Efficacy and survival outcomes of alectinib vs. crizotinib in ALK-positive NSCLC patients with CNS metastases: A retrospective study

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Abstract. Anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitors (TKIs) have transformed the treatment paradigm for patients with ALK-positive non-small cell lung cancer (NSCLC). Yet the differential efficacy between alectinib and crizotinib in treating patients with NSCLC and central nervous system (CNS) metastases has been insufficiently studied. A retrospective analysis was conducted of clinical outcomes of patients with ALK-positive NSCLC and CNS metastases treated at the Shandong Cancer Centre. Based on their initial ALK-TKI treatment, patients were categorised into either the crizotinib group or the alectinib group. Efficacy, progression-free survival (PFS), intracranial PFS and overall survival (OS) were evaluated. A total of 46 eligible patients were enrolled in the present study: 33 patients received crizotinib and 13 patients received alectinib. The median OS of the entire group was 66.8 months (95% CI: 48.5-85.1). Compared with the patients in the crizotinib group, the patients in the alectinib group showed a significant improvement in both median (m)PFS (27.5 vs. 9.5 months; P=0.003) and intracranial mPFS (36.0 vs. 10.8 months; P<0.001). However, there was no significant difference in OS between the alectinib and crizotinib groups (not reached vs. 58.7 months; P=0.149). Furthermore, there were no significant differences between patients receiving TKI combined with radiotherapy (RT) vs. TKI alone with respect to mPFS (11.0 vs. 11.7 months, P=0.863) as well as intracranial mPFS (12.5 vs. 16.9 months, P=0.721). In the present study, alectinib exhibited superior efficacy to crizotinib for treating patients with ALK-positive NSCLC and CNS metastases, especially in terms of delaying disease progression and preventing CNS recurrence. Moreover, the results demonstrated that it might be beneficial to delay local RT for patients with ALK-positive NSCL and CNS metastases.

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Introduction

For patients with non-small cell lung cancer (NSCLC), brain metastasis is present at diagnosis in 10-20% of cases and develops in up to 50% of patients during the course of their disease (1,2). Within this context, anaplastic lymphoma kinase (ALK) rearrangement, accounting for 3-7% of all NSCLC cases (3), is of particular concern. Brain metastases are identified at the time of diagnosis in 25-40% of patients with ALK-positive NSCLC, and over half can develop brain metastases during their treatment (4,5). According to Rangachari *et al* (6) retrospective study, the incidence of brain metastases in patients with ALK-positive NSCLC was 45.5 and 58.4% at two and three years, respectively. These are notably higher rates than in other NSCLC subtypes.

The occurrence of brain metastases is frequently associated with a poor prognosis, with median overall survival (mOS) times ranging from 3 to 6 months (7,8). Crizotinib has proven to be effective in patients with ALK-positive NSCLC, but the progression in the central nervous system (CNS) remains the primary cause of treatment failure (9). Costa *et al* (2) retrospective study revealed that 72% of patients with pre-existing brain metastases who received crizotinib experienced secondary CNS progression. Second-generation ALK tyrosine kinase inhibitors (TKIs)-ceritinib, brigatinib and alectinib-were developed to overcome crizotinib resistance. These inhibitors have shown superior CNS penetration (10-12). In the ALEX trial, the median progression-free survival (mPFS) for patients

treated with alectinib was 27.7 months (13), and this increased to 42.3 months for the Asian population in the ALESIA trial (14). However, the efficacy of crizotinib and alectinib in patients with ALK-positive brain metastases has not been established in a real-world setting.

Radiotherapy (RT) is a prevalent therapeutic approach for NSCLC patients, especially those with brain metastasis, and is often used in combination with systemic therapy. In epidermal growth factor receptor-mutant NSCLC patients with brain metastases, several retrospective studies have demonstrated that combining targeted therapy with intracranial radiation improves both intracranial PFS and OS compared with targeted therapy alone (15-17). However, for patients with ALK-positive and brain metastases, the evidence is limited, particularly in real-world settings.

Therefore, a comparative analysis on the efficacy of alectinib and crizotinib in patients with ALK-positive NSCLC and CNS metastases in a real-world setting was undertaken.

Materials and methods

Patients. The present retrospective study included patients with ALK-positive NSCLC and CNS metastases who visited the Shandong Cancer Centre (Jinan, China) between January 2016 and December 2020. The inclusion criteria included patients with CNS metastases at baseline as well as those without CNS metastases at initial diagnosis but developed them as the disease progressed at the time of ALK-TKI therapy initiation. The exclusion criteria included: i) chemotherapy alone, ii) presence of other malignancies and iii) predicted survival <3 months. The present study was reviewed and approved (approval no. SDTHEC2023008007) by the Institutional Review Board of Shandong Cancer Centre (Jinan, China).

Data collection. Clinical data, including demographic characteristics (sex and age), smoking status, Eastern Cooperative Oncology Group (ECOG) performance score, disease stage, histologic type, treatment regimen and disease regression were retrieved from electronic databases of the Shandong Cancer Centre and medical record system. All patients underwent enhanced computed tomography scans and brain magnetic resonance examinations at baseline, tumor assessment was performed every 8 weeks thereafter.

