Original Article

Alectinib continuation beyond progression in *ALK*-positive non-small cell lung cancer with alectinib-refractory

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Background: Alectinib, a next-generation anaplastic lymphoma kinase tyrosine kinase inhibitor (ALK-TKI), has demonstrated noteworthy efficacy in the treatment of non-small cell lung cancer (NSCLC). Unfortunately, 53.3% of untreated patients receiving first-line treatment with alectinib developed resistance to alectinib. However, despite the widespread use of alectinib, studies on the efficacy and safety of continuing alectinib with other necessary therapies after progression of alectinib and possible population of benefit are still limited.

Methods: This retrospective cohort study included fifteen patients with *ALK*-positive NSCLC from nine institutions in China who experienced disease progression after first- or second-line treatment and continued to receive alectinib treatment between 2019 and 2022. This study aimed to evaluate the median progression-free survival (mPFS), objective response rate (ORR), median overall survival (mOS), and adverse events (AEs) of continuing alectinib combined with other therapies after the emergence of drug resistance.

Results: Among fifteen patients eligible for this study, all patients started continuing treatment with alectinib after oligoprogression or central nervous system (CNS) progression. The mPFS for the whole cohort receiving continuing alectinib with other necessary therapies was 8 months [95% confidence interval (CI): 4 to not applicable (NA)], with an ORR of 46.7%. The mOS was not reached. During continuing alectinib treatment, only one patient experienced grade 2 elevation of aspartate aminotransferase (AST) and serum glutamic-oxaloacetic transaminase (SGOT).

Conclusions: The continuation of alectinib treatment combined with other necessary therapies demonstrates favorable response and safety in patients with *ALK*-positive NSCLC who experienced oligoprogression or CNS progression following alectinib in first- or second-line therapy. Instead of immediately switching to another ALK-TKI, continuing alectinib combined with other necessary therapies may offer greater survival benefits to the patients.

Keywords: Alectinib; anaplastic lymphoma kinase-tyrosine kinase inhibitor (ALK-TKI); non-small cell lung cancer (NSCLC); *ALK*-positive; resistance

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Introduction

Rearrangement of the anaplastic lymphoma kinase (*ALK*) gene is a significant oncogenic driver in patients with non-small cell lung cancer (NSCLC), and it has been confirmed to be a molecular target for this disease. Approximately 3–7% of all NSCLC cases are characterized by *ALK*-positive (1,2). With the rapid development of antitumor therapy, tyrosine kinase inhibitors (TKIs) that specifically act on the ALK receptor tyrosine kinase have shown notable efficacy in treating patients with *ALK*-positive NSCLC (2-8). The remarkable efficacy and safety profile of these ALK-TKIs has led to the accelerated development of three generations of ALK inhibitors in less than a decade (9-12).

Among the ALK-TKIs, alectinib, a next-generation ALK-TKI, has demonstrated remarkable efficacy in comparison to crizotinib, a first-generation ALK-TKI (10,13). The global ALEX study reported a median progression-free survival (mPFS) of 34.8 months and an objective response rate (ORR) of 82.9% for alectinib in untreated ALK-positive NSCLC patients (10,13,14). Furthermore, the Asian population-based ALESIA study showed even better efficacy, with an mPFS of 41.6 months and an ORR of 91%. However, despite the significant clinical benefits achieved with alectinib, resistance to alectinib occurred in 53.3% of patients treated with alectinib as the first-line therapy, leading to disease progression, and more progressive disease occurred in second-line alectinib treatment (4,15-17). ALK-TKIs resistance mainly arises from *ALK* mutations and *ALK* amplification, such as the *G1202R* mutation (18). In addition, resistance can occur due to bypass activation or downstream pathway activation, such as *MET*-amplification, or phenotypical changes (18-20). Subsequent therapeutic decision-making will be based firstly on the type of progression and secondly on the mechanism of resistance (4,21). Progression can be divided into oligoprogression, central nervous system (CNS) progression, and systemic progression (4,17). Oligoprogression is defined as a tumor disease that progresses in a limited number of sites (17). CNS progression is defined as progression involving only the CNS. When the disease suffers progression in more sites, it is defined as systemic progression (17). It can be considered that oligoprogression or CNS progression does not necessarily indicate a complete failure of the prior TKI treatment, it may be due to heterogeneity within and between tumors. However, systemic progression often represents the failure of the prior TKI treatment (21). If systemic progression occurs, medication selections are made to target the mechanism of acquired resistance (4). According to established guidelines, patients with *ALK*-positive advanced NSCLC who experience oligoprogression or CNS progression during TKI treatment have the option to continue with their current TKI therapy combined with local therapies or switch to an alternative ALK-TKI (4,21). However, several studies have indicated that sequential ALK-TKI treatment may ultimately result in the development of highly resistant complex *ALK* mutations, which could potentially limit the survival benefits of patients (22). Fortunately, some clinical studies have shown the superiority of continuing the original ALK-TKI treatment combined with other treatments after the progression of next-generation ALK-TKI (18,23). Lin *et al.* demonstrated that in patients who underwent chemotherapy in combination with ALK-TKI after developing resistance to next-generation ALK-TKI, the mPFS was 6.8 months, which was significantly longer than the patients who received chemotherapy alone (6.8 *vs.* 3.2 months). In a Phase II clinical trial investigating non-squamous NSCLC

