and may promote better treatment compliance.

Keywords: ALK fusion; non-small cell lung cancer (NSCLC); crizotinib; alectinib
Introduction

Lung cancer therapy has entered into the era of precision medicine. For patients harboring driver oncogenes, molecular targeted therapies have unlocked a dramatic improvement in survival. The anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase encoded by the ALK gene and is often associated with lung cancer when mutated. This kinase is typically expressed in the central and peripheral nervous systems (1). ALK is reported to regulate several different pathways involved in cellular proliferation and survival, such as PI3K-AKT-mTOR, RAS-RAF-MEK-ERK, and the JAK-STAT pathway, once it dimerizes and is activated by autophosphorylation after binding with its ligands, pleiotrophin (PTN), and midkine (MK) (2,3). For the population of patients with advanced non-small cell lung cancer (NSCLC) with anaplastic lymphoma kinase (ALK) fusion, which comprises 3% to 13% of NSCLC cases (4), approval has been granted for the use of several first- or second-generation ALK-tyrosine kinase inhibitors (ALK-TKI), including crizotinib, ceritinib, alectinib, and brigatinib (5,6).

Alectinib and brigatinib were recommended by the National Comprehensive Cancer Network guidelines (version 1, 2021) as the preferred first-line therapies for advanced NSCLC with anaplastic lymphoma kinase (ALK) fusion, which comprises 3% to 13% of NSCLC cases (4), approval has been granted for the use of several first- or second-generation ALK-tyrosine kinase inhibitors (ALK-TKI), including crizotinib, ceritinib, alectinib, and brigatinib (5,6).

Alectinib and brigatinib were recommended by the National Comprehensive Cancer Network guidelines (version 1, 2021) as the preferred first-line therapies for advanced NSCLC with ALK fusion (14). However, access to these novel drugs is still largely limited mainly because it depends on approval and reimbursement decisions. For instance, a recent survey showed that crizotinib still being the main treatment as alectinib is still not available in the majority of central European countries because of a long lag interval between EMA or national MA and national reimbursement decisions (15). Therefore, we will inevitably encounter the situation that next-generation ALK-TKIs such as alectinib are available for these patients who did still not progress from the initial treatment of crizotinib after alectinib was approval. However, the therapeutic efficacy and side effects of patients who switch to next-generation ALK-TKI without crizotinib-refractory after initial crizotinib treatment are still largely unknown.

In this study, we prospectively collected 53 patients with ALK-fusion NSCLC whose initial crizotinib treatment did not fail and subsequently received alectinib as following therapy. We observed further significant tumor shrinkage and better side effects after the alectinib treatment, which suggests that the strategy of switching to alectinib might be a therapeutic option for patients whose disease does not progress from initial treatment with crizotinib.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/atm-21-2769).

Methods

Patients enrollment

Patients with \textit{ALK}-fusion NSCLC who received the ALK-TKI crizotinib as a first-line treatment followed by alectinib without showing crizotinib resistance were enrolled from the following Chinese institutions between September 2015 and March 2020: “The Department of Medical Oncology, Shanghai Pulmonary Hospital”, “The First Affiliated Hospital of Xiamen University”, “Department of Respiratory Oncology, Anhui Provincial Cancer Hospital (The First Affiliated Hospital of USTC West District)”, “Department of Respiratory Medicine, The First Affiliated Hospital of Qingdao University”, “Department of Respiratory Medicine, The First Affiliated Hospital,
Zhejiang University School of Medicine”, “Department of Thoracic Oncology, Zhejiang Cancer Hospital”, “Department of Medical Oncology, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital”, “Department of Internal Medicine-Oncology, Shandong Cancer Hospital and Institute”, and “Tongji Medical College of HUST, Tongji Hospital”. All patients had a pathological diagnosis of lung cancer based on the World Health Organization (WHO) classification (16).