Treatment. ALK-TKIs including crizotinib 250 mg twice-daily, alectinib 600 mg twice-daily. Based on their initial ALK-TKI treatment, patients were categorised into either the alectinib group or crizotinib group. Whole-brain radiation therapy or stereotactic radiosurgery was conducted at the initial of TKI administration if radiation was applied.

Statistical analysis. The efficacy of treatment was assessed using the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, encompassing complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). PFS was defined as the interval from the initiation date of the ALK-TKI therapy in patients with CNS metastases to disease progression or death. Intracranial PFS was determined as the period from the commencement date of the ALK-TKI therapy in patients with CNS metastases to the detection of CNS progression. OS was defined as the duration from the diagnosis of lung cancer to the date of death or the last follow-up. Survival curves were constructed using the Kaplan-Meier method and compared with the log-rank test. For continuous variables, differences between groups were tested with the unpaired t-test. Categorical variables were analysed using Pearson's chi-square test or Fisher's exact test, as appropriate. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using the Cox proportional hazards regression model. $P<0.05$ was considered to indicate a statistically significant difference. All statistical analyses were conducted by using SPSS software, version 27.0 (IBM Corp.).

Results

Patient characteristics. A total of 57 patients with ALK-positive NSCLC and CNS metastases were screened at baseline or progressing CNS metastases from January 2016 to December 2020 and 46 patients met the eligibility criteria (Fig. 1). The patient baseline characteristics are detailed in Table I. The majority of patients were women (61%), 39 patients (85%) had never been smokers and 38 patients (83%) had an ECOG performance status score of <2. The major histological subtype was adenocarcinoma, accounting for 91.3% of cases. The remaining 8.7% (4 out of 46 patients) were diagnosed with non-adenocarcinoma subtypes, consisting of adeno-squamous carcinoma (n=1), large-cell carcinoma (n=1), signet-ring cell carcinoma (n=1) and squamous cell carcinoma (n=1). Based on the initial ALK-TKI received, patients were categorised into the crizotinib (n=33) group and the alectinib (n=13) group.

Efficacy. Among patients in the crizotinib group from the initiation date of TKI therapy, 14 exhibited PR and 5 achieved SD, resulting in an overall response rate (ORR) of 42.4% (14/33) and a disease control rate (DCR) of 57.6% (19/33). By contrast, the alectinib group demonstrated superior response: The ORR and DCR were 84.6% (11/13) and 92.3% (12/13), with 1 CR, 10 PR and 1 SD. The difference between the two groups was statistically significant for ORR (P=0.002), as shown in Table II. In addition, with regard to intracranial efficacy, the crizotinib group had 0 CR, 15 PR, 7 SD and 11 PD cases, leading to an ORR of 45.5% (15/33) and a DCR of 66.7% (22/33). The alectinib group, however, reported 1 CR, 11 PR, 1 SD and no PD, resulting in an ORR of 92.3% (12/13) and a DCR of 100% (13/13). In the two groups, there were significant differences in intracranial ORR (P=0.004) and DCR (P=0.045), as demonstrated in Table III.

Outcomes. The mOS of the entire group was 66.8 months (95% CI, 48.5-85.1), as can be observed in Fig. 2A. The median duration of follow-up from the date of original diagnosis was 41.2 months with the alectinib group and 55.4 months with the crizotinib group. The mPFS was significantly improved in the alectinib group (27.5 months; 95% CI, 9.5-45.5) vs. the crizotinib group (9.5 months; 95% CI, 6.0-13.1; P=0.003) (Fig. 2B). Intracranial mPFS was also significantly prolonged in the alectinib group (36.0 months; 95% CI, 21.2-50.8) compared with the crizotinib group (10.8 months; 95% CI, 7.9-13.7; P<0.001) (Fig. 2C). However, there was no significant difference in OS between the alectinib group [not reached (NR)] and

Table I. Baseline characteristics of patients.

Characteristic	Crizotinib group (n=33)	Alectinib group (n=13)	P-value
Age (mean ± SD)	50.7±11.65	54.46±10.30	0.318
Sex, n (%)			0.540
Male	12 (36.4)	6 (46.2)	
Female	21 (63.6)	7 (53.8)	
Smoking status, n (%)			0.540
Never-smoker	29 (87.9)	10 (76.9)	
Smoker	4 (12.1)	3 (23.1)	
ECOG at TKI initiation, n (%)			0.836
<2	28 (84.8)	10 (76.9)	
≥2	5 (15.2)	3 (23.1)	
Stage at initial diagnosis, n (%)			0.971
III	2 (6.1)	0 (0.0)	
IV	31 (93.9)	13 (100)	
Histology, n (%)			0.275
Non-adenocarcinoma	4 (12.1)	0 (0.0)	
Adenocarcinoma	29 (87.9)	13 (100)	
CNS metastasis status at initial diagnosis, n (%)			0.275
No	13 (39.4)	2 (15.4)	
Yes	20 (60.6)	11 (84.6)	
ALK testing, n (%)			0.002
ARMS-PCR	22 (66.7)	2 (15.4)	
NGS	11 (33.3)	11 (84.6)	
Max dimension of brain metastasis at TKI initiation, n (%)			1.000
<3 cm	28 (84.8)	11 (84.6)	
≥3 cm	5 (15.2)	2 (15.4)	
Number of brain metastasis at TKI initiation, n (%)			0.284
≤3	29 (87.9)	9 (69.2)	
>3	4 (12.1)	4 (30.8)	
Cranial radiotherapy at TKI initiation, n (%)			0.275
TKI alone	17 (51.5)	9 (69.2)	
TKI + radiotherapy	16 (48.5)	4 (30.8)	
Extracranial metastasis at ALK-TKI initiation, n (%)			1.000
No	10 (30.3)	4 (30.8)	
Yes	23 (69.7)	9 (69.2)	
Treatment lines, n (%)			0.539
First line	16 (48.5)	5 (38.5)	
Second line	17 (51.5)	8 (61.5)	