Highlight box

Key findings

- Alectinib continuation beyond progression of first- or second-line alectinib in patients with anaplastic lymphoma kinase (*ALK*)-positive non-small cell lung cancer (NSCLC) resulted in an 8-month median progression-free survival (mPFS) and a favorable safety profile.

What is known and what is new?

- Alectinib demonstrates outstanding efficacy and a favorable safety profile as a next-generation *ALK*-tyrosine kinase inhibitor (TKI). It could provide an mPFS of 34.8 months. However, 53.3% of patients develop resistance to this drug according to ALEX research.
- We investigated the efficacy, safety, and population most likely to benefit from continuing alectinib with other necessary therapies in ALK-positive NSCLC patients who developed resistance to prior alectinib therapy.

What is the implication, and what should change now?

- Treatment consisting of continuing alectinib and other necessary therapies in *ALK*-positive NSCLC patients who suffered oligoprogression or central nervous system progression using alectinib yielded favorable efficacy and good safety. In this scenario, the option of continuing alectinib therapy in combination with other necessary therapies may be favorable over switching to another TKI.

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patients with combined alectinib and bevacizumab following resistance to alectinib, the study resulted in an mPFS of 3.1 months (23). The above studies suggest that even if disease progression occurs, tumors can remain responding to TKIs (18,23). This may be due to the persistence of TKI-sensitive clones (24). In this scenario, considering the circumstances, it may be an advisable choice to continue the existing TKI treatment and explore the potential benefits of combining it with other therapeutic approaches. However, despite the widespread use of alectinib, studies on the efficacy and safety of continuing alectinib with other necessary therapies after progression of alectinib and possible population of benefit are still limited.

In this study, we conducted a real-world investigation to assess the efficacy, safety, and the population most likely to benefit of continuing alectinib treatment with other necessary therapies in patients with *ALK*-positive NSCLC who have experienced disease progression following initial or second-line alectinib therapy. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-798/rc).

Methods

Patient population

We enrolled eligible patients in this study who had histologically or cytologically confirmed stage IV NSCLC and who tested positive for *ALK* using fluorescence *in situ* hybridization, immunohistochemical analysis, or next-generation gene sequencing. These patients had previously received first- or second-line alectinib therapy and experienced disease progression as assessed based on periodic and radiological surveillance. The study excluded patients who had uncertain tumor conditions and who were lost to follow-up.

Treatment

Patients received continuing alectinib treatment from the time of disease progression on prior alectinib until repeated disease progression, an unacceptable adverse event (AE), or death occurred. If necessary, additional systemic or local therapies were administered concurrently with alectinib treatment.