Patients’ clinicopathological information was obtained from their medical records, which were available electronically from the institutions. All patients had chosen to switch crizotinib to alectinib therapy before crizotinib resistance developed, and carried on with the alectinib therapy until disease progressed [according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1] (17), or experienced unbearable toxicity, withdrew consent, or died of any reason. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study does not require ethical approval, as human blood and histological specimens were not involved in the study. Prior to receiving any treatments, all participants gave written informed consent for their clinical information to be used for research purposes.

Assessments

Each patient underwent computed tomography (CT) examination. Tumors were evaluated based on RECIST 1.1. Size changes of target tumor lesions were calculated as relative changes in the sum of the target lesions based on the investigator’s measurements.

The efficacy of alectinib was determined by comparing the patients’ situation when their therapy was switched to alectinib with their situation after alectinib treatment. The ORR was taken as the percentage of patients who had a complete response (CR) or partial response (PR), as determined by RECIST 1.1. The disease control rate (DCR) was calculated on the basis of percentages of patients with CR, PR, and stable disease after treatment according to RECIST 1.1. The National Cancer Institute’s Common Terminology Criteria for Adverse Events version 4.03 was used for the classification and grading of adverse events (AEs).

ALK-fusion analyses were performed at the different hospitals. Patients’ ALK status was determined on the basis of fluorescence in situ hybridization (FISH), reverse transcription PCR, immunohistochemistry (IHC), or next-generation sequencing (NGS). A diagnosis of ALK-fusion NSCLC was confirmed by a positive result for any of these tests (18).

Statistical analyses

Standard descriptive statistics were used to analyze patients’ demographic and clinical information at baseline. Frequencies and percentages were used to describe categorical variables. SPSS version 22.0 Software (SPSS, Inc., Chicago, IL) was employed to perform the statistical analysis. Excel (Microsoft 2016) and R studio were used to create the figures.

Results

Patients’ baseline characteristics

Fifty-three patients with ALK-fusion NSCLC whose disease was measurable with RECIST criteria 1.1 at baseline were identified. The study participants had a median age of 51 (range, 31–80) years old, and females accounted for 62.3% of the cohort. Among the participants, 88.7% had never smoked. Most cases (96.2%) were histologically classified as non-squamous NSCLC. In 98.1% of cases, the Eastern Cooperative Oncology Group performance status score was 0 or 1. Stage III and IV disease accounted for 33.9% and 60.4% of cases, respectively. Of the patients, 58.5% had intrathoracic metastasis and 77.4% had extrathoracic metastasis. Table 1 shows the characteristic information of the study participants. All participants received crizotinib as first-line treatment and then switch to alectinib after experiencing no disease progression from crizotinib.

Regarding ALK status testing, 35.8% of patients were tested by NGS, 35.9% of patients tested positive with IHC [VENTANA anti-ALK (D5F3) rabbit monoclonal primary antibody, Roche], and 24.5% were tested using PCR. FISH was used in only 2 (3.8%) cases in our study.

All patients in the cohort took crizotinib as a first-line ALK-TKI without disease progression. Of the patients, 34.0% changed the treatment to alectinib due to crizotinib intolerance, and 28.3% changed because their best response to crizotinib was stable disease, and they wanted to seek a more efficacious treatment. The other 37.7% of patients changed treatment for other reason, of note, alectinib was officially approved for coverage under Chinese Medical
Pan et al. Alectinib may benefit patient without crizotinib-resistance

Insurance in 2020, and the price of alectinib decreased to a considerable extent as a result.

Therapeutic responses to ALK-TKI treatment in patients

In the study cohort, the ORR of first-line crizotinib was 54.7%, and the DCR reached 100% (Table 2). The ORR and DCR of sequential alectinib were 73.6% and 100%, respectively (Table 2 and Figure 1), which showed no statistical decrease from the rates previously reported (14). The last follow-up date was November 30, 2020; at this point, all of the patients had switched to receive alectinib as sequential therapy, and their responses to this treatment were good. The treatment regimen of each patient is shown in Figure 2. Figure 3 shows the overall response of the patients. In the majority of cases, the disease response continued, which suggests that switching to alectinib after taking crizotinib without disease progression may not influence the efficacy of alectinib. Figure 4 shows representative CT images of one patient in the study.