ECOG, Eastern Cooperative Oncology Group; CNS, central nervous system; TKI, tyrosine kinase inhibitors; ARMS-PCR, Amplification Refractory Mutation System polymerase chain reaction; NGS, Next-Generation Sequencing; Max, maximum; ALK, anaplastic lymphoma kinase.

the crizotinib group (58.7 months; 95% CI, 39.1-78.3; P=0.149) (Fig. 2D).

A subset analysis was conducted among patients receiving CNS RT. The analysis indicated that there were no significant differences between patients receiving TKI combined with RT vs. those receiving TKI alone with respect to mPFS (11.0 vs. 11.7 months, respectively; P=0.863) as well as intracranial mPFS (12.5 vs. 16.9 months, respectively; P=0.721) (Fig. 3A and B).

In the crizotinib group, there were no significant differences between patients receiving TKI plus RT and those receiving TKI alone both for mPFS (7.1 months vs. 10.8 months, respectively; P=0.253) and intracranial mPFS (10.8 vs. 9.5 months, respectively; P=0.274) (Fig. 4A and B).

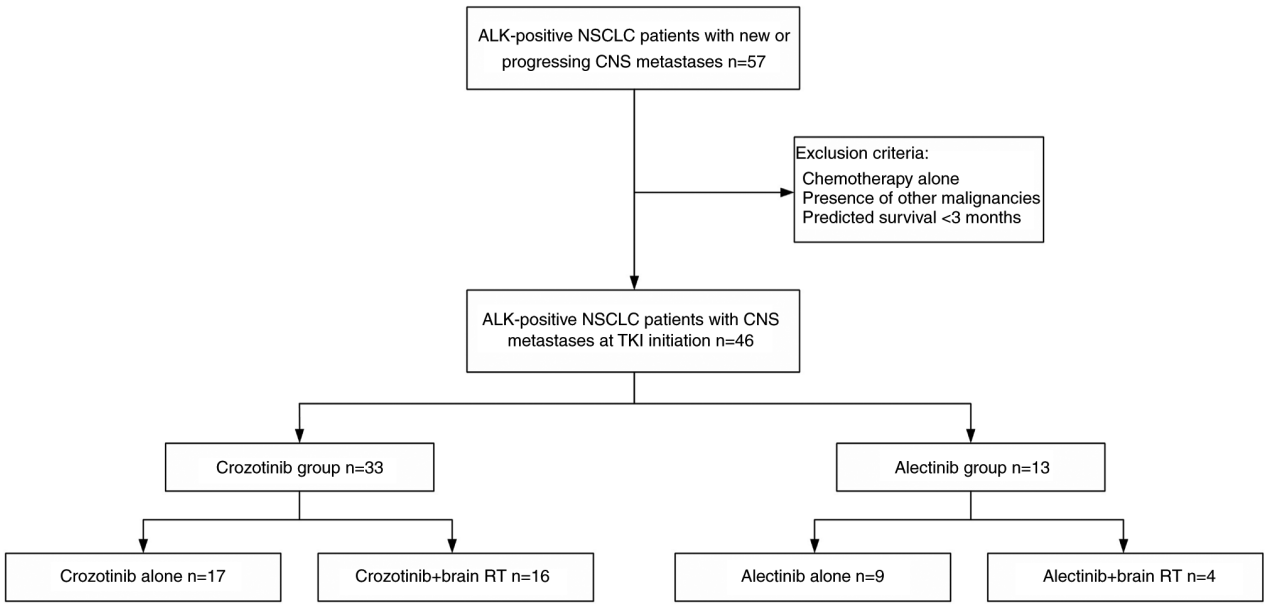

Figure 1. Patient flowchart. ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; CNS, central nervous system; TKI, tyrosine kinase inhibitors; RT, radiotherapy.

Table II. Overall efficacy.

Outcome	Crizotinib (n=33)	Alectinib (n=13)	P-value
CR	0	1	-
PR	14	10	-
SD	5	1	-
PD	14	1	-
ORR (%)	42.4	84.6	0.002
DCR (%)	57.6	92.3	0.056

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Table III. Intracranial efficacy.