Study design

This retrospective cohort study included a total of fifteen patients from nine institutions in China due to the rarity of the study population. These patients experienced disease progression after first- or second-line alectinib and continued to receive alectinib treatment between 2019 and 2022. This study was approved by the Ethics Review Committee of the First Affiliated Hospital of Xi'an Jiaotong University (No. XJTU1AF2023LSK-364) and adhered to the ethical guidelines of the Helsinki Declaration (as revised in 2013). Individual consent for this retrospective analysis was waived. All participating institutions were informed and agreed with this study. The primary objective of the study was to evaluate the safety and the mPFS of the continuing alectinib, as assessed by the investigators. Secondary endpoints included the ORR of alectinib continuation and the median overall survival (mOS) of the study participants as assessed by the investigators. To assess tumor response, computed tomography (CT) or magnetic resonance imaging (MRI) was applied every 2 months and evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) v. 1.1 guidelines. AEs are recorded in terms of type and severity, and the severity of toxicity was evaluated using the Common Terminology Criteria for Adverse Events v. 5.0. The study was a single-arm cohort study that was compared with previous studies.

Statistical analysis

PFS was considered to be the time to progression or death following initial progression with alectinib. OS was calculated from the initiation of alectinib treatment to the time of death. ORR was considered to be the ORR during the continuation of alectinib. Kaplan-Meier survival curves were generated for PFS and OS. The "swimplot" package and "ggplot" package in R software were used for creating swim plots. All statistical analyses were conducted using R software version 4.2.3 and Jamovi software version 2.3.18 for Microsoft Windows 64.

Results

Patient characteristics

A total of fifteen patients were enrolled in the study

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Table 1 Clinical and pathologic characteristics of the study cohort receiving alectinib for the first time (n=15)

Characteristic	Value
Sex	
Male	5 (33.3)
Female	10 (66.7)
Age at diagnosis, years	43 [17–57]
Smoking history	
Yes	1 (6.7)
None	11 (73.3)
Unknown	3 (20.0)
Histology (adenocarcinoma)	15 (100.0)
TNM stage at diagnosis (stage IV)	15 (100.0)
Brain metastases at diagnosis	4 (26.7)
Bone metastases at diagnosis	8 (53.3)
Line of prior alectinib	
1	13 (86.7)
2	2 (13.3)
Prior exposure to chemotherapy before alectinib	
Yes	2 (13.3)
None	13 (86.7)
Prior exposure to ALK-TKI before alectinib	
Yes	3 (20.0)
None	12 (80.0)
ECOG performance status	
1	8 (53.3)
2	6 (40.0)
3	0
4	1 (6.7)

Data are presented as n (%) or median [range]. TNM, tumour-nodes-metastasis; ALK-TKI, anaplastic lymphoma kinase-tyrosine kinase inhibitor; ECOG, Eastern Cooperative Oncology Group.

between 2019 and 2022. Patient characteristics at the baseline of the first alectinib treatment are presented in *Table 1*. Out of the fifteen patients, ten were female, and the median age was 43 years. Among them, only one patient had a specific history of smoking. All the patients had advanced *ALK*-positive lung adenocarcinoma. In the baseline, there were four patients with brain metastases and eight patients with bone metastases. Thirteen patients received first-line treatment with alectinib, two patients were treated with alectinib as second-line therapy. Two patients had prior exposure to chemotherapy and three patients had previously exposed to ALK-TKI. As shown in Table S1, patient No. 9 received one cycle of chemotherapy after diagnosis while awaiting the result of the genetic test, followed by crizotinib in combination with cranial gamma knife radiosurgery and alectinib after the progression of the prior treatment. Patient No. 3 was treated with crizotinib for 2.5 months, which was then discontinued based on individual decision, followed by alectinib for better efficacy. Patient No. 2 received one cycle of chemotherapy during the post-diagnostic genetic test and thereafter received alectinib. Other patients who received first-line treatment with alectinib were previously untreated. The Eastern Cooperative Oncology Group (ECOG) performance status of fourteen patients ranged from 1 to 2, indicating relatively good performance status, while one patient had an ECOG performance status of 4.

Table 2 presents the baseline characteristics of patients who continued treatment with alectinib. Thirteen patients achieved partial response at the prior alectinib treatment, and two patients achieved stable disease. Seven patients started continuing alectinib after oligoprogression, while eight patients continued alectinib because of CNS progression. Six patients developed new intracranial lesions, and one patient developed new bone metastases. Fourteen patients had an ECOG performance status of 1–2, while one patient had an ECOG performance status of 3. Among the fifteen patients, ten were treated with a combination of radiotherapy and continuing alectinib treatment, two received alectinib monotherapy, and the remaining three underwent chemotherapy, bevacizumab, and radiofrequency ablation, respectively. The median follow-up time for OS was 35 months [95% confidence interval (CI): 32 to not applicable (NA)] for all patients.

