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A real-world study of treatment patterns and survival outcome in advanced anaplastic lymphoma kinase-positive non-small-cell lung cancer

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Abstract. Crizotinib is an anti-cancer drug with a substantial beneficial effect in advanced non-small-cell lung cancer (NSCLC) patients harboring anaplastic lymphoma kinase (ALK) rearrangement. However, the real-world data currently available on this drug are limited. Thus, the present study aimed to retrospectively examine the treatment patterns and survival outcome of 83 advanced NSCLC patients with ALK rearrangement in a single center in China. Of the 83 patients enrolled, 33 (39.8%) patients received crizotinib and the remaining 50 (60.2%) patients received chemotherapy as the initial therapy. The first-line use of crizotinib prolonged the PFS1 (progression-free survival to the first detection of subsequent disease progression) compared with chemotherapy (median, 18.5 vs. 4.9 months; P<0.001), however, it did not prolong the overall survival (OS; P=0.802). At the last follow up, 71 (85.5%) patients had received crizotinib and 12 (14.5%) patients were crizotinib-naive. Patients who had received crizotinib exhibited a significantly longer OS as compared with those who were crizotinib-naive [hazard ratio (HR) for mortality, 0.279; 95% confidence interval, 0.107-0.727; P<0.05). Among the 71 patients who had received crizotinib, this was administered as a first-line therapy in 33 (46.5%) cases, as a second-line therapy in 22 (31.0%) cases and after the second-line therapy in 16 (22.5%) cases. No significant difference in the OS among the three groups was observed (P=0.577). The Cox multivariate analysis identified the following independent negative prognostic factors for OS: Smoking history (HR=4.565), liver invasion at diagnosis (HR=4.294) and bone invasion at diagnosis (HR=2.587). In addition, the use of crizotinib (HR=0.319) was identified as a positive prognostic factor for OS. In conclusion, the present real-world study revealed that the use of crizotinib improved the long-term survival of patients with ALK-positive advanced NSCLC. There was no difference in survival outcome between patients with initial use of crizotinib and those with subsequent use of crizotinib after first-line therapy.

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Introduction

Lung cancer is the leading cause of cancer-associated mortality in China and worldwide (1). In 2015, an estimated 733,300 new cases of lung and bronchial cancer were diagnosed, and 610,200 mortalities were estimated to occur in China as a result of this disease (2). Approximately 80% of lung cancer cases involve non-small-cell lung cancer (NSCLC), which has an overall 5-year relative survival rate of <20%, while an exceptionally high mortality rate is reported for patients with advanced NSCLC (3). During the past decades, genomic medicine has increased our understanding of the molecular characterization of cancer. The treatment strategy for advanced NSCLC has changed from the traditional chemotherapy based on pathologic histology to individualized precision treatment based on the oncogenic drivers (3).

Fusions of the echinoderm microtubule-associated protein-like 4 (EML4) gene and the anaplastic lymphoma kinase (ALK) gene along with other ALK gene rearrangements (referred to as ALK-positive) are detected in 3-7% of NSCLC patients. The EML4-ALK translocation was first identified as an oncogene in a small proportion of patients with NSCLC in 2007, and the chemical inhibition of the EML4-ALK fusion protein demonstrated an anti-tumor effect *in vivo* and *in vitro* (4,5).

Crizotinib, a multitargeted tyrosine kinase inhibitor of ALK, MET and ROS1, had been originally developed as an inhibitor of the c-MET growth factor receptor tyrosine kinase (6). In 2011, this drug received accelerated approval under the US Food and Drug Administration (FDA) for treating ALK-positive advanced NSCLC patients based on two single-arm clinical trials, namely PROFILE 1001 and PROFILE 1005 (7,8). Subsequently, crizotinib was evaluated

in several randomized clinical trials, demonstrating superior response rate (RR) and progression-free survival (PFS) to chemotherapy, in first- and second-line settings (PROFILE 1007 and PROFILE 1014) (9,10). Recently, another first-line randomized trial (PROFILE 1029) with the same design as PROFILE 1014, confirmed that crizotinib was able to improve the objective RR (ORR) and PFS compared with chemotherapy in the Asian populations (11). To date, crizotinib has been approved by the China FDA for the treatment of advanced or metastasis ALK-translocated NSCLC.

