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RESEARCH PAPER

Oligo-residual disease in metastatic ALK-positive NSCLC treated with alectinib

Xi Yang[1,2,3,4] · Xiao Chu[1,2,3,4] · Ruiting Ye[1,2,3,4] · Jianjiao Ni[1,2,3,4] · Ya Zeng[5] · Yue Zhou[1,2,3,4] · Qing Xia[6] · Shengping Wang[2,7] · Qiao Li[2,7] · Shuai Liu[2,8] · Zhengfei Zhu[1,2,3,4] · Li Chu[1,2,3,4]

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Abstract

Accumulating evidence suggests local consolidative therapy may delay resistance and benefit metastatic NSCLC patients with oligo-residual disease (ORD) after effective systemic therapy. However, the incidence and clinical features of ORD in Alectinib-treated metastatic ALK-positive NSCLC remain unclear. We retrospectively reviewed serial scans of metastatic ALK-positive NSCLC patients treated with Alectinib. ORD was defined as the presence of five or fewer residual metastatic lesions (including the primary site) among those developed partial response as the best response after Alectinib treatment. Initial patterns of recurrence were classified as involving only residual-site recurrence (RR), only new-site recurrence (NR), or a combination of both (RNR). Among 128 patients, 62 patients had PR as the best response, among whom 18 (29.0%) had ORD. The median time to tumor volume nadir was 4.9 (range, 1.1–19.2) months and no independent predictor of ORD was found. To date, 50.0% (9/18) patients with ORD developed their initial progressive disease (PD), mostly (5, 55.6%) with only residual sites. Among the 9 PD patients, 6 patients (6/9, 66.7%) with brain lesions at baseline. Half (3/6, 50.0%) were involved in only brain residual sites. Our study found ORD is not rare in Alectinib treated ALK-positive NSCLC, with 55.6% having initial PD at originally involved sites. Similar recurrence pattern is also observed in PD patients with baseline BMs. These findings indicate that residual disease may enable the emergence of acquired resistance in both CNS and other organs, thus supporting potential clinical benefits for LCT in these ORD patients.

Clinical trial number Not applicable.

Highlights

- Oligo-residual disease (ORD) persists despite Alectinib treatment, potentially leading to localized progression at residual disease sites.
- Brain metastases play a key role in localized progression, suggesting the need for targeted intracranial interventions.
- Local consolidative therapy (LCT) offers potential to control residual disease and delay the onset of systemic resistance.

Keywords Non-small cell lung cancer · Anaplastic lymphoma kinase translocations · Targeted therapy · Oligo-residual disease

Introduction

Oncogene-driven cancer is a distinct subtype of non-small cell lung cancer (NSCLC) that responds well to targeted tyrosine kinase inhibitors (TKIs). Anaplastic lymphoma kinase (ALK) rearrangements present in 2–7% of NSCLC patients [1], and several generations of ALK-TKIs have been developed over the past few decades. Alectinib, a second-generation ALK-TKI, has demonstrated significant efficacy in treating ALK-positive NSCLC that has progressed after platinum-based doublet chemotherapy and crizotinib, with improvements in progression-free survival

Xi Yang, Xiao Chu and Ruiting Ye contributed equally to this work.

Extended author information available on the last page of the article

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(PFS) and central nervous system (CNS) objective response rate (ORR) (54.2% vs. 0%) compared to conventional chemotherapy in the ALUR phase III trial [2]. Furthermore, Alectinib has been demonstrated to have superior CNS penetration due to its favorable lipophilicity and molecular structure, allowing it to effectively target CNS metastases, and Alectinib has been shown to be an effective first-line treatment for advanced ALK-positive NSCLC, with prolonged PFS and improved intracranial control compared to crizotinib in clinical trials such as J-ALEX [3], ALEX [4], and ALESIA [5]. These clinical trials have led to the approval of Alectinib as a guideline-recommended treatment for advanced ALK-positive NSCLC. However, the development of acquired resistance remains a significant challenge in achieving long-term tumor control despite the impressive results achieved with Alectinib.