Outcome	Crizotinib (n=33)	Alectinib (n=13)	P-value
CR	0	1	-
PR	15	11	-
SD	7	1	-
PD	11	0	-
ORR, %	45.5	92.3	0.004
DCR, %	66.7	100	0.045

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

Similarly, no significant differences were observed in the alectinib group for either mPFS (21.1 vs. 27.5 months, respectively; P=0.849) or intracranial mPFS (alectinib plus RT, 41.2 months vs. alectinib, 27.5 months; P=0.688) (Fig. 5A and B).

Subsequent therapy after crizotinib-resistance. During the follow-up period, in the crizotinib group, disease progression occurred in 32 out of 33 patients (97.0%). Of those who progressed on crizotinib, six patients opted for symptomatic supportive therapy, two chose chemotherapy and 24 received subsequent ALK-TKI therapy (alectinib, brigatinib, ceritinib and lorlatinib). Among the patients who underwent ALK-TKI therapy, 12 patients received alectinib as a sequential treatment and had an mPFS time of 16.2 months (95% CI, 0.0-39.6). A total of five patients were treated with brigatinib and had an mPFS time of 12.4 months (95% CI, 5.6-19.2). A total of six patients received ceritinib and had an mPFS time of 5.9 months (95% CI, 5.3-6.5). The difference in mPFS among the three groups was statistically significant (P=0.010) (Fig. 6). In addition, one patient was treated with the ALK-3rdG lorlatinib after resistance to crizotinib and achieved an mPFS of 33.07 months (data not shown).

Univariate and multivariate analysis. In a multivariate analysis, the maximum dimension of brain metastasis was significantly associated with an elevated risk for intracranial PFS (HR=3.389; 95% CI, 1.249-9.915; P=0.040). Alectinib therapy was associated with superior PFS (HR=0.292; 95% CI, 0.131-0.650; P=0.003) and intracranial PFS (HR=0.175; 95% CI, 0.066-0.462; P<0.001), compared with crizotinib (Tables IV and V). The results from the multivariate analysis of OS revealed that female patients (HR=4.475; 95% CI, 1.221-16.394; P=0.024) and individuals with a score of ECOG ≥2 (HR=3.860; 95% CI, 1.166-12.783; P=0.027) demonstrated a poorer outcome compared with their counterparts. Conversely, patients with a histologic diagnosis of adenocarcinoma exhibited superior OS relative to those with non-adenocarcinoma (HR=0.073; 95% CI, 0.015-0.357; P=0.001) (Table VI).