To date, published real-world data on the treatment patterns and outcomes of patients with ALK-positive advanced NSCLC in China are limited. Therefore, the present study aimed to characterize the treatment patterns and to estimate the survival of patients in China with locally advanced or metastatic ALK-positive NSCLC. Exploratory experimentation was used to investigate independent prognostic factors associated with survival in this cohort.

Patients and methods

Ethical approval. All procedures performed in the present study involving human participants were in accordance with the ethical standards of the Research Ethics Committee of Zhejiang Cancer Hospital and with the 2013 Declaration of Helsinki. Since this is a retrospective study, patient informed consent was not required.

Patient enrollment. A total of 83 patients with locally advanced or metastatic ALK-positive NSCLC who were treated at the Zhejiang Cancer Hospital (Hangzhou, China) during the period of July 2010 and April 2017 were included in the present study. Exclusion criteria in this study were as follows: (i) patients with other types of malignancy; (ii) patients who did not pursue treatment after diagnosis, and (iii) patients who were lost to follow up. Patient data were collected including the following variables: Gender, age, histological subtype, stage (8th edition of the American Joint Committee on Cancer Tumor-Node-Metastasis staging system) (12), smoking history, metastatic sites, therapeutic regimens, efficacy of treatment, date of progression, site of progression and date of mortality. ALK rearrangements were detected by the Ventana ALK (D5F3) CDx immunohistochemical assay (Ventana Medical Systems, Inc., Tucson, AZ, USA), according to the manufacturer's protocol (13).

Follow-up procedures. Patients receiving chemotherapy were evaluated for response every two treatment cycles during treatment and then every 2 months after treatment. Among the 50 patients receiving first-line chemotherapy, 27 were treated with pemetrexed (administered at a dose of 500 mg/m^2 by intravenous infusion on day 1 and every subsequent 21 days, for 4-6 cycles) in addition to cisplatin (administered at a dose of 25 mg/m^2 by intravenous infusion daily on days 1 to 3 and every subsequent 21 days, for 4-6 cycles)/carboplatin [administered at a dose of AUC (area under the curve)=5 by intravenous infusion on day 1, and every subsequent 21 days, for 4-6 cycles], 11 were treated with docetaxel (administered at a dose of 75 mg/m^2 by intravenous infusion on day 1, and every subsequent 21 days for 4-6 cycles) in addition to cisplatin/carboplatin, and 12 were treated with gemcitabine (administered at a dose of 1,000 mg/m^2 on day 1 and day 8, and every subsequent 21 days for 4-6 cycles) in addition to cisplatin/carboplatin.

Patients receiving crizotinib were evaluated for response 1 month after the initial treatment and then every 2 months during treatment. Brain or bone lesions that were detected at the time of screening were evaluated in all subsequent tumor assessments. For patients without brain or bone metastasis at baseline assessment, brain and bone scanning was repeated every 6 months or when related symptoms appeared.

The response evaluation of the tumor to therapy was based on computed tomography or magnetic resonance imaging scanning. The short-term efficacy was defined based on version 1.1 of the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (14). The long-term efficacy was evaluated according to the PFS and overall survival (OS). PFS1 was defined as the time from the initiation of treatment to the radiological evidence of first progressive disease (PD). PFS2 was defined as the time between the first and the second RECIST-defined PD. OS was calculated from the initiation of treatment to mortality.

Statistical analysis. Statistical analysis was performed using SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Statistically significant differences was indicated by $P<0.05$. χ^2-test was applied to examine the association between the efficacy and therapeutic regimens. Survival rates were analyzed using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analysis were performed with the Cox proportional hazard model.

