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Clinical observation of crizotinib in the treatment of ALK-positive advanced non-small cell lung cancer

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ABSTRACT

Background: ALK is a prognostic and predictive tumor marker in non-small cell lung carcinoma (NSCLC), and is more often found in lung adenocarcinomas.

Methods: The clinical and pathological data of 87 patients confirmed to have NSCLC by pathology or cytology were selected from April 2014 to January 2017 at the Tumor Hospital of Hebei Province.

Results: Of the 87 ALK-positive-patients, 47 patients were treated with oral administration of crizotinib. The objective response rate (ORR) was 61.7%, the disease control rate (DCR) was 93.6%, and the mPFS was 19 months. In an analysis of the number of metastatic sites, the patients who had more than three metastatic sites, the ORR, DCR, and mPFS were 63.9%, 94.5%, and 19 months, compared with the 45.5%, 91%, and 11 months in the patients with less sites ($P = 0.040$). For patients of 60 years or older, ORR and DCR were 40% and 100%, the other group was 71.9% and 90.6%, respectively($P = 0.036$). The timing of treatment was analyzed. At the first application of crizotinib, ORR and DCR were 78.2% and 100% corresponding 45.8% and 87.5% at the second and final application of crizotinib group ($P = 0.022$). Baseline brain metastases were present in 25.5% (12/47) of patients in this study. 9 of the patients who developed disease progression during crizotinib treatment had new brain metastases or increased preexisting cranial foci. Most of them took the treatment strategy of continuing crizotinib or replacing the second/third generation ALK-TKI treatment combined with local radiotherapy for brain metastases.

Conclusions: The efficacy of crizotinib in patients with advanced NSCLC is related to the number of metastatic organs, age and timing of treatment. The use of crizotinib is prone to intracranial progression, and progression of simple brain metastases is not an indication that crizotinib is discontinued. Patients will continue to benefit from combination of local radiotherapy.

1. Introduction

Lung cancer is also one of the most common malignancies worldwide [1], and non-small cell lung cancer (NSCLC) accounts for > 85% of cases [2]. At present, the concept of precise medical treatment is popular, and targeted treatment is particularly prominent in the treatment of lung cancer [3]. Among the treatment options currently available, epidermal growth factor receptor-related drugs are widely used in the clinic and have achieved remarkable curative effects, opening the era of targeted therapy of NSCLC [4]. ALK, as a receptor tyrosine kinase, belongs to the insulin receptor superfamily. ALK plays an important role in tumorigenesis and development, although its normal physiological function is not clear. ALK translocations have been found in more than 20 different malignancies [5]. Currently, there are many methods for ALK gene fusion detection, and the recommended detection methods in China include Ventana IHC, RT-PCR, and FISH.

This study examined 87 patients with NSCLC to further clarify the clinical and pathological features in ALK-positive patients.

2. Materials and methods

2.1. Inclusion and exclusion criteria

Lung cancer patients confirmed by pathology or cytology were selected from 1851 NSCLC cases from April 2008 to January 2017 at the

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Tumor Hospital of Hebei Province. All specimens were formalin-fixed paraffin embedded tissues. Histological classification and genetic expression were evaluated by hematoxylin-eosin(HE) staining and/or IHC/FISH. All sections were examined by a senior diagnostic physician by light or fluorescence microscopy. NSCLC was confirmed by cytology and histopathology (WHO Classification of Tumors of the Lung, Pleura, Thymus and Heart).

ALK gene detection was performed using Ventana-IHC, Fluorescence In Situ Hybridization(FISH), Realtime Polymerase Chain Reaction(RT-PCR), or Next Generation Sequencing(NGS) methods approved by the Food and Drug Administration(FDA). The relevant examinations of all patients were undertaken to determine whether the primary cancer was lung cancer if necessary.

2.2. Follow-up

Imaging data were collected within one month before treatment as a baseline. The first imaging review evaluated the efficacy after crizotinib treatment for one month by RECIST1.1 solid tumor evaluation criteria, and regular imaging reviews and follow-ups were conducted every two months after treatment. The follow-up deadline was February 2017.

2.3. Statistical methods

SPSS21.0 statistical software was used for data analysis and t-tests and chi-square tests were performed. Survival curve data was drawn using the Kaplan–Meier method. P-values of < 0.05 were determined to be statistically significant.