Systemic AEs of ALK-TKI treatment in patients

We further recorded the AEs of crizotinib and alectinib in patients. Table 3 and Figure 5 show all-cause AEs reported in the patients during the course of either treatment. Elevated transaminase levels (22.6%), vomiting (22.6%), and visual disorders (18.9%) occurred more frequently with crizotinib, whereas constipation (45.3%), edema (41.5%), and skin toxicities (26.4%) were reported more frequently with alectinib. Of the all-cause AEs of grades 3 and 4 with crizotinib, increased transaminase levels (5.7%)
and dizziness (1.9%) occurred most frequently. No AEs of grades 3 or 4 have been reported with alectinib among the study participants so far.

**Discussion**

To the best of our knowledge, the present work is the first investigation of alectinib’s efficacy and side effects in patients with advanced NSCLC with ALK fusion who experienced no disease progression after initial treatment with crizotinib. We respectively enrolled 53 patients with ALK-fusion NSCLC and observed an ORR of 73.6%. Furthermore, 90.5% of patients had further tumor shrinkage after receiving alectinib. We also observed significantly fewer side effects among the patients after treatment with alectinib compared with crizotinib. At the last-follow up, 90.5% of the study participants were still receiving alectinib treatment, which suggests that the
strategy of switching from crizotinib to alectinib could be an alternative regimen for patients with advanced ALK fusion NSCLC whose initial crizotinib treatment has not failed.

Recently, a dramatic change has occurred in the treatment of patients with advanced NSCLC and ALK fusion. Crizotinib is a first-generation ALK-TKI which shows a superior ORR and PFS compared with standard
chemotherapeutic regimens for advanced disease in the first- and second-line settings (19,20). However, as many pre-clinical and clinical models have suggested, most patients develop resistance to crizotinib through various mechanisms within a year (21,22), particularly in the CNS because of insufficient penetration of the blood-brain barrier (23,24). Secondary mutations in the ALK gene are considered to be the most frequent mechanisms mediating resistance to ALK inhibitors which render crizotinib less effective by decreasing ligand affinity for its active site (18,25).

Alectinib, a powerful and selective, Adenosine triphosphate (ATP)-competitive, second-generation TKI, whose main activity is targeting ALK fusion and rearranged during transfection (RET) gene rearrangements (26). Upon discovery, crizotinib targets MET, ROS1 and ALK. Crizotinib and ceritinib are both targets of p-glycoprotein (P-gp), a membrane protein that pumps xenobiotics out