Results

Patient characteristics. A total of 83 patients, treated at the Zhejiang Cancer Hospital between July 2010 and April 2017, were enrolled into the present study. The patient characteristics are listed in Table I. The median age at diagnosis was 50 years (ranging between 23 and 79 years), and more than half of the patients were female (56.6%). The most common histological type was adenocarcinoma (92.8%), and 61.4% of the patients were not smokers. In total, 7 (8.4%) patients were diagnosed with stage IIIB disease and 76 (91.6%) patients with stage IV disease. Among them, 34.9% displayed intrapulmonary metastasis, 10.8% had intracranial metastasis, 20.5% had liver metastasis, 34.9% had bone metastasis, and 32.5% presented pleural effusion. Until the last follow up (June 7, 2017), the median follow-up time was 23.6 months (range, 1.2-66.9 months).

Efficacy and survival of initial therapy. The treatment efficacy of the 83 patients was listed in Table II. Among these patients, 33 (39.8%) received crizotinib and 50 (60.2%) received chemotherapy as the initial therapy. Among the 50 patients receiving first-line chemotherapy, 27 were treated with pemetrexed (administered at a dose of 500 mg/m^2 by intravenous infusion on day 1, every 21 days) plus cisplatin (administered at a dose of 25 mg/m^2 by intravenous infusion daily on days 1 to 3, every 21 days)/carboplatin (administered at a dose of AUC=5 by intravenous infusion on day 1, every

21 days), 11 were treated with docetaxel (administered at a dose of 75 mg/m^2 by intravenous infusion on day 1, every 21 days) plus cisplatin/carboplatin, and 12 were treated with gemcitabine (administered at a dose of 1,000 mg/m^2 on day 1 and day 8, every 21 days) plus cisplatin/carboplatin. The ORR was significantly higher in patients receiving crizotinib as compared with those treated with chemotherapy (72.7 vs. 38%, respectively; P=0.003).

Until the last follow-up, 67 patients had disease progression. The median PFS1 was 18.5 months [95% confidence interval (CI), 12.4-24.6 months] among patients in the crizotinib group, as compared with 4.9 months (95% CI, 2.8-7.1 months) among patients in the chemotherapy group [hazard ratio (HR) for progression or mortality in crizotinib group, 0.345; 95% CI, 0.201-0.594; P<0.001; Fig. 1A]. Intracranial lesion progression or development of new intracranial lesions was reported in significantly more patients in the crizotinib group (n=10; 50%) as compared with those in the chemotherapy group (n=4; 8.5%; P<0.001; data not shown). Intrapulmonary lesion progression was reported in a significantly higher number of patients in the chemotherapy group (n=17; 36.2%) as compared with that in the crizotinib group (n=2; 10.0%; P<0.05). There was no difference between the pleural lesion progression in the crizotinib group (n=4; 20%) and the chemotherapy group (n=13; 27.7%; P=0.760). In addition, there was no significant difference in the OS between patients who received crizotinib and those who received chemotherapy in the first-line setting (P=0.802; Fig. 1B).

Survival of patients following the first progression. Table III presents the treatment patterns of the 83 patients. Of the 50 patients receiving chemotherapy as the initial therapy, 47 experienced disease progression until the final follow-up. Among them, crizotinib was administered as second-line therapy in 22 (46.8%) cases, the chemotherapy regimen was changed in 19 (40.4%) cases, and 6 (12.8%) patients did not receive any other therapy beyond the first progression. The median PFS2 was 16.4 months (95% CI, 6.4-26.4 months) among patients in the crizotinib group, as compared with 3.5 months (95% CI, 1.0-6.1 months) among patients in the chemotherapy group (P<0.001) and 3.2 months (95% CI, 1.0-5.3 months) among patients in the first-line treatment only group (P=0.001; Fig. 2).