Interestingly, clinical observations on the residual disease and recurrence patterns in metastatic NSCLC with epidermal growth factor receptor (EGFR) mutations treated with EGFR-TKIs indicate that TKI therapy can shift the metastatic balance towards oligometastatic and oligo-progressive disease status [6–9]. Oligo-progressive disease was defined by advancement at a restricted number of sites.

This clinical phenomenon emphasizes the growing importance of local consolidative therapy (LCT), in minimizing or eliminating oligo-residual disease (ORD) on TKI therapy. A previous multi-institutional retrospective study found that LCT could improve PFS for patients with oligo-residual lesions at the time of maximal response to EGFR-TKI [10], which was supported by the prospective ATOM study, in which preemptive local therapy to ORD after EGFR-TKI prolonged PFS for patients with EGFR-mutant NSCLC [11]. Combining Stereotactic Body Radiation Therapy (SBRT) with TKI therapy was found to be potential to improve the survival outcomes of stage IV EGFR-mutant NSCLC [8].

However, the natural history and use of local therapy in the oligo-residual for metastatic ALK-positive NSCLC remains unexplored fields. Knowledge gaps persist regarding the frequency of ORD, patterns of recurrence, and the potential feasibility of LCT in ALK-positive NSCLC treated with Alectinib. Thus, we conducted this retrospective study to provide a detailed analysis of response and ORD of ALK-positive NSCLC patients treated with Alectinib.

Materials and methods

Patients

The medical records of patients diagnosed with metastatic ALK-positive NSCLC and treated with Alectinib at Fudan University Shanghai Cancer Center, Shanghai Jiao Tong University Affiliated Chest Hospital between July 2018 and May 2023 were retrospectively reviewed. Patients who had not received any prior ALK-TKI treatment (first-line Alectinib) or those who had received one or more prior ALK-TKI treatments (posterior-line Alectinib) were included.

All enrolled patients had complete follow-up scans to assess response and recurrence patterns. Baseline brain metastases (BMs) were confirmed through brain magnetic resonance imaging (MRI), and ALK status was evaluated using immunohistochemistry, fluorescence in situ hybridization, or reverse-transcriptase polymerase chain reaction. Electronic medical records were used to extract patient characteristics, including sex, age at diagnosis, TNM stage, organs with metastatic disease, number of metastases, prior systemic therapies. Patients with local therapy after Alectinib treatment were excluded. Data on Alectinib initiation, maximal response to Alectinib, disease progression, last follow-up, and death were collected. The data cutoff date for this study was May 28, 2023 (Fig. 1). Ethical approval was obtained from the institutional ethical committees of Fudan University Shanghai Cancer Center (NO. 1612167-18).

Follow-up and brain metastases response assessment

Follow-up scans were conducted every 6–8 weeks. For patients without baseline brain metastases, brain MRI during the follow-up period were not mandatory unless clinically indicated by the treating physician.

Tumor responses were evaluated by two experienced radiologists using the Response Evaluation Criteria in Solid Tumors version (RECIST version 1.1). RECIST version 1.1 would be modified (m RECIST) in measuring the response of clinically evaluable brain lesions [12], as shown in Fig. 2.

Definition of ORD

We conducted the retrospective evaluation of residual disease on follow-up scans at the point of maximal Alectinib response. Maximal response was defined as the last follow-up scan before achieving target lesion stabilization. As shown in Fig. 2, ORD was defined as residual disease limited to five or fewer residual metastatic lesions (including the primary site) in those who had PR as the best response [13]. For the purposes of this analysis, we considered positive thoracic lymph nodes (including mediastinal, hilar, and supraclavicular nodes) as a single metastatic lesion. Disappeared or resolved lesions, such as pleural or pericardial effusion, were also considered eligible criteria for inclusion after Alectinib. For the patients achieving ORD, initial patterns of recurrence were also analyzed, which classified as