| Table 3 Adverse events reported in patients in during the course of either treatment |
|---------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Adverse events | Crizotinib | | | | Alectinib | | | |
| | Grade 1 | Grade 2 | Grade 3–4 | All grades | Grade 1 | Grade 2 | All grades |
| Elevated transaminase levels | 4 (7.5) | 5 (9.4) | 3 (5.7) | 12 (22.6) | 9 (17.0) | 1 (1.9) | 10 (18.9) |
| Diarrhea | 4 (7.5) | 7 (13.2) | 1 (1.9) | 12 (22.6) | 1 (1.9) | 0 | 1 (1.9) |
| Visual disorder | 9 (17.0) | 1 (1.9) | 0 | 10 (18.9) | 0 | 0 | 0 |
| Vomiting | 3 (5.7) | 8 (15.1) | 1 (1.9) | 12 (22.6) | 0 | 0 | 0 |
| Edema | 11 (20.8) | 2 (3.8) | 0 | 13 (24.5) | 18 (34.0) | 4 (7.5) | 22 (41.5) |
| Headache | 7 (13.2) | 1 (1.9) | 0 | 8 (15.1) | 0 | 0 | 0 |
| Dizziness | 8 (15.1) | 0 | 1 (1.9) | 9 (17.0) | 1 (1.9) | 1 (1.9) | 2 (3.8) |
| Abdominal pain | 1 (1.9) | 0 | 0 | 1 (1.9) | 0 | 0 | 0 |
| Pain in extremity | 7 (13.2) | 0 | 0 | 7 (13.2) | 7 (13.2) | 0 | 7 (13.2) |
| Anemia | 1 (1.9) | 0 | 0 | 1 (1.9) | 1 (1.9) | 0 | 1 (1.9) |
| Decreased appetite | 5 (9.4) | 3 (5.7) | 0 | 8 (15.1) | 0 | 0 | 0 |
| Fatigue | 11 (20.8) | 3 (5.7) | 2 (3.8) | 16 (30.2) | 17 (32.1) | 0 | 17 (32.1) |
| Nausea | 9 (17.0) | 3 (5.7) | 0 | 12 (22.6) | 2 (3.8) | 0 | 2 (3.8) |
| Constipation | 13 (24.5) | 1 (1.9) | 0 | 14 (26.4) | 19 (35.8) | 5 (9.4) | 24 (45.3) |
| Cough | 5 (9.4) | 1 (1.9) | 0 | 6 (11.3) | 0 | 0 | 0 |
| Chest pain | 2 (3.8) | 0 | 0 | 2 (3.8) | 6 (11.3) | 0 | 0 |
| Pyrexia | 0 | 2 (3.8) | 0 | 2 (3.8) | 0 | 0 | 0 |
| Decreased blood albumin | 1 (1.9) | 0 | 0 | 1 (1.9) | 0 | 0 | 0 |
| Dysgeusia | 6 (11.3) | 1 (1.9) | 0 | 7 (13.2) | 0 | 0 | 0 |
| Increased blood creatine phosphokinase | 11 (20.8) | 1 (1.9) | 0 | 12 (22.6) | 16 (30.2) | 1 (1.9) | 17 (32.1) |
| Elevated blood bilirubin | 10 (18.9) | 1 (1.9) | 0 | 11 (20.8) | 18 (34.0) | 2 (3.8) | 20 (37.7) |
| Skin toxicities | 1 (1.9) | 1 (1.9) | 0 | 2 (3.8) | 10 (18.9) | 4 (7.5) | 14 (26.4) |
| Weight gain | 0 | 0 | 0 | 0 | 0 | 1 (1.9) | 1 (1.9) |

Data represent the number of patients with at least 1 event (% of total patients).
of the central nervous system (CNS), whereas alectinib is not (27). For this reason, the brain is a common site of relapse in patients treated with crizotinib (28). Unlike crizotinib, alectinib is a CNS penetrant; it is not a substrate of P-glycoprotein, a key efflux transporter located at the blood-brain barrier (29). With strong CNS penetration ability, alectinib was demonstrated to be a growth inhibitor of ALK fusion CNS lesions in an intracranial tumor xenograft model (30). Furthermore, 3 phase III trials (9,14,31) produced consistent evidence that alectinib is superior to crizotinib alone with respect to PFS, OS, and toxicity in the first-line setting, with the median PFS reaching 34.1 and 34.8 months in the J-ALEX (number: JapicCTI-132316) and ALEX (number: NCT02075840) trials, respectively. Therefore, alectinib was recommended as one of the preferred options over crizotinib in the latest NCCN guidelines.

Despite the tremendous changes that have been achieved for patients with lung cancer, the worldwide availability of novel anti-cancer drugs is often delayed. Alectinib, for instance, was first approved in September 2018; however, only in January 2020 was it approved for coverage under the health insurance reimbursement system in China. Moreover, a recent survey showed that alectinib is still not available in majority of countries in central Europe (15).