Of the 33 patients receiving crizotinib as the initial therapy, 20 experienced disease progression until the final follow-up. Among them, treatment was changed to chemotherapy in 6 (30.0%) cases, crizotinib treatment was continued along with local radiotherapy in 13 (65%) cases and 1 (5%) case did not receive any other therapy beyond the first progression. Of the 13 patients continued on crizotinib and receiving local radiotherapy, the median follow-up time beyond the first progression was 42.7 weeks (95% CI, 0.6-122.1 weeks). Until the last follow up, the median PFS2 of these patients had not been reached.

Survival of crizotinib patients. At the last follow up, 71 (85.5%) patients had received crizotinib, and 12 (14.5%) patients were crizotinib naive. Of the 71 patients receiving crizotinib, 33 (46.5%) received this therapy in the first-line setting, 22 (31%) received this in the second-line setting, and 16 (22.5%) received crizotinib in the third-line or further

Table I. Patient characteristics.

Characteristic	Value (%)
Sex, n	
Female	47 (56.6)
Male	36 (43.4)
Age, years	
Median	50
Range	23-79
Histological type, n	
Adenocarcinoma	77 (92.8)
Squamous cell carcinoma	3 (3.6)
Adenosquamous carcinoma	3 (3.6)
Stage[a]	
IIIB	7 (8.4)
IV	76 (91.6)
Smoking history, n	
Yes	32 (38.6)
No	51 (61.4)
Intrapulmonary metastasis, n	
Yes	29 (34.9)
No	54 (65.1)
Intracranial metastasis, n	
Yes	9 (10.8)
No	74 (89.2)
Liver metastasis, n	
Yes	17 (20.5)
No	66 (79.5)
Bone metastasis, n	
Yes	29 (34.9)
No	54 (65.1)
Pleural effusion, n	
Yes	27 (32.5)
No	56 (67.5)

[a]8th edition of American Joint Committee on Cancer Tumor-Node-Metastasis staging system.

Table II. Response to first-line therapy in the included patients.

Parameter	Crizotinib (n=33), n (%)	Chemotherapy (n=50), n (%)	P-value
CR	4 (12.1)	0 (0.0)	0.022
PR	20 (60.6)	19 (38.0)	0.036
SD	6 (18.2)	19 (38.0)	0.045
PD	3 (9.1)	12 (24.0)	0.073
ORR	24 (72.7)	19 (38)	0.003
DCR	30 (90.9)	38 (76)	0.143

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

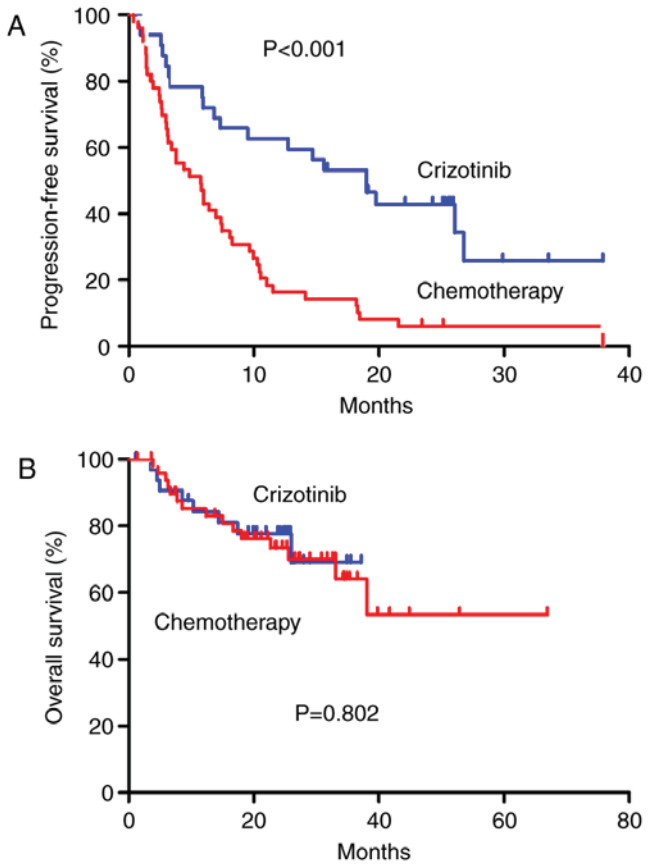

Figure 1. Kaplan-Meier curves of (A) progression-free survival (hazard ratio for progression or mortality in the crizotinib group, 0.345; 95% confidence interval, 0.201-0.594; P<0.001), and (B) overall survival (P=0.802) are presented for the 83 enrolled patients receiving chemotherapy or crizotinib as the first-line treatment.