3. Results

3.1. Patient clinical features

In total, 36 (42.2%) patients were males and 51 (57.8%) females, with an average age of 53.6 ± 11.4 years. The age range spanned 26–79 years, and there were 31 patients (36.7%) of ≥60 years and 56 patients (63.3%) of < 60 years. ALK-positive patients were identified in each age group in varying proportions. Non-smoking accounted for 75.6% of patients, stage I for 7.3%, stage II for 6.1%, stage III for 26.8% and stage IV for 59.8% (Table 1).

3.2. Patient pathological features

Of the 87 patients, there were 73 cases of adenocarcinoma (83.9%), four of squamous cell carcinoma (4.3%), six of adenosquamous carcinoma (6.9%), one of sarcomatoid carcinoma (1.2%), and three of pathologically unknown status (3.4%). Sixty-one patients (70.1%) had tissue pathologically taken from the primary tumor and 26 (29.9%) cases from metastasis mass. A total of 95.4% cases were confirmed by histopathology and 4.6% by cytology (Table 1). Among the patients, 49 cases (56.3%) were detected by Ventana IHC, 3 (3.4%) of which were positive. 32 cases (36.8%) by FISH, 2 (6.3%) of which were positive. Five (5.7%) by RT-PCR and one (1.2%) by NGS but no positive. Four cases analyzed by cytology included two cases positive for ALK by Ventana IHC and two positive by FISH. (Fig. 1, Table 1).

3.3. General curative effect of crizotinib in advanced NSCLC patients

Forty-seven of 87 patients with advanced or locally advanced NSCLC were treated with oral administration of crizotinib. The objective response rate (ORR) was 61.7%, the disease control rate (DCR) was 93.6%, and the mPFS was 19 months (Fig. 2).

In an analysis of the number of metastatic sites, ORR, DCR, and mPFS in patients with fewer than three sites were 45.5%, 91%, and 11 months, respectively; in patients with more than three metastatic sites, ORR, DCR, and mPFS were 63.9%, 94.5%, and 19 months, respectively.

Table 1
The clinical and pathological characteristics of patients.

Characteristics	N = 87/47	Constituent Ratio(%)
Gender		
female	51	57.8
male	36	42.2
AGE		
≥60	31	36.7
< 60	56	63.3
Smoking		
yes	20	24.4
no	67	75.6
No. of metastatic organ		
< 3	36	76.6
≥3	11	23.4
Clinical stages		
Stage III	11	23.4
Stage IV	36	76.6
Treatment opportunity		
First-line	23	48.9
Second or above	24	51.1
Baseline brain metastasis		
yes	12	25.5
no	35	74.5
Pathological type		
Adenocarcinoma	73	83.9
Squamous cell carcinoma	4	4.6
adenosquamous cell carcinoma	6	6.9
Sarcomatoid carcinoma	1	1.2
Pathological type unknown	3	3.4
Pathological site		
Primary focus	61	70.1
Metastatic focus	26	29.9
Test method		
FISH	49	56.3
VENTANA IHC	32	36.8
RT-PCR	5	5.7
NGS	1	1.2

There were significant differences between the mPFS values only between the two groups ($P = 0.040$) (Table 2).

For patients of 60 years or older, ORR and DCR were 40% and 100%, respectively; ORR and DCR in patients younger than 60 years were 71.9% and 90.6%, respectively. ORR values were significantly different ($P = 0.036$) between the two groups but there was no significant difference between the DCR values ($P = 0.0225$) (Table 3).

The timing of treatment was analyzed, and at the first application of crizotinib, ORR and DCR were 78.2% and 100%, respectively. At the second and final application of crizotinib, ORR and DCR were 45.8% and 87.5%, respectively. ORR values were significantly different ($P = 0.022$) between the two groups but DCR values were not ($P = 0.083$) (Table 4).

Age, sex, smoking history, stage, duration of treatment, baseline brain metastasis, pathological type, test specimen acquisition, and detection method were not associated with PFS (Table 5). The patient's sex, smoking history, stage, baseline brain metastasis, number of organ metastases, pathological type, test specimen acquisition method, and detection method were unrelated to ORR (Table 6).