Patients with ALK-fusion NSCLC will inevitably face the situation that initial treatment resistance of crizotinib and simultaneously had the availability of more potent second-generation ALK-TKI as sequential therapy. Our study is the first investigation of alectinib's efficacy and side effects in patients with ALK fusion for whom initial treatment with crizotinib did not fail. We observed that 90.5% of patients experienced further tumor shrinkage after using alectinib, which indicates that the residual tumors are still dependent on the ALK pathway (32).

Several second-line trials of alectinib have shown that some patients can experience tumor shrinkage after crizotinib failure (33). For example, in the phase III clinical trial ALUR (number: NCT02604342), the investigator-assessed ORR (Intention-To-Treat, ITT) of alectinib after crizotinib failure was 37.5% (27/72 patients) (34). Further, WJOG9516L (35) reported that the ORR of sequential alectinib was 35.6% in the progressive-disease subgroup of patients who had received crizotinib, which indicates that crizotinib does not completely inhibit the ALK signal.

Reducing the occurrence of systemic AEs constitutes a central aspect of individualized medicine and targeted therapy. In our study, gastrointestinal AEs and increased transaminase levels were the highest-occurring AEs, and severe gastrointestinal AEs significantly decreased patient
compliance. Alectinib is viewed as one of the most tolerable ALK-TKIs, as a result, it is rarely refused by patients (36).

In this study, 34.0% of patients switched to alectinib because of crizotinib intolerance. After treatment switching, the enrolled patients displayed significantly fewer side effects such as nausea/vomiting, which further supports the strategy of switching treatments used in this study.

There were several limitations to this study that should be mentioned. Firstly, due to the longer median PFS with first-line alectinib treatment, the observation period was not sufficient to reach the median PFS and OS, and therefore, AEs experienced by the patients may not have been fully reported. Secondly, the number of patients enrolled in this study was limited. Therefore, selection bias cannot be ignored and might be responsible for the favorable outcomes. Thirdly, due to medical insurance and reimbursement policies, the use of alectinib is more widespread in China and fewer patients receive crizotinib in the first-line setting than before, which also stresses the importance of the current study.

In conclusion, patients with ALK-fusion NSCLC who received initial crizotinib treatment without progression disease exhibited significant tumor shrinkage and less severe side effects after switching to alectinib therapy. Our observations suggest that switching from crizotinib to alectinib could be an alternative treatment strategy for patients with advanced NSCLC with ALK fusion. We expect that the long-term PFS and OS follow-up data of these patients will further support our conclusions.

Acknowledgments

**Funding:** This work was supported by the National Natural Science Foundation of China (No. 81772467 to SR, No. 81972167 to SR), Shanghai Shenkang Hospital Development Center (No. SHDC12019133 to SR) and Shanghai Innovative Collaboration Project (No. 2020CXJQ02 to CZ).

**Footnote**

**Reporting Checklist:** The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-2769

**Data Sharing Statement:** Available at https://dx.doi.org/10.21037/atm-21-2769

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-2769). YP, CZ, SR report that this work was supported by the National Natural Science Foundation of China (No. 81772467 to SR, No. 81972167 to SR), Shanghai Shenkang Hospital Development Center (No. SHDC12019133 to SR) and Shanghai Innovative Collaboration Project (No. 2020CXJQ02 to CZ). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study does not require ethical approval, as human blood and histological specimens were not involved in the study. Prior to receiving any treatments, all participants gave written informed consent for their clinical information to be used for research purposes.