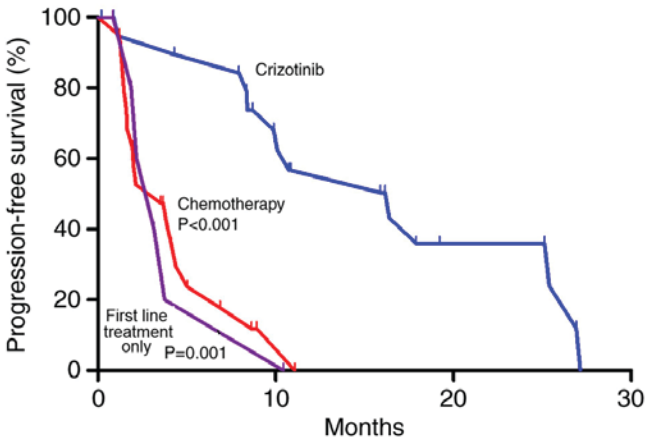

Figure 2. Kaplan-Meier progression-free survival curves are shown for the 47 patients demonstrating disease progression after the initial treatment. Patients subsequently received crizotinib treatment, an alternative chemotherapy regimen (P<0.001) or no second-line treatment (P=0.001).

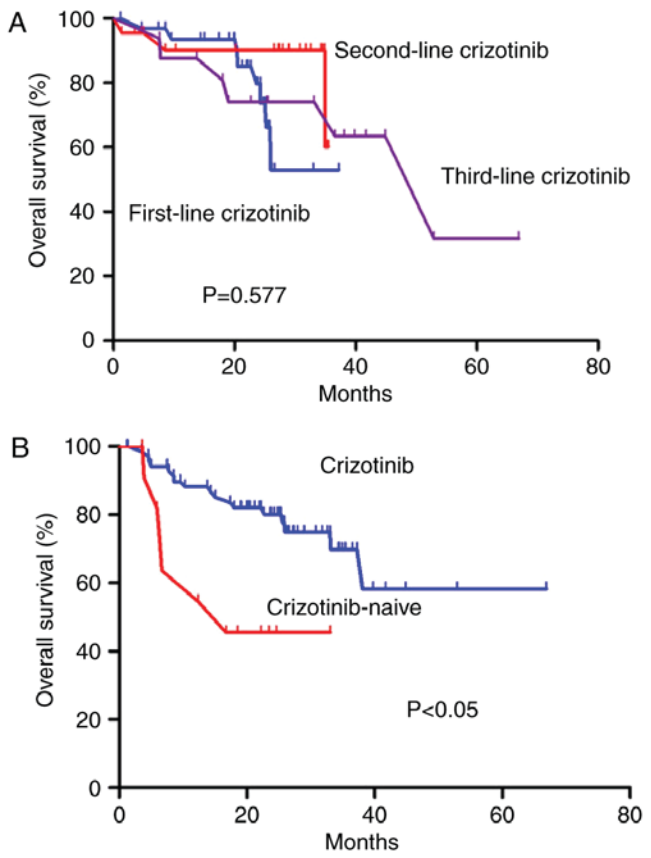

Figure 3. (A) Kaplan-Meier overall survival curves are shown for the 71 patients receiving crizotinib treatment at the first-line, second-line, and third-line or further setting (P=0.577). (B) Kaplan-Meier overall survival curves are shown for the 83 enrolled patients who received crizotinib or were crizotinib-naive (hazard ratio for mortality in the crizotinib group, 0.279; 95% confidence interval, 0.107-0.727; P<0.05).

setting. There was no significant difference in OS among these three groups (P=0.577; Fig. 3A). However, patients receiving crizotinib had an improved OS as compared with patients that were crizotinib-naive (HR, 0.279; 95% CI, 0.107-0.727; P<0.05; Fig. 3B).