Brain metastasis treatment strategy: Baseline brain metastases were present in 25.5% (12/47) of patients in this study. 9 of the patients who developed disease progression during crizotinib treatment had new brain metastases or increased preexisting cranial foci. Most of them took the treatment strategy of continuing crizotinib or replacing the

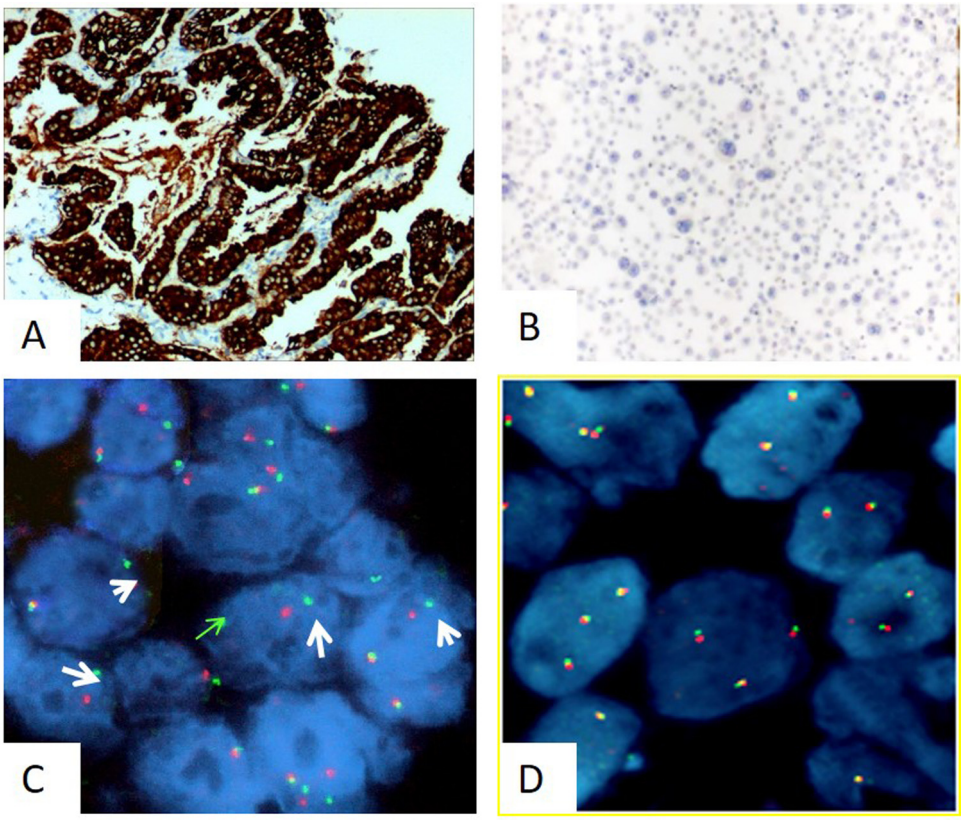

Fig. 1. The results of ALK test. A, ALK positive by VENTANA IHC; B, ALK negative by VENTANA IHC; C, ALK rearrangement positive by FISH; D, ALK rearrangement negative by FISH. (A,B 200× ; C,D 1000×).

second/third generation ALK-TKI treatment combined with local radiotherapy for brain metastases.

4. Discussion

The ELM4–ALK fusion gene was first discovered by Soda et al. in 2007 [6,7] and was identified as a specific molecular subtype of NSCLC. Since then, ALK-related research has become a focus of research. Data reported in 2007 showed that ALK gene translocations were found in approximately 3–5% of NSCLC. Previous studies had shown that ALK-

Table 2
The Efficacy of patients.

Efficacy evaluation	N = 47	constituent ratio(%)
CR	1	2.1
PR	28	59.6
SD	15	31.9
PD	3	6.4
ORR	–	61.7
DCR	–	93.6