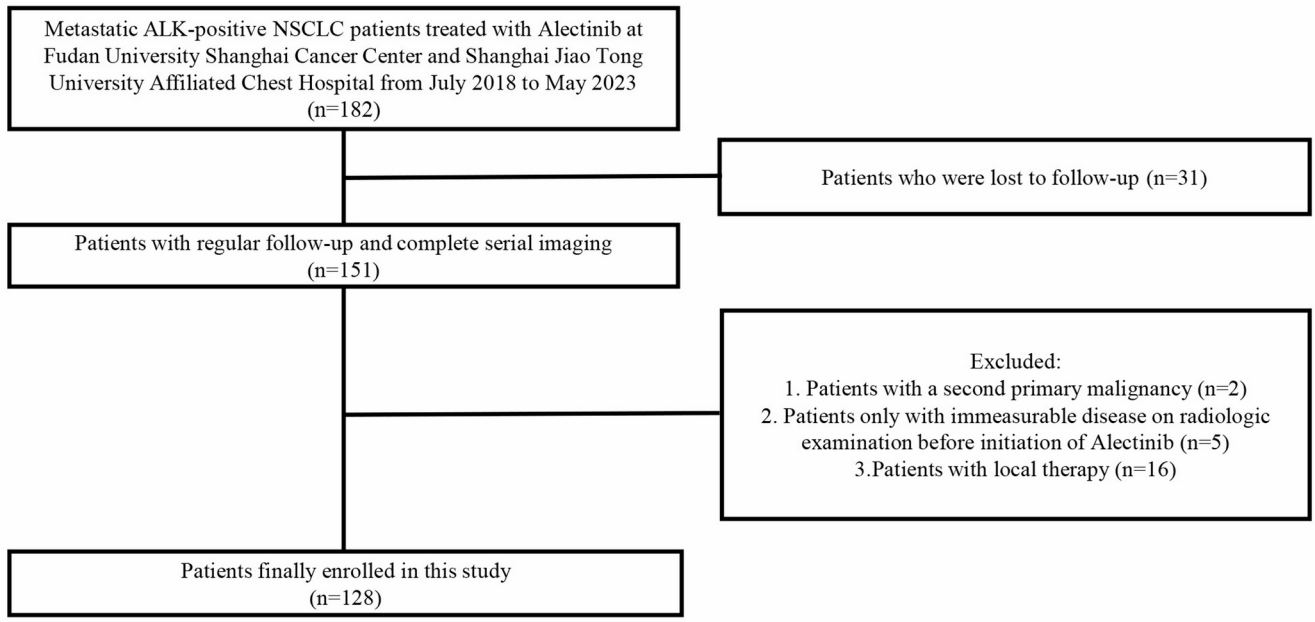

Fig. 1 Diagram of selection process for metastatic ALK-positive NSCLC patients treated with Alectinib. NSCLC, non-small cell lung cancer