Univariate analysis for OS. Factors that were analyzed by univariate analysis are listed in Table IV. The gender (P=0.028), smoking history (P=0.011), liver invasion at diagnosis (P=0.023), bone invasion at diagnosis (P=0.01) and the use of crizotinib (P=0.018) were significantly associated with the OS. However, crizotinib used in the first-line setting, in the second-line setting or after the second-line setting was not associated with the OS.

Multivariate analysis. The Cox multivariate analysis identified the following independent negative prognostic factors for OS: Smoking history (HR=4.565), liver invasion at diagnosis (HR=4.294) and bone invasion at diagnosis (HR=2.587). In addition, the use of crizotinib (HR=0.319) was identified as positive prognostic factor for OS (Table V).

The 2 year OS rate for patients who had never smoked was 85%, with a rate of 54% for those who were former or current smokers. Patients with liver invasion at diagnosis had a 2-year OS rate of 81%, as compared with the rate of 49% for patients with non-liver invasion. Furthermore, patients with bone invasion at diagnosis had a 2-year OS rate of 83%, as compared with the rate of 59% for those with non-bone invasion. Patients who received crizotinib had a 2-year OS rate of 80%, as compared with the rate of 42% for those who were crizotinib-naive.

Table III. Treatment patterns of the 83 patients.

Treatment		Number of patients
First line	Second line	
Crizotinib (n=33)	Crizotinib	13
	Chemotherapy	6
	No treatment	1
Chemotherapy (n=50)	Crizotinib	22
	Chemotherapy	19
	No treatment	6

Table IV. Univariate analysis for overall survival.

Characteristic	HR (95% CI)	P-value
Gender		
Male		
Female	0.391 (0.167-0.915)	0.028
Age (years)		
<50		
≥50		0.529
Stage		
IIIB		
IV		0.931
Smoking history		
No		
Yes	2.957 (1.276-6.855)	0.011
Intrapulmonary metastasis		
Yes		
No		0.666
Intracranial metastasis		
Yes		
No		0.561
Liver metastasis		
No		
Yes	2.934 (1.227-7.018)	0.023
Bone metastasis		
No		
Yes	2.967 (1.299-6.775)	0.010
Pleural effusion		
Yes		
No		0.832
Crizotinib as first-line therapy		
Yes		
No		0.802
Crizotinib as second-line therapy		
Yes		
No		0.138
Crizotinib after second-line therapy		
Yes		
No		0.943
Use of crizotinib		
No		
Yes	0.279 (0.107-0.727)	0.018

HR, hazard ratio; 95% CI, 95% confidence interval.

Discussion

Molecular targeted therapy of advanced NSCLC represents the paradigm of personalized treatment of malignancies. Several druggable cancer driver genes have been identified thus far, with epidermal growth factor receptor mutation and ALK gene rearrangements being the most characteristic features of the disease (15). ALK rearrangements occur in 3-7% of patients with NSCLC. Although the proportion of ALK-positive patients is relatively low, the number of ALK-positive patients in China is anticipated to be significant due to the large population base and the high incidence of lung cancer. In China, crizotinib has been approved as a first-line monotherapy for advanced or metastatic patients with ALK-positive NSCLC, and as a second-line monotherapy for those who have received prior chemotherapy. However, to date, limited data have been published on the treatment patterns and outcomes of Chinese ALK-positive NSCLC patients.