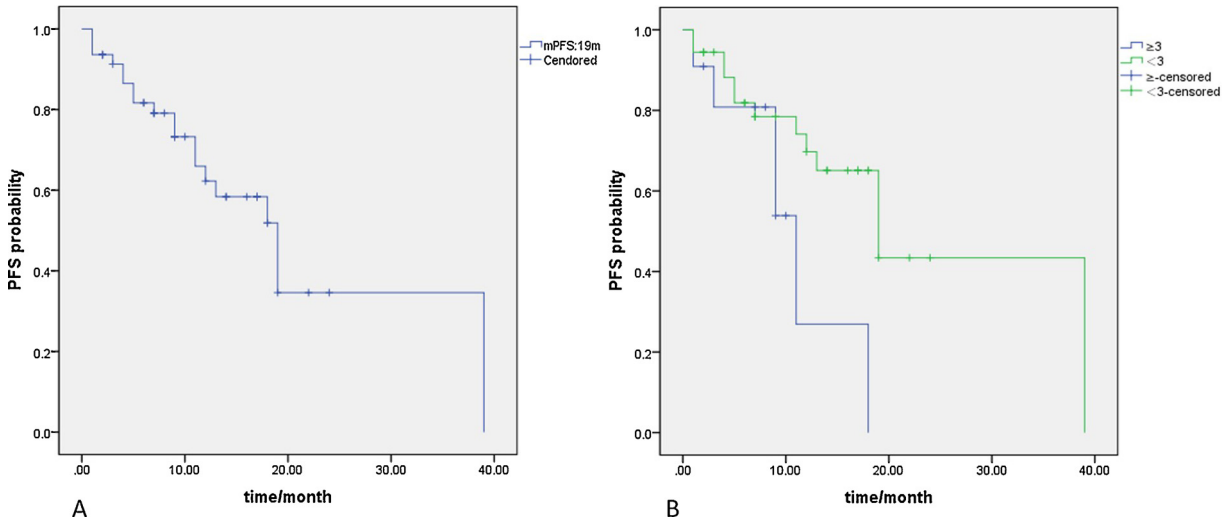

Fig. 2. Kaplan-Meier Survival curve of progressive-free survival(PFS). A, The PFS of the patients with oral administration of crizotinib; B, The relationship between PFS and the number of metastatic sites.

Table 3
The relationship between age and the therapeutic efficacy.

Age	CR N(%)	PR N(%)	SD N(%)	PD N(%)	ORR (%)	DCR (%)
≥60	0	6(40)	9(60)	0(0)	40*	100△
<60	1(3.1)	22(68.8)	6(18.7)	3(9.4)	71.9	90.6

* Compared with age ≥ 60 and age < 60, $P = 0.036$.
△ Compared with age ≥ 60 and age < 60, $P = 0.225$.

Table 4
Timing of treatment and the relationship between ORR and DCR.

Treatment opportunity	CR N(%)	PR N(%)	SD N(%)	PD N(%)	ORR (%)	DCR (%)
First-line	1(4.3)	17(73.9)	5(21.8)	0(0)	78.2△	100*
Second or above	0(0)	11(45.8)	10(41.7)	3(12.5)	45.8	87.5

△ Compared with first-line and second-line or above treatment, $P = 0.022$.
* Compared with first-line and second-line or above treatment, $P = 0.083$.

Table 5
General characteristics of patients with PFS(Log-rank test).

Item	N	Median post-progression survival (95%CI)	*P*
Age			0.585
≥60	15	12(7.2-12.8)	
<60	32	19(17.2-20.8)	
Gender			0.16
Female	28	19(17.8-20.2)	
Male	19	11(5.1-16.9)	
Smoking			0.139
Yes	13	11(3.7-18.3)	
No	34	19(17.7-20.2)	
Clinical stages			0.793
Stage III	11	19(6.9-31.0)	
Stage IV	36	18(11.5-24.5)	
Treatment opportunity			0.280
First-line	23	18(-)	
Second or above	24	13(6.2-19.8)	
Baseline brain metastasis			0.381
yes	12	18(13.1-30.4)	
no	35	19(8.4-29.5)	
No. of metastatic organ			0.040
< 3	36	19(11.4-26.6)	
≥3	11	11(4.9-17.1)	
Pathological type			0.920
Adenocarcinoma	40	19(11.3-26.7)	
Nonadenocarcinoma	7	19(5.8-22.1)	
Pathological site			0.703
Primary focus	27	19(8.2-29.7)	
Metastatic focus	20	18(9.4-26.5)	
Test method			0.591
FISH	27	18(12.2-23.7)	
VENTANA IHC	13	–	
RT-PCR	5	–	

positivity was more common in young female non-smoking adenocarcinoma patients [8]. Patients who fulfilled at least two of these clinical characteristics in parallel had a higher positive rate [9,10]. In this study, 57.8% cases were women, 75.6% cases were non-smoking, and the average age was 53.6 ± 11.4 years; the proportion of patients with adenocarcinoma and adenosquamous carcinoma was 90.8%,