Efficacy and safety

All patients exhibited measurable disease as per the RECIST criteria. At the final follow-up on May 31, 2023, eleven patients experienced progressive disease (PD), and among the eleven patients, two deaths occurred. *Figure 1* shows that the mPFS of continuing alectinib combined with other necessary therapies was 8 months (95% CI: 4 to NA), while the mOS was not reached. *Figure 2A,2B* provide

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Table 2 Clinical and pathologic characteristics of the study cohort continuing to receive alectinib (n=15)

Characteristic	Value
Age at continuation of alectinib, years	44 [18–59]
Best response to prior alectinib therapy	
SD	2 (13.3)
PR	13 (86.7)
Progression type of prior alectinib	
Oligoprogression	7 (46.7)
CNS progression	8 (53.3)
New brain metastases at PD	6 (40.0)
New bone metastases at PD	1 (6.67)
ECOG performance status	
1	8 (53.3)
2	6 (40.0)
3	1 (6.7)
4	0
Combination therapy	
None	2 (13.3)
Bevacizumab	1 (6.7)
Radiation	10 (66.7)
Chemotherapy	1 (6.7)
Radiofrequency ablation	1 (6.7)

Data are presented as n (%) or median [range]. SD, stable disease; PR, partial response; CNS, central nervous system; PD, progressive disease; ECOG, Eastern Cooperative Oncology Group.

details of patients receiving continued treatment with alectinib in combination with other necessary therapies. During the continuation of alectinib, seven patients achieved partial response (PR), six had stable disease (SD), and two experienced PD, resulting in an ORR of 46.7% (*Figure 2C*).

These patients demonstrated a favorable safety profile during initial treatment with alectinib. One patient experienced a grade 1 skin rash and grade 1 elevation in alanine aminotransferase (ALT), while another patient experienced a grade 2 elevation in bilirubin. Both patients showed improvement with symptomatic supportive therapy, and no dose reduction or discontinuation of alectinib was necessary. Additionally, one patient underwent a dose reduction due to the development of a grade 2 skin rash. Among the patients who continued receiving alectinib, only one patient experienced a grade 2 elevation of aspartate aminotransferase (AST) and serum glutamic-oxaloacetic transaminase (SGOT), which also improved with symptomatic supportive therapy without the need for dose reduction or discontinuation.

Discussion

Our study demonstrated a cohort who received continuing alectinib combined with other therapies after prior alectinib resistance in the first- or second-line treatment, achieving an mPFS of 8 months. All patients started continuing alectinib because of oligoprogression or CNS progression. Eleven (73.3%) patients combined local treatment, and two patients received systemic therapy. Notably, two patients continued monotherapy with alectinib after progression,

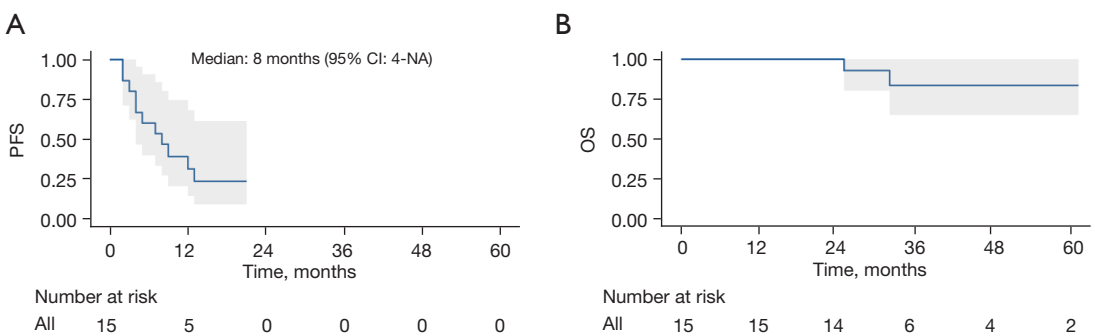

Figure 1 Kaplan-Meier curves for progression-free survival (A) and overall survival (B). CI, confidence interval; NA, not applicable; PFS, progression-free survival; OS, overall survival.