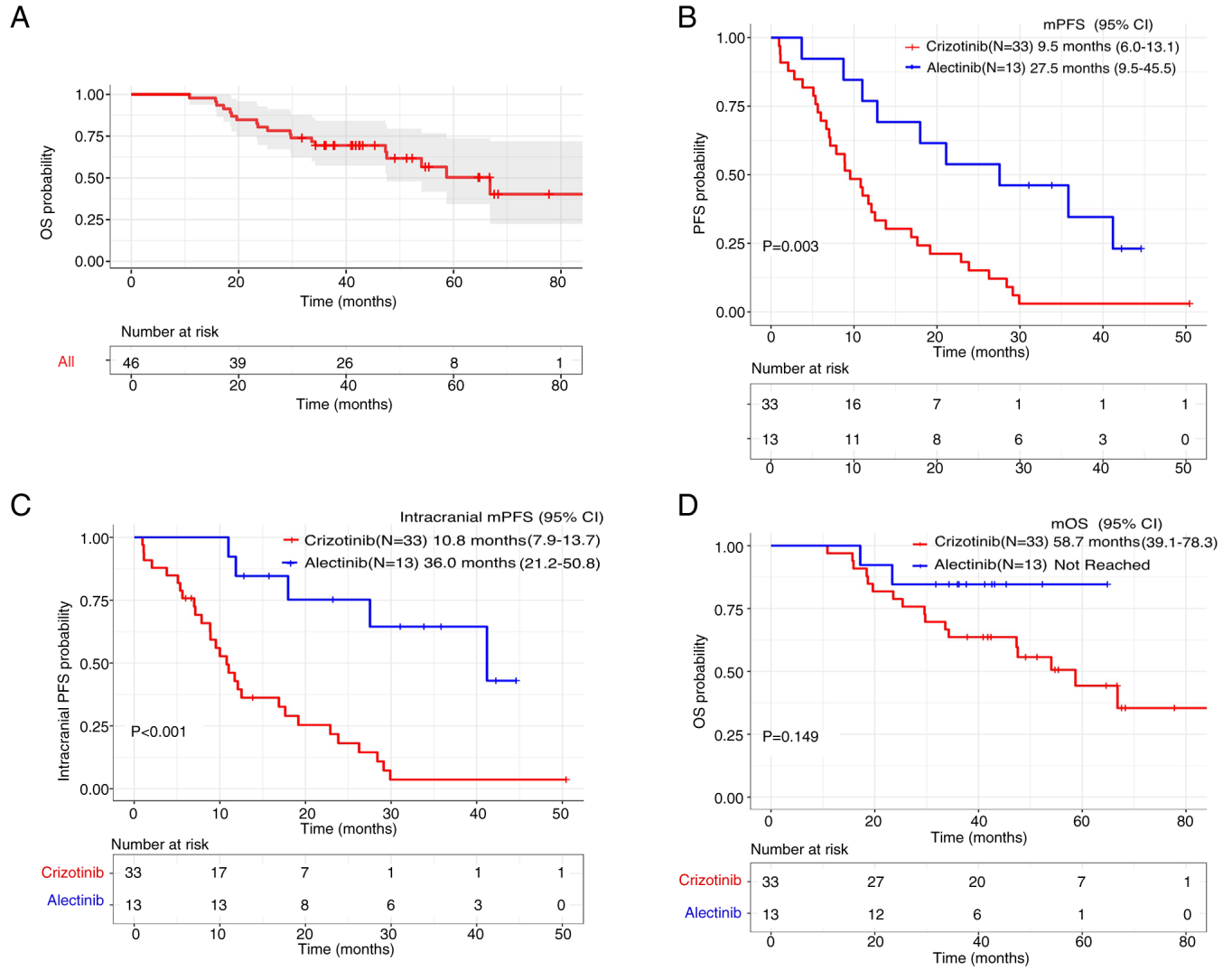

Figure 2. Kaplan-Meier curves for (A) OS in overall population. Kaplan-Meier curves for (B) PFS, (C) intracranial mPFS and (D) mOS in patients treated with crizotinib or alectinib. OS, overall survival; PFS, progression-free survival; mOS, median OS; mPFS, median PFS; CI, confidence interval.

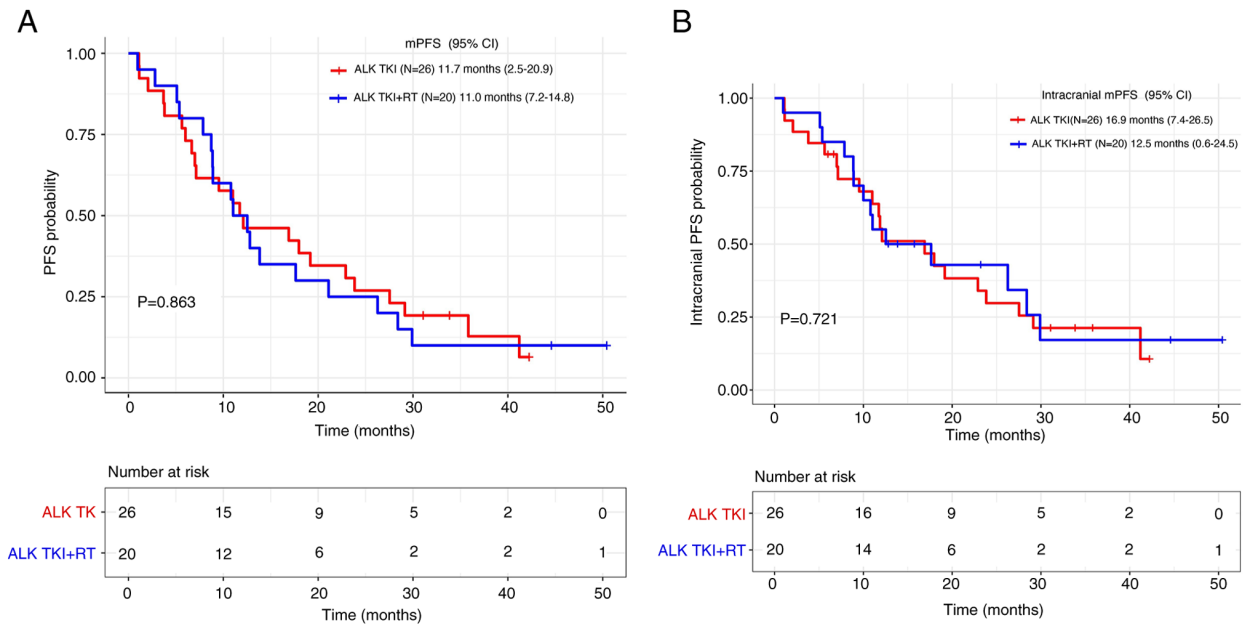

Figure 3. Kaplan-Meier curves for (A) PFS and (B) intracranial PFS in patients treated with TKI + RT or TKI alone. PFS, progression-free survival; CI, confidence interval; TKI, tyrosine kinase inhibitor; RT, radiotherapy; mPFS, median PFS.