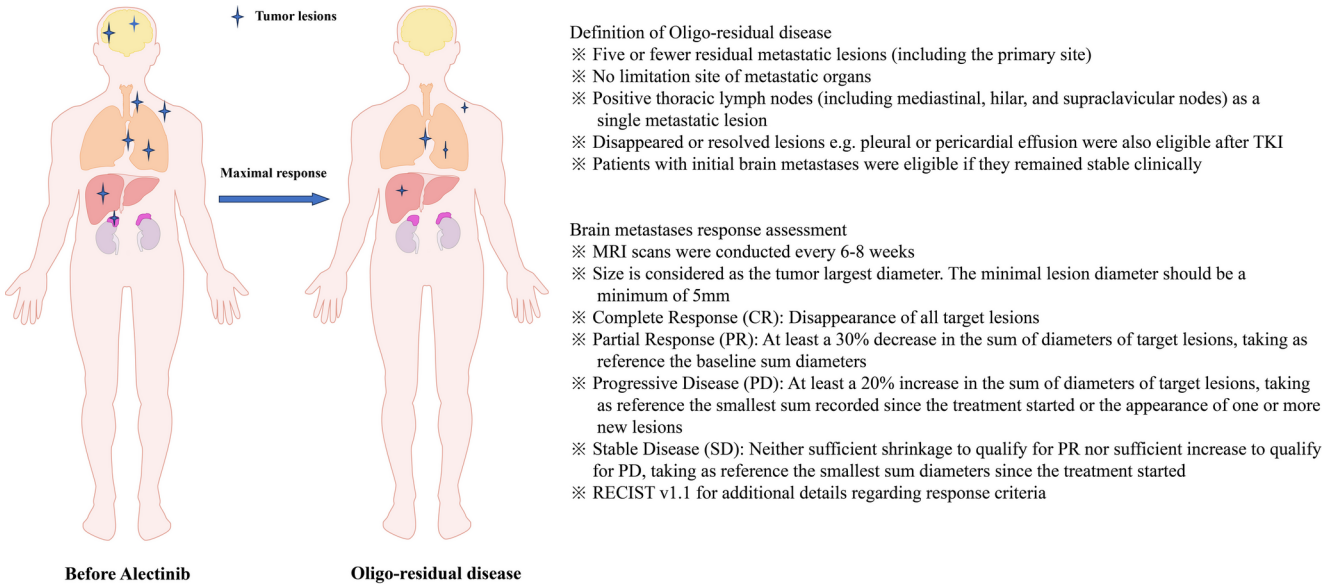

Fig. 2 The criteria and legends for ORD and brain metastases response assessment. MRI, magnetic resonance imaging. TKI, tyrosine kinase inhibitor

involving only residual sites (RR), only new sites (NR), or a combination of both (RNR).

Statistical analysis

The study conducted a frequency analysis of patients' clinical and treatment characteristics. Categorical variables were compared using either the $\chi 2$ test or Fisher's exact test, while continuous variables were compared using either t-tests or Mann-Whitney U tests. PFS was assessed using the Kaplan-Meier method and compared using the log-rank test. Statistical significance was set at a two-sided p-value of less than 0.05. Univariate simple logistic regression analysis was used to examine the association between prognostic factors and cancer metastasis. Factors with a *P* value less than 0.1 were considered to be associated with LCT eligibility and included as candidates for multivariate analysis. Stepwise multiple logistic regression analysis was performed to evaluate meaningful risk factors affecting LCT eligibility. Prognostic factors with *P* value less than

0.05 were considered statistically significant for LCT eligibility. All statistical analyses were performed using SPSS 21.0 (SPSS, Chicago, IL, USA).

Results

Characteristics of the patients and efficacy of alectinib

We identified 128 eligible patients with metastatic ALK-positive NSCLC who were treated with Alectinib at two participating institutions between July 2018 and May 2023 (Fig. 1). Table 1 shows the characteristics of the patients. Alectinib was used as first-line therapy in 77 patients (60.2%), while the remaining 51 patients (39.8%) received posterior-line ALK-TKI treatments. 68 (53.1%) patients had baseline brain metastases (BMs) before initiation of Alectinib, including 19 patients treated with first-line Alectinib and 49 in those receiving posterior-line Alectinib.

With a median follow-up of 23.4 (range, 2.2–72.0) months. of these 128 patients included in the study, 44 patients had the stable disease (SD), disease progression occurred in 7 patients, 15 patients achieved CR, 62 patients achieved PR. Overall response rate was 74.0% (57/77) and 47.1% (24/51) for those receiving first-line and posterior-line Alectinib therapy, respectively. Meanwhile, 68 (53.1%) patients had baseline brain metastases (BMs) before initiation of Alectinib. Intracranial response rate was 84.2% (16/19) and 67.3% (33/49) for those receiving first-line and posterior-line Alectinib therapy, respectively. In the PR patients 29.0% (18/62) presented with ORD at the time of maximal response that was considered potential feasibility to LCT. As Tables 2 and 3 showed, no independent predictor of ORD was found.

Table 1 Baseline characteristics of the 128 patients

Characteristic	Patient number ($n=128$)	Proportion (%)
Gender		
Male	52	40.6%
Female	76	59.4%
Treatment line for Alectinib		
1st line	77	60.2%
2nd or later line	51	39.8%
Metastatic site before Alectinib		
lymph node	96	75.0%
lung	69	54.0%
brain	68	53.1%
bone	53	41.4%
pleura	34	26.6%
liver	17	13.2%
adrenal	6	4.7%
other	8	6.3%
	Range	Median
Age at diagnosis (years)	28–75	49
Time to best response (months)	0.9–18.2	4.83