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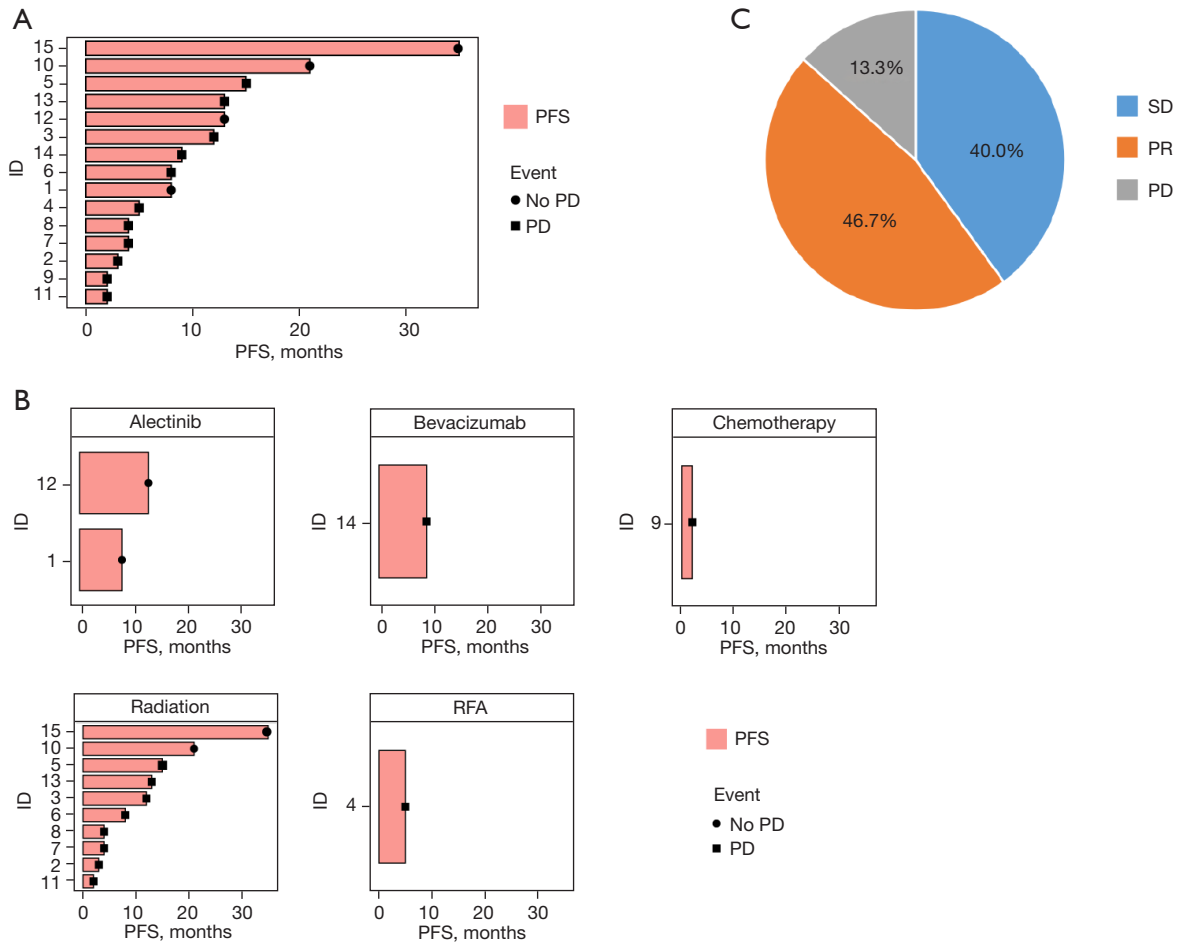

Figure 2 The swimmer plot and pie plot of continuing alectinib with other therapies in patients with alectinib-refractory *ALK*-positive NSCLC. (A) Progression-free survival and progression of continuing alectinib with other therapies. (B) Progression-free survival and progression of different combination therapies with continued alectinib. (C) Best tumor response to alectinib continuation with other necessary therapies. ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; PD, progressive disease; PFS, progression-free survival; RFA, radiofrequency ablation; SD, stable disease; PR, partial response.

considering their favorable response to the prior alectinib treatment. Until the end of the follow-up, they had stable disease and had not experienced progression. According to guidelines, when oligoprogression or CNS progression occurs in advanced NSCLC patients on ALK-TKIs, patients can continue existing ALK-TKI combined with local therapy or switch to another ALK-TKI. However, sequential ALK-TKI treatment may ultimately result in the development of highly resistant complex *ALK* mutations, which could potentially limit patient survival benefits (22). Consequently, the potential for continuing alectinib in combination with other therapies should be explored.