In the current real-world study, the characteristics of patients were consistent with those reported in previous studies (16,17). More specifically, ALK rearrangement occurred in relatively young patients, >50% of the patients had no history of smoking and almost all patients were diagnosed with adenocarcinoma. In addition, bone and pleural metastasis at diagnosis was reported in approximately one third of the patients, while brain metastasis at diagnosis was observed in ~10% of patients in the present study. It has previously been reported that ALK-positive NSCLC does not appear to be associated with an increased risk of brain metastases at the first diagnosis (16). The incidence of intracranial invasion in newly diagnosed ALK-positive advanced NSCLC patients has been demonstrated to range from 20-30%, which was similar to that of non-ALK-positive disease (18,19). In the univariate analysis conducted in the current study, smoking history was associated with worse OS. A study that provided a 50-year perspective on the evolution of smoking-associated risks in the United States has demonstrated that, among patients with lung cancer, smokers had an increased mortality rate as compared with nonsmokers (20). Another study revealed that the rate of mortality from any cause among current smokers was ~3 times that reported among individuals who had never smoked (21).

Although two randomized stage III clinical trials (10,11) have demonstrated a higher ORR and longer PFS of first-line crizotinib treatment when compared with that in patients receiving chemotherapy, more than half (60.2%) of the 83 patients selected chemotherapy as the initial therapy in the present study. The main reason for this phenomenon is the

Table V. Independent prognostic factors as determined by multivariate analysis.

Factor	HR (95% CI)	P-value
Smoking history	4.565 (1.697-12.279)	0.003
Liver metastasis	4.294 (1.489-12.379)	0.007
Bone metastasis	2.587 (1.067-6.275)	0.035
Use of crizotinib	0.319 (0.110-0.928)	0.036

HR, hazard ratio; 95% CI, 95% confidence interval.

fact that crizotinib is not currently included in the medical insurance catalogue in China, leading to certain patients unable to afford such an expensive drug at the beginning of treatment. In the current study, the ORR and PFS1 were also significantly improved in the crizotinib group as compared with the chemotherapy group. Notably, the PFS of patients receiving crizotinib as the initial therapy (median PFS, 18.5 months) was longer compared with the PFS results of the PROFILE 1014 (median PFS, 10.9 months) and PROFILE 1029 (median PFS, 11.1 months) trials. A similar PFS result (median PFS, 17.6 months) was reported in another real-world study from a single center in China (22). In the previous clinical trials (10,11), brain and bone scanning was repeated every 12 weeks to monitor for new lesions in the follow-up schedule. By contrast, in the present study, brain and bone scanning was repeated every 6 months or when associated symptoms appeared in patients without brain or bone metastasis at the baseline assessment. This may have resulted in an artificially prolonged PFS in the crizotinib group since intracranial progression occurred in half of the patients with disease progression. In addition, according to previous studies, different EML4-ALK variants may exhibit a different response to crizotinib, of which the EML4-ALK variant 1 had significantly longer PFS in comparison with other EML4-ALK variants (median, 31.1 vs. 5.7 months, respectively; P=0.003) (23,24). This may be one of the reasons for the PFS difference between the current study and previous clinical trials; however, further investigation is required to test this hypothesis.

The estimation of OS in patients treated with crizotinib has not yet been fully documented. In the present analysis, there was no significant difference in OS between patients receiving crizotinib and those receiving chemotherapy in the first-line setting. Similar results were observed in the PROFILE 1014 and PROFILE 1029 trials comparing crizotinib to pemetrexed-plus-platinum as the first-line therapy, possibly due to a cross-over in the chemotherapy arm. Indeed, in the current study, 38 (76.0%) of the 50 patients receiving chemotherapy as the initial therapy were administered crizotinib as subsequent therapy. In addition, there were no statistically significant difference in the OS among patients using crizotinib in the first-line, second-line and third-line or further setting in the present study. However, patients receiving crizotinib exhibited improved OS in comparison with patients who were crizotinib-naive. A retrospective analysis comparing 30 crizotinib-treated ALK-positive NSCLC patients with 23 crizotinib-naive patients reported similar results, with the patients in the crizotinib group exhibiting a longer OS (25). The current Cox multivariate analysis also identified the use of crizotinib, but not the line of usage as an independent prognostic factor for OS.