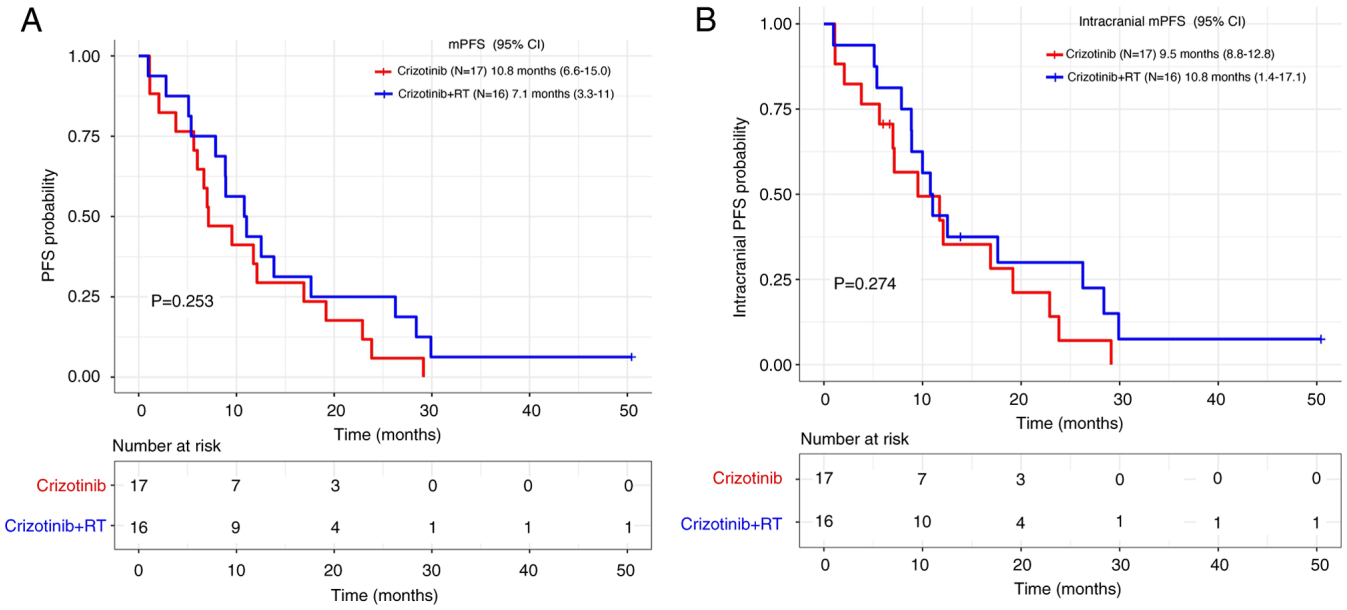

Figure 4. Kaplan-Meier curves for (A) PFS and (B) intracranial PFS in patients treated with crizotinib + RT or crizotinib alone. PFS, progression-free survival; CI, confidence interval; RT, radiotherapy; mPFS, median PFS.

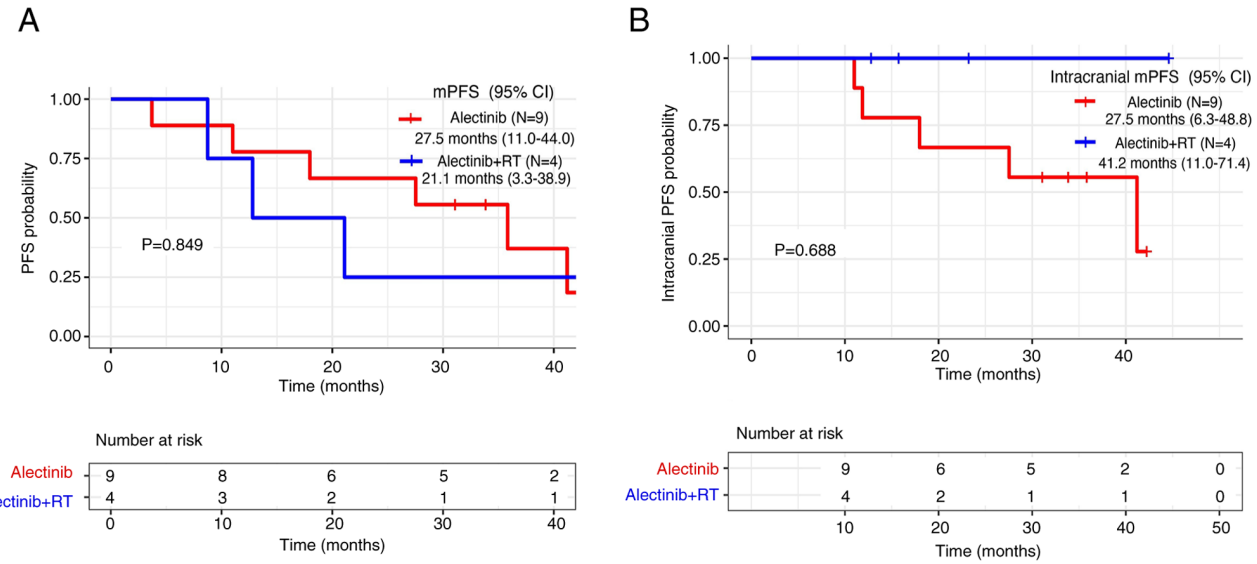

Figure 5. Kaplan-Meier curves for (A) PFS and (B) intracranial PFS in patients treated with alectinib + RT or alectinib alone. PFS, progression-free survival; CI, confidence interval; RT, radiotherapy; mPFS, median PFS.

Discussion

The efficacy of different generations of ALK-TKIs in patients with NSCLC exhibits considerable variation. Alectinib is preferentially recommended in the guidelines for ALK-positive NSCLC, considering its enhanced efficacy and safety profile (18). In the ALEX trial (13), the mPFS of alectinib was greater than that of crizotinib [27.7 vs. 7.4 months (HR=0.35; 95% CI, 0.22-0.56)]. However, the real-world effectiveness of alectinib in patients with brain metastases from ALK-positive NSCLC merits further investigation.