Table 6
General characteristics of patients with ORR.

item	N	ORR(%)	*P*
Age			0.036
≥60	15	40	
<60	32	71.8	
Gender			0.096
Female	28	71.4	
Male	19	47.3	
Smoking			0.498
Yes	13	53.8	
No	34	64.7	
Clinical stages			0.881
Stage III	11	63.6	
Stage IV	36	61.1	
Treatment opportunity			0.022
First-line	23	78.2	
Second or above	24	45.8	
Baseline brain metastasis			0.881
yes	11	63.6	
no	36	61.1	
No.of metastatic organ			0.581
< 3	36	63.9	
≥3	11	54.6	
Pathological type			0.790
Adenocarcinoma	40	62.5	
Nonadenocarcinoma	7	57.1	
Pathological site			0.689
Primary focus	27	59.2	
Metastatic focus	20	65	
Test method			0.591
FISH	27	55.6	
other	20	70	

similar to previous studies. This indicates that ALK-positive-predominant populations were young non-smokers with adenocarcinoma.

Some studies showed that in NSCLC patients who had no mutations in genes such as EGFR, KRAS, HER2 or TP53, ALK-positivity was approximately 25% [11]. Chinese researchers reported that, in adenocarcinoma patients with wild-type EGFR and KRAS, the positive rate of ALK can be as high as 30–42% [12,13]. Another study of ALK showed that ALK gene fusions also exist in patients with lung adenosquamous cell carcinoma, squamous cell carcinoma, and KRAS mutations or EGFR mutations [14]. Six patients (6.9%) with adenosquamous carcinoma, four patients (4.6%) with squamous cell carcinoma, and one (1.1%) patient with sarcomatoid carcinoma were included in this study, which also confirmed the existence of ALK gene fusions in a particular pathological type of lung cancer [15,16]. In the meantime, a case of rare co-integration of ALK and ROS1 was also found in our hospital and the case is currently under study.

In recent years, targeting drug as a new type of therapeutic drugs has been more targeted, can enhance the killing of tumor cells, reduce toxic side effects on normal cells, and become a hot spot of NSCLC drug treatment. Crizotinib is one of them for the treatment of patients with ALK-positive NSCLC. Studies have shown that crizotinib significantly improves the objective response rate of patients with lung cancer, has a good tolerability, and significantly improved the patients with advanced lung cancer. Quality of Life. Related clinical trials have shown that whether crizotinib is first-line or second-line therapy is better than chemotherapy [17,18]. Based on the above findings, crizotinib was approved by the Food and Drug Administration (FDA) in 2011 for the treatment of patients with locally advanced or metastatic NSCLC. In

2013, it received the Chinese Food and Drug Administration (FDA). Approved. As crizotinib is listed later in China, it lacks large-scale real-world research. This study included some patients who were actually taking crizotinib orally in our province to further observe the effective population and efficacy, and found rare adverse reactions.

The results of this study showed that 47 patients had an objective remission rate of 61.7%, a disease control rate of 93.6%, a first-line treatment efficacy rate of 78.2%, and a second-line treatment rate of more than 45.8%. This result is similar to the results of previous international large studies. The median PFS was 19 months, which was significantly higher than the previous study results. Maybe due to the low data maturity (40%) in this study, we will continue to follow up to improve the follow-up data. Previous studies have shown that ORR and PFS in crizotinib first-line treatment appear to be superior to second-line therapy. The timing of crizotinib treatment was analyzed in this study. The efficacy of first-line treatment was greater than that of second-line and above, with statistical significance between the two. The difference (78.2% vs 45.8%, P = 0.022) indicates that the use of crizotinib as early as possible may be better for ALK-positive patients with advanced NSCLC.

The results of this study showed that patients with more than 3 metastatic organs had significantly longer mPFS than those with 3 or more metastatic organs (19.0 months vs 11.0 months, P = 0.040), suggesting that tumor burden may be related to efficacy.

At the same time, the results of this study also showed that patients aged < 60 years were more effective than those aged ≥60 years and there was a statistically significant difference between them (71.8% vs 40.0%, P = 0.036), suggesting that the smaller the age, the better the effect may be. However, the patient's gender, smoking history, and treatment have nothing to do.