Previous studies have demonstrated the persistence of TKI-sensitive clones in lung cancers that have developed resistance to TKIs (24-29). The current definition of acquired resistance is the occurrence of disease progression after 6 months of ongoing TKI therapy (4). However, it is necessary to confirm this resistance before switching therapies for the benefit of the patients (30). It is well-known that prolonged exposure to epidermal growth factor receptor (EGFR) inhibitors can lead to the emergence of a secondary *T790M* mutation, which restores EGFR phosphorylation in the presence of TKI (31-33). Recent findings indicate that discontinuation of TKI in cell lines and patients with acquired resistance results in a gradual loss of the *T790M* mutation, allowing these cells to regain

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sensitivity to EGFR-TKI (25,26). This phenomenon might be attributed to the inactivation of *T790M*-mutant cell growth, leading to the overgrowth of parental cells that carry only *EGFR*-sensitizing mutations. Another possibility is that *EGFR* alleles are located extrachromosomally in double minutes, and they can be lost from the cells without appropriate selection pressure (25,27). These observations suggest the potential reversibility of acquired resistance and give clinicians mechanistic evidence to continue the original TKI therapy. As a matter of fact, it is not only in the laboratory but also in clinical practice. Chaft *et al.* summarized case reports of gefitinib-resistant patients with *EGFR*-mutated NSCLC who were reintroduced to gefitinib, indicating that the majority of patients retained sensitivity to gefitinib, which was attributed to the presence of tumor cells that exhibit partial resistance to EGFR-TKI (24). Ultimately, increasing the TKI dosage could overcome the acquired resistance in these patients (27,28). In an American cohort of patients with relapsed *EGFR*-mutant NSCLC, some patients experienced relapse after adjuvant treatment with EGFR-TKI, but the majority still responded favorably to EGFR-TKI reintroduction (29). This further supports the aforementioned hypothesis.

In other patients with NSCLC treated with ALK-TKI, similar findings have been observed. A study conducted in the United States reported on a group of patients who remained on their initial treatment of crizotinib and erlotinib in combination with local ablative therapy after developing acquired resistance. The mPFS for this cohort was 6.2 months (34). Another American cohort of 120 patients continued on crizotinib treatment despite crizotinib resistance, and this group had a longer mOS from the first dose of crizotinib (29.6 *vs.* 10.8 months) compared to patients who discontinued treatment after acquiring resistance (35). Hong *et al.* reported on a Chinese cohort for whom crizotinib therapy was continued after resistance had developed (36). This cohort achieved an mPFS of 16 weeks, patients who received local therapy after disease progression had a significantly longer PFS (P=0.039), and patients with a longer PFS in prior TKI treatment also experienced a longer PFS in continuing TKI therapy (36). Similarly, in a Chinese cohort studied by Lei *et al.*, patients who continued on crizotinib treatment after experiencing CNS progression achieved an mPFS of 6.3 months (37). Most of these patients received localized CNS therapy, including whole-brain radiation therapy or stereotactic radiosurgery (37). In another cohort of patients resistant to alectinib, those who received a platinum-pemetrexed combination with ALK-TKI had a longer duration of PFS compared to those receiving platinum or pemetrexed alone (6.8 *vs.* 3.2 months) (18). Additionally, in the phase II clinical NLCTG1501 trial, twelve alectinib-resistant patients treated with bevacizumab in combination with alectinib achieved an mPFS of 3.1 months (95% CI: 1.2–16.1) and an mOS of 24.1 months (95% CI: 8.3 to NA). These findings are in line with our study.