In the present study, alectinib significantly prolonged the mPFS compared with crizotinib (27.5 vs. 9.5 months), and alectinib was associated with a 70% lower risk of disease progression (HR, 0.292; P=0.003). In a cohort of patients with CNS metastases in the US (19), the administration of alectinib yielded a discernible advantage in PFS over crizotinib (24.5 vs. 5.9 months), reflecting a HR of 0.28 (95% CI, 0.16-0.52), which is less than the PFS of the present study. In addition, the OS advantage favouring alectinib over crizotinib was first discerned in patients with brain metastases (HR, 0.58; 95% CI, 0.34-1.00) in the ALEX trial (20). However, neither the WJOG9516L (21), J-ALEX (22) trials, nor the present study presented an OS benefit of alectinib over crizotinib. This could potentially be attributable to limited follow-up duration or patient crossover to a second-generation TKI post-crizotinib progression.

Table IV. Univariate and multivariate analysis of PFS in patients.

Variable	Univariate analysis (P-value)	Multivariate analysis		
		Hazard ratio	95% CI	P-value
Sex (male vs. female)	0.276			
Age (<60 vs. ≥60 years)	0.744			
ECOG at TKI initiation (<2 vs. ≥2)	0.018	2.390	0.907-6.299	0.078
Smoking status (never-smoker vs. smoker)	0.138			
CNS metastasis status at diagnosis initiation (no vs. yes)	0.543			
Extra-cranial metastasis at TKI initiation (no vs. yes)	0.065	1.823	0.907-6.299	0.124
Histology (non-adenocarcinoma vs. adenocarcinoma)	0.257			
Max dimension of brain metastases (<3 vs. ≥3)	0.006	2.253	0.791-6.415	0.128
Number of brain metastases (≤3 vs. >3)	0.375			
Cranial radiotherapy at TKI initiation (no vs. yes)	0.863			
TKI treatment (crizotinib vs. alectinib)	0.004	0.292	0.131-0.650	0.003

PFS, progression-free survival; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitor; CNS, central nervous system; Max, maximum.

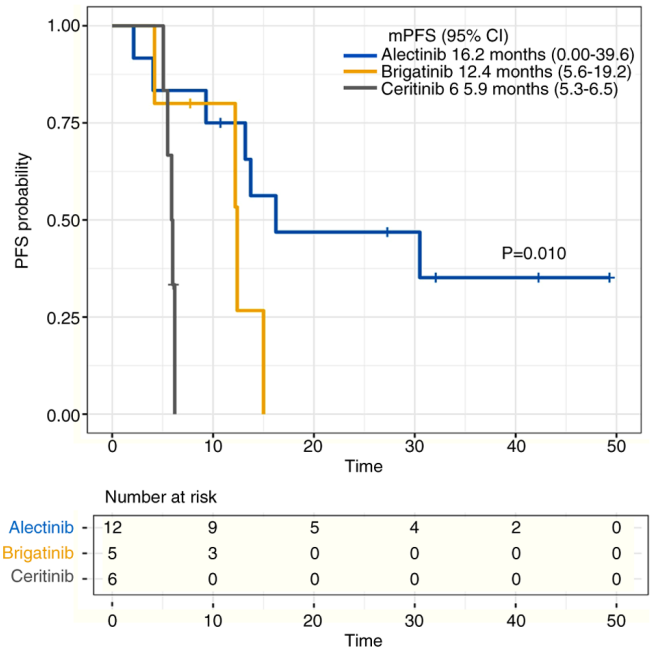

Figure 6. Kaplan-Meier curves for PFS in patients treated with alectinib, brigatinib or ceritinib after resistance to crizotinib. PFS, progression-free survival; CI, confidence interval; mPFS, median PFS.

In terms of intracranial efficacy, the intracranial ORR with alectinib in the present study was 92.3%, which was in consistency with a national multicentre retrospective study (23). It reduced the risk of CNS progression by 83% relative to crizotinib in the present study. The intracranial mPFS of alectinib markedly surpassed that of crizotinib (36.0 vs. 10.8 months). This may be related to the blood-brain barrier penetration of alectinib and its status as a non-substrate for P-glycoprotein (24). In addition, in the findings of the present study, the intracranial mPFS of patients with alectinib was extended by eight months compared with the intracranial mPFS of patients with crizotinib. For patients with ALK-positive NSCLC and brain metastases initially treated with alectinib, extracranial metastases might predominantly drive disease progression. These results further underscore the potent CNS activity of alectinib.