Despite a great response rate, the vast majority of patients with ALK-rearranged NSCLC inevitably experienced acquired resistance in ~1 year. The central nervous system (CNS) has been reported to be a frequent site of acquired resistance to crizotinib in patients with ALK-positive NSCLC (26-28). In the present study, cerebral progression occurred in more patients in the crizotinib group (n=10; 50%) in comparison with those in the chemotherapy group (n=4; 8.5%). Consistently, the prevalence of CNS metastases in crizotinib-refractory patients was approximately twice as high as that of crizotinib-naive patients in previous studies (29,30). This phenomenon can be largely attributed to the following two reasons: Firstly, crizotinib is a substrate of P-glycoprotein, a membranous transporter overexpressed in the hematoencephalic barrier and responsible for the efflux of the drug. Low cerebrospinal fluid-to-serum ratios have been reported for crizotinib in the range between 0.06 and 0.26% (31,32). Furthermore, crizotinib extended the patient survival, which to a certain extent may be contributed to the higher incidence of CNS metastases as compared with chemotherapy.

In the current study, of the patients receiving crizotinib as the initial therapy, 20 experienced disease progression, 13 (65%) were continued on crizotinib and received local radiotherapy beyond the first progression. In these 13 patients, the median follow-up time subsequent to the first progression was 42.7 weeks. Until the last follow-up, the median PFS2 of these patients had not been reached. Prior to second-generation ALK inhibitors being available, treatment with crizotinib was often continued beyond disease progression in clinical practice and trials. For instance, in the phase 3 randomized trial PROFILE 1014 (10), 73% of patients with previously untreated ALK-positive NSCLC were continued on crizotinib beyond disease progression for a median of 3.1 months. A retrospective analysis of patients in the PROFILE 1001 and PROFILE 1005 studies revealed that 62% (120/194) of the patients continued crizotinib therapy after the RECIST-defined PD. Among the 120 patients, 51% had brain metastases as the sole site of PD, and the results revealed that this treatment strategy may improve survival (33). The therapeutic strategy of continuing crizotinib beyond disease progression has also been supported by several retrospective studies, in which continued ALK inhibition with crizotinib was associated with clinical benefits and prolonged OS (34-36). In a recently published physician survey and retrospective chart review study in the US, the majority of physicians (75%) would add local therapy and resume crizotinib when a new symptomatic isolated lesion was detected in ALK-positve NSCLC treated with crizotinib (37).

Mechanisms of acquired resistance to crizotinib commonly include secondary mutations within the ALK tyrosine kinase domain. Therefore, during the last decade more potent and structurally different inhibitors have been developed (38,39). Since the development of second-generation ALK-inhibitors, which were demonstrated to be effective in crizotinib-resistant patients, are not available in China, the continuation of crizotinib plus local treatment may be a feasible option to maximize

the overall clinical benefits for patients with local-site progression post crizotinib.

In conclusion, the present real-world study demonstrated that the use of crizotinib improved the long-term survival of advanced NSCLC patients with ALK rearrangement as compared with crizotinib-naive patients. There was no difference in the survival outcome between patients with initial use of crizotinib and those with subsequent use of crizotinib beyond first-line therapy. CNS was a frequent site of acquired resistance to crizotinib, and the continuation of crizotinib plus local treatment may improve the survival. However, head-to-head trials comparing second- or third-generation ALK inhibitors with the continuation of crizotinib beyond progression are necessary to provide the optimum treatment strategy.

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Availability of data and materials

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

Authors' contributions

YJ contributed to the acquisition of data and prepared the manuscript. YC performed the statistical analysis. XY revised the manuscript critically for important intellectual content. XS and XY designed the study.

Ethics approval and consent to participate

All procedures performed in the present study involving human participants were in accordance with the ethical standards of the Research Ethics Committee of Zhejiang Cancer Hospital (Zhejiang, China) and with the 2013 Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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