Alectinib is currently recommended as the first-line treatment for patients with *ALK*-positive NSCLC in international guidelines due to its broad application base. Consequently, there is a significant clinical demand for addressing resistance to this treatment (38). At present, when patients develop resistance to next-generation TKI, the decision-making to replace another TKI depends on the mechanism of acquired resistance, such as the location of the resistance within the *ALK* domain or off-target (4). If the resistance is caused by mutations such as *G1202R*, lorlatinib becomes the primary treatment option, leading to an mPFS of approximately 10 months (38-42). However, if the resistance occurs outside the kinase domain, chemotherapy is considered the best choice, resulting in an mPFS of around 3 months (18,43). According to some research findings, patients who switch to other next-generation ALK-TKI after resistance can achieve an mPFS of approximately 3 months (44,45). This suggests that switching to other next-generation ALK-TKI may have some benefits in extending disease control time in cases of resistance (44,45). The mPFS obtained in our study was 8 months. When alectinib becomes resistant again, it can still be used in combination with chemotherapy or switched to another ALK-TKI such as lorlatinib, depending on the underlying resistance mechanism. This approach has the potential to prolong OS in patients.

Certainly, the decision-making of combination therapy should be established based on the specific disease status and mechanisms of drug resistance. For instance, if an isolated brain metastatic lesion progresses, radiotherapy is usually preferred to control the brain metastatic lesion due to the existence of the blood-brain barrier (46,47). Similarly in our study, a total of 75% of patients (6/8) with CNS progression received cranial radiotherapy, and they exhibited positive responses to the treatment. Other localized lesion control can also rely on radiotherapy (48,49). When there is progression of multiple lesions or resistance occurs outside the kinase domain, despite oligoprogression, CNS progression rather than systemic progression, systemic treatments such as chemotherapy and antiangiogenesis therapy will likely need to be considered to control all

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lesions (18,23). Additionally, it is worth further exploration in future studies to determine the most appropriate treatment strategy by exploring the synergistic effects of alectinib and radiotherapy, chemotherapy, or antiangiogenic drugs to make an accurate decision. Our study provides a significantly beneficial therapy for alectinib-resistant patients. It balances the treatment of TKI-sensitive clones and possible off-target TKI-insensitive clones, avoiding the generation of complex resistance and providing more possibilities for subsequent ALK-TKI such as lorlatinib. Unfortunately, in this study, it is disappointing to see that several patients had limited benefits from continuing alectinib. It is necessary to explore the biomarkers associated with the benefits of continuing alectinib to guide clinical practice more accurately (50). In the study by Ou *et al.*, patients who continued treatment with the original TKI after crizotinib resistance had a better ECOG performance status and a better ORR on prior crizotinib therapy compared to patients who switched to another TKI, which might give us some insights (35). However, we were limited by the fact that our study only included patients who continued alectinib and failed to compare the differences.

Our study has certain limitations, many of which are inherent to the retrospective study designs. First, the study had a limited sample size, consisting only of a small number of patients. Since all patients were recruited from academic institutions, the findings may not be fully representative of the broader *ALK*-positive population. Second, the mechanisms of resistance in most patients with disease progression are unknown due to the low frequency of re-biopsies, especially when progressive metastases occur in the brain, where biopsies cannot be conveniently conducted. Moreover, it is rare for re-biopsy to be performed in patients with oligoprogression, considering the existence of TKI-sensitive clones, the progression is usually due to tumor heterogeneity. Therefore, we have not been able to explore the population that might benefit from this therapy from the results of genetic tests. Furthermore, retrospective studies are prone to limitations in data collection, potentially leading to incomplete or insufficient data. Finally, the physician's decision to continue alectinib treatment might have been influenced by various factors, such as the patient's ECOG performance status, the extent of the CNS and extracranial disease, tumor genotyping, smoking history, and the patient's response and tolerability to previous ALK-TKI. These confounding factors might have influenced the observed PFS, which is the main focus of our study.

Conclusions

In our study, we found that continuing alectinib treatment combined with other necessary therapy after the oligoprogression or CNS progression of the first- or second-line alectinib in patients with *ALK*-positive NSCLC yielded a favorable response and maintained safety. Our findings suggest that instead of immediately switching to another ALK-TKI, continuing alectinib combined with other necessary therapies after the oligoprogression or CNS progression of the first- or second-line alectinib treatment may offer greater survival benefits to patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-798/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-798/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-798/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-798/coif). The 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. This retrospective study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University (No. XJTU1AF2023LSK-364). Individual consent for this retrospective analysis was waived.

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All participating institutions were informed and agreed with this study.

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