In terms of the management of the intracranial progression, RT is frequently used as a local treatment. It is often considered to disrupt the blood-brain barrier and exert synergistic antitumour effects when combined with TKIs (25,26). However, the results of the present study demonstrated no PFS (11.0 vs. 11.7 months; P=0.863) or intracranial PFS (12.5 vs. 16.9 months; P=0.721) benefit from the addition of RT to TKI vs. TKI alone. A multicentre study (27) failed to show any benefit in either time to progression (11.4 vs. 13.4 months; P=0.98) or time to intracranial progression (18.1 vs. 21.8 months; P=0.65). One MATA analysis (28) revealed that adding RT did not result in any PFS or OS advantage compared with an ALK-TKI alone. However, a study by Ni *et al* (29) suggested that RT in conjunction with an ALK-TKI extended survival in patients with ALK-positive brain metastases. The effectiveness of incorporating RT for patients with ALK brain metastases remains to be elucidated. Given the limited evidence supporting its efficacy, RT should perhaps not be considered the best first choice of combination therapies in the treatment plan. It might be beneficial to delay the initiation of RT for patients with ALK brain metastases.

For patients with post-crizotinib resistance, second-generation TKIs are the standard therapies. They have superior abilities of blood-brain barrier penetration and blocking multiple resistance sites, including L1196M, 1151Tins, C1156Y, G1269A, F1174L and I1171T (30-33). In the present study, an analysis was conducted to explore the therapeutic efficacy of sequential TKIs for patients with brain metastases developing post-crizotinib resistance. The mPFS for crizotinib-resistant patients was 5.9 months on ceritinib, but it was extended to 12.4 months by brigatinib, 16.2 months by alectinib and 33.07 months by the lorlatinib

Table V. Univariate and multivariate analysis of intracranial PFS in patients.

		Multivariate analysis		
Variable	Univariate analysis (P-value)	Hazard ratio	95% CI	P-value
Sex (male vs. female)	0.283			
Age (<60 vs. ≥60 years)	0.465			
ECOG at TKI initiation (<2 vs. ≥2)	0.120			
Smoking Status (never-smoker vs. smoker)	0.215			
CNS metastasis status at diagnosis initiation (no vs. yes)	0.398			
Extra-cranial metastasis at TKI initiation (no vs. yes)	0.113			
Histology (non-adenocarcinoma vs. adenocarcinoma)	0.115			
Max dimension of brain metastases (<3 vs. ≥3)	0.040	3.389	1.249-9.195	0.017
Number of brain metastases (≤3 vs. >3)	0.637			
Cranial radiotherapy at TKI initiation (no vs. yes)	0.721			
TKI treatment (crizotinib vs. alectinib)	0.001	0.175	0.066-0.462	<0.001

PFS, progression-free survival; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitor; CNS, central nervous system; Max, maximum.

Table VI. Univariate and multivariate analysis of OS in patients.

		Multivariate analysis		
Variable	Univariate analysis (P-value)	Hazard ratio	95% CI	P-value
Sex (male vs. female)	0.071	4.475	1.221-16.394	0.024
Age (<60 vs. ≥60 years)	0.533			
ECOG at TKI initiation (<2 vs. ≥2)	0.002	3.860	1.166-12.783	0.027
Smoking Status (never-smoker vs. smoker)	0.306			
CNS metastasis status at diagnosis initiation (no vs. yes)	0.853			
Extra-cranial metastasis at TKI initiation (no vs. yes)	0.048	2.973	0.683-12.941	0.147
Histology (non-adenocarcinoma vs. adenocarcinoma)	0.006	0.073	0.015-0.357	0.001
Max dimension of brain metastases (<3 vs. ≥3)	0.244			
Number of brain metastases (≤3 vs. >3)	0.323			
Cranial radiotherapy at TKI initiation (no vs. yes)	0.146			
TKI treatment (crizotinib vs. alectinib)	0.161			

OS, overall survival; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitor; CNS, central nervous system; Max, maximum.

when administered sequentially. Crizotinib followed by alectinib proved to be substantially superior to brigatinib and ceritinib. The ALK-3rdG lorlatinib yielded the best effect of all ALK inhibitors (34), which resulted from its potency against all known single ALK-resistant mutations, including ALK G1202R (32,35). However, it causes severe lipid abnormalities and cognitive impairment (36). According to data from the CROWN study (37), the global use of lorlatinib did not significantly improve patients' quality of life scores clinically. Considering the clinical safety concerns and cost constraints associated with lorlatinib, its use in the clinic remains restricted. Hence, establishing the optimal sequencing and combination of ALK inhibitors for patients is crucial (38,39).

There are several limitations in the present study. First, it was a retrospective study and the number of enrolled patients was relatively small and they were all from a single institution. Second, the majority of the initial TKI treatments were crizotinib and alectinib-treated patients had shorter follow-up time; accordingly, OS outcomes for these patients were likely less mature.

In conclusion, the present study indicated the superior clinical activity of alectinib in Chinese patients with brain metastases. Furthermore, it offers preliminary indications

that pairing RT with ALK-TKIs as a starting combination treatment may not be required.

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Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Authors' contributions

ZW, XH and JG were involved in the conception and design of the present study. QL and YF collected and analysed the data. QL drafted the manuscript. CF, CZ and NT provided advice on research design and contributed to interpretation of the data. QL and YF revised the manuscript. XH, ZW and CF confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved (approval no. SDTHEC2023008007) by the Ethics Committee of Shandong Cancer Hospital approved (Jinan, China). In the present retrospective study, the privacy and personal information of all patients were protected, and the present study was performed in accordance with the Declaration of Helsinki (2013).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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