In this study, 25.5% (12/47) of patients had baseline brain metastases and achieved good results after crizotinib treatment, indicating that crizotinib is still an indication for patients with brain metastases. Nine out of four patients who progressed on crizotinib treatment were brain lesions. Most of them continued to take crizotinib or replace second- and third-generation ALK-TKI with brain radiotherapy to achieve intracranial lesions. Control, extracranial lesions were stable, and the greatest survival benefit was achieved. As of the date of follow-up, only one of these 9 patients died, confirming that progression of simple brain metastases is not an indication that crizotinib is discontinued, and combined local radiotherapy can Continue to benefit the patient, suggesting that continuing crizotinib or replacing the new generation of ALK-TKIs in patients with brain metastases and combined with local brain radiotherapy is a treatment.

The study found that brain metastasis was present in nearly half of the patients who continued to benefit after oral administration of crizotinib. It was considered that crizotinib penetrated the blood-brain barrier and the CSF/plasma drug concentration ratio was only 0.26%. Intracranial solitary progression is due to lower drug concentrations, rather than true resistance to crizotinib; for patients with oligo-metastases, local radiotherapy combined with continued oral crizotinib prolongs 6 months of PFS [19].

Retrospective analysis of PROFILE1005 and PROFILE1007 studied the efficacy of crizotinib in 275 patients with brain metastases. The rate of CNS control at 12 weeks was 56% and 62%, respectively; and 60% of patients with cranial radiotherapy were compared with those who had not received cranial brain radiotherapy. CNS patients had higher objective CNS efficacy (33% vs 18%) and prolonged progression of intracranial lesions (13 months vs 7 months) [20].

About ALK-positive lung squamous cell carcinoma, there is currently a lack of extensive literature reports, only seen in some cases. In this study, we included 2 patients with ALK-positive lung squamous cell carcinoma, 1 of whom were elderly nonsmokers and had received treatment before. The efficacy evaluation of PR has been used for ten months. It has been used for 19 months. The lesion is stable. At the follow-up date, the patient's PFS has not yet been achieved. Another patient with ALK-positive squamous cell carcinoma is an elderly male smoker who has received treatment before. The efficacy of dentinum was evaluated as SD, followed by the development of new brain metastasis, PFS was 7 months, OS was 33 months, indicating that patients with ALK positive squamous cell carcinoma can also obtain better efficacy from crizotinib.

AlK-positive sarcomatoid carcinoma is rarely reported, and this type is not sensitive to radiotherapy and chemotherapy, and the prognosis is very poor. One case (2.1%) of young patients with ALK-positive sarcomatoid carcinoma was included in this study. Simultaneous immunohistochemistry with C-MET (3 +) was performed, but no FISH test confirmed that the best effect of crizotinib treatment was PR, which has been administered orally for 9 months, is currently in stable condition, suggesting that crizotinib is also effective for ALK-positive lung cancers with specific pathological types.

In summary, this study further confirmed that ALK fusions commonly occur in young non-smoking adenocarcinoma patients by analyzing the clinical and pathological features of 87 patients with NSCLC. ALK gene mutations may also occur in lung adenosquamous carcinoma, squamous cell carcinoma, or sarcomatoid carcinoma. The current common technologies used to detect ALK are FISH, Ventana IHC and RT-PCR. The clinical efficacy of crizotinib in the treatment of ALK-positive and ROS-1 positive NSCLC patients was confirmed in this study, while crizotinib was also effective in patients with ALK-positive special pathological types. The patient's gender, smoking history, stage, pathological type, test method, method of obtaining specimens, and baseline brain metastasis were not related to efficacy. Patients with more than 3 organ metastases have a poor prognosis, which may indicate that the greater the tumor burden, the poorer the efficacy of crizotinib. The first line of crizotinib treatment is better. For patients with simple brain metastasis, the treatment strategy of continuous crizotinib combined with local cranial radiotherapy can be used. Patients with secondary crizotinib resistance can replace the second or third generation of ALK-TKI treatment. However, at the end of the study, only 7 patients died and 19 patients had disease progression, which is not sufficient to count OS data. We will continue to monitor up to improve the follow-up data.

Availability of data and materials

The supporting data can be accessed by email the corresponding authors.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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