Patterns of maximal response

Due to the COVID-19 pandemic, some patients underwent examinations at local hospitals during the follow-up period. The assessment selected patients who have been continuously followed up and evaluated on Computed Tomography (CT) and MRI at Fudan University Shanghai Cancer Center or Shanghai Jiao Tong University Affiliated Chest Hospital. We evaluated the changes in size of each evaluable lesion throughout the course of Alectinib treatment and presented spider plots depicting tumor burden changes for intracranial and extracranial lesions ($n=181$), intracranial evaluable lesions ($n=65$) over time (Fig. 3A and B). We also analyzed the alignment of individual evaluable lesion responses with the overall response of each patient. Violin plots of the time to achieve response of individual evaluable lesions in responders (148/181 intracranial and extracranial lesions) were displayed in Fig. 4A, indicating that 51% and 80% of lesions responded within 3 and 6 months, respectively, from the first responding lesion. Moreover, Fig. 4B showed the timing of response of individual intracranial evaluable lesions in CR/PR patients with baseline brain metastases (57/65 intracranial lesions). Specifically, 38% and 68% of brain metastases responded within 3 and 6 months, respectively, from the first responding brain metastasis lesion. The study indicated that the median time to achieve tumor volume nadir and maximal intracranial response to Alectinib was 4.9 months (range, 1.1–19.2 months) and 4.4 months (range, 0.9–21.3 months), respectively. 44 patients reached stable disease (SD), disease progression occurred in 7 patients, 15 patients achieved CR, 62 patients achieved PR. In the PR patients 29.0% (18/62) presented with ORD at the time of maximal response that was considered potential feasibility to LCT.

Patterns of initial recurrence

Our analysis revealed that patients receiving first-line Alectinib had significantly longer PFS compared to those receiving second- or later-line Alectinib (median PFS: NR vs. 16.3 months; hazard ratio: 0.31; 95% confidence interval: 0.17–0.57, $p<0.001$; Fig. 5A). Overall survival data is not yet mature. 18 PR patients (29.0%, 18/62) with ORD were identified at the time of maximal response. 50.0% (9/18) ORD patients developed PD, among those, 55.5% (5/9) patients were involved only in RR. NR, and RNR

Table 2 Baseline characteristics of the 62 partial response patients

	All patients *n* (%)	Patients with ORD* (*n* = 18) *n* (%)	Patients with non-ORD* (*n* = 44) *n* (%)	*P*-value
Age(years)				0.420
Median	54.5	54	54.5	
Range	30–75	39–75	30–72	
Sex				0.377
Male	29(46.8%)	10(55.6%)	19(43.2%)	
Female	33(53.2%)	8(44.4%)	25(56.8%)	
ECOG PS score				0.976
0–1	58(93.5%)	18(100.0%)	40(90.9%)	
2	4(6.5%)	0(0%)	4(9.1%)	
T stage				**0.022**
T0-2	27(43.5%)	12(66.7%)	15(34.1%)	
T3-4	35(56.5%)	6(33.3%)	29(65.9%)	
N stage				0.720
N0-2	22(35.5%)	7(38.9%)	15(34.1%)	
N3	40(64.5%)	11(61.1%)	29(65.9%)	
Number of metastatic lesions				0.204
≤5	30(48.4%)	11(61.1%)	19(43.2%)	
>5	32(51.6%)	7(38.9%)	25(56.8%)	
Number of metastatic organs				**0.018**
1–2	33(53.2%)	14(77.8%)	19(43.2%)	
>2	29(46.8%)	4(22.2%)	25(56.8%)	
Lung metastases				**0.015**
Yes	26(41.9%)	3(16.7%)	23(52.3%)	
No	36(58.1%)	15(83.3%)	21(47.7%)	
Brain metastases				1.000
Yes	29(46.8%)	9(50.0%)	20(45.5%)	
No	33(53.2%)	9(50.0%)	24(54.5%)	
Liver metastase				0.496
Yes	10(16.1%)	2(11.1%)	8(5.9%)	
No	52(83.9%)	16(88.9%)	36(94.1%)	
Bone metastases				0.955
Yes	22(35.5%)	6(13.3%)	16(36.4%)	
No	40(64.5%)	12(86.7%)	28(63.6%)	
Adrenal metastases				0.855
Yes	4(6.5%)	1(5.6%)	3(6.8%)	
No	58(93.5%)	17(94.4%)	41(93.2%)	
Pleural metastasis				0.180
Yes	18(29.0%)	3(16.7%)	15(34.1%)	
No	44(71.0%)	15(83.3%)	29(65.9%)	
Pericardial metastasis				**0.0005**
Yes	2(3.2%)	0(0%)	2(4.5%)	
No	60(96.8%)	18(100%)	42(95.5%)	

***ORD**, Oligo-Residual Disease

were observed in 11.1% (1/9), and 33.3% (3/9) of patients, respectively (Fig. 5B).