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References

1. Wellstein A. ALK receptor activation, ligands and therapeutic targeting in glioblastoma and in other cancers. Front Oncol 2012;2:192.
2. Morales La Madrid A, Campbell N, Smith S, et al. Targeting ALK: a promising strategy for the treatment of non-small cell lung cancer, non-Hodgkin’s lymphoma, and neuroblastoma. Target Oncol 2012;7:199-210.
3. Shaw AT, Solomon B. Targeting anaplastic lymphoma kinase in lung cancer. Clin Cancer Res 2011;17:2081-6.
4. Wu J, Savoogi J, Liu D. Second- and third-generation ALK inhibitors for non-small cell lung cancer. J Hematol Oncol 2016;9:19.
5. Sullivan I, Planchard D. Treatment modalities for
advanced ALK-rearranged non-small-cell lung cancer. Future Oncol 2016;12:945-61.

6. Sgambato A, Casaluce F, Maione P, et al. Targeted therapies in non-small cell lung cancer: a focus on ALK/ROS1 tyrosine kinase inhibitors. Expert Rev Anticancer Ther 2018;18:71-80.

7. Camidge DR, Kim HR, Ahn MJ, et al. Brigatinib Versus Crizotinib in Advanced ALK Inhibitor-Naive ALK-Positive Non-Small Cell Lung Cancer: Second Interim Analysis of the Phase III ALTA-1L Trial. J Clin Oncol 2020;38:3592-603.

8. Shaw AT, Kim TM, Crinò L, et al. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2017;18:874-86.

9. Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet 2017;390:29-39.

10. Reckamp K, Lin HM, Huang J, et al. Comparative efficacy of brigatinib versus ceritinib and alectinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small cell lung cancer. Curr Med Res Opin 2019;35:569-76.

11. Waqar SN, Morgenszttern D. Lorlatinib: a new-generation drug for ALK-positive NSCLC. Lancet Oncol 2018;19:1555-7.

12. Kuang S, Leighl NB. Lorlatinib in ALK-Rearranged Lung Cancer. Cancer Cell 2021;39:25-7.

13. Gadgeel S, Peters S, Mok T, et al. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive non-small cell lung cancer. J Thorac Oncol 2021;16:1487-94.

14. Gadgeel SM, Gandhi L, Riely GJ, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study. Lancet Oncol 2014;15:1119-28.

15. Katayama R, Sakashita T, Yanagitani N, et al.
P-glycoprotein Mediates Ceritinib Resistance in Anaplastic Lymphoma Kinase-rearranged Non-small Cell Lung Cancer. EBioMedicine 2016;3:54-66.

30. Kodama T, Hasegawa M, Takanashi K, et al. Antitumor activity of the selective ALK inhibitor alectinib in models of intracranial metastases. Cancer Chemother Pharmacol 2014;74:1023-8.

31. Zhou C, Kim SW, Reungwetwattana T, et al. Alectinib versus crizotinib in untreated Asian patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer (ALESIA); a randomised phase 3 study. Lancet Respir Med 2019;7:437-46.

32. Ito K, Hataji O, Kobayashi H, et al. Sequential Therapy with Crizotinib and Alectinib in ALK-Rearranged Non-Small Cell Lung Cancer-A Multicenter Retrospective Study. J Thorac Oncol 2017;12:390-6.

33. Asao T, Fujiwara Y, Itahashi K, et al. Sequential Use of Anaplastic Lymphoma Kinase Inhibitors in Japanese Patients With ALK-Rearranged Non-Small-Cell Lung Cancer: A Retrospective Analysis. Clin Lung Cancer 2017;18:e251-8.

34. Novello S, Mazières J, Oh IJ, et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study. Ann Oncol 2018;29:1409-16.

35. Ito K, Yamanaka T, Hayashi H, et al. Sequential therapy of crizotinib followed by alectinib for non-small cell lung cancer harbouring anaplastic lymphoma kinase rearrangement (WJOG9516L): A multicenter retrospective cohort study. Eur J Cancer 2021;145:183-93.

36. Zhu V, Ou SH. Safety of alectinib for the treatment of metastatic ALK-rearranged non-small cell lung cancer. Expert Opin Drug Saf 2017;16:509-14.

(English Language Editor: J. Reynolds)