Among the ORD PD patients, 66.7% patients (6/9) with brain lesions at baseline. 50.0% (3/6) progressed only in original brain sites, while NR, and RNR were observed in 33.3% (2/6), 16.7% (1/6) of patients, respectively (Fig. 5C).

Discussion

Our Study investigated the persistent residual tumor, which can be the potential guides for additional Local Consolidative Therapy (LCT) for deeper and longer response, because it prevents Complete Response (CR) in the markedly effective Alectinib targeted therapy. The persistent tumor core tends to be the site of subsequent tumor regrowth representing oligoprogressive disease, eventually leading to treatment failure. Two main reasons for proposing this: First, at the time of maximal response, the tumor burden is lowest, and local therapy delivered to the residual disease at this time point has the potential to achieve potent treatment efficacy with minimal toxicities. Second, TKI therapy may ultimately fail due to TKI-resistant clones in residual tumor sites [6].

There is growing evidence suggests that LCT may improve survival rates in patients with oligo-residual disease (ORD) following systemic therapy [10]. The concept of "oligo- disease state" could be applied to patients with metastatic NSCLC undergoing first-line TKI treatment, which was generally a more homogeneous population than those advanced NSCLC patients with distinct genetic backgrounds and different treatment regimens [14–16]. On Osimertinib-treated patients, our previous retrospective analysis with ORD found that LCT was associated with improved PFS [10]. Consistent findings have also been observed in several prospective trials, such as the phase II trial by Gomez et al., which showed a significant improvement in PFS for patients who received LCT after front-line systemic therapy, compared to those in the maintenance group. The study showed EGFR/EML4-ALK status was correlated with a reduced risk of death. Considering the small size of patient cohort (only 2 EML4-ALK positive patients), additional exploratory assessments with EGFR/EML4-ALK status were not considered [15]. The use of LCT in ALK-positive patients treated with ALK-TKIs remains rarely explored.

To the best of our knowledge, this is the first retrospective study to provide a comprehensive analysis of response and oligo-residual lesions patterns in metastatic ALK-positive NSCLC patients treated with Alectinib. The findings from this study may inform the design of future prospective trials investigating the potential feasibility of LCT to oligo-residual tumor sites at the time of maximal Alectinib

Table 3 Results of univariate and multivariate logistic regression analysis for predictors of ORD

	Univariate Analysis			Multivariate Analysis		
	OR	95%CI	*P*	OR	95%CI	*P*
Age(≤54y vs.>54y)	1.637	0.495–5.416	0.420			
Sex (male vs. female)	1.645	0.545–4.964	0.377			
ECOG (0–1 vs. 2)	>999.999	<0.001,>999.999	0.976			
T stage (T1-2 vs. T3-4)	3.867	1.210-12.352	**0.022**	2.369	0.623-9.000	0.206
N stage (N0 vs. N1-3)	1.230	0.396–3.825	0.720			
Number of metastatic lesions (≤5 vs.>5)	2.068	0.675–6.336	0.204			
Number of metastatic organs (1–2 vs.>2)	4.605	1.305–16.253	**0.018**	3.177	0.817–12.362	0.095
Lung metastases (No vs. Yes)	0.183	0.046–0.721	**0.015**	0.378	0.078–1.824	0.226
Brain metastases (No vs. Yes)	1.000	0.334–2.994	1.000			
Liver metastases (No vs. Yes)	0.563	0.107–2.951	0.496			
Bone metastases (No vs. Yes)	0.967	0.303–3.088	0.955			
Adrenal metastases (No vs. Yes)	0.804	0.078–8.285	0.855			
Pleural metastases (No vs. Yes)	0.387	0.097–1.549	0.180			
Pericardial metastases (No vs. Yes)	<0.001	<0.001->999.999	**0.0005**	<0.001	<0.001->999.999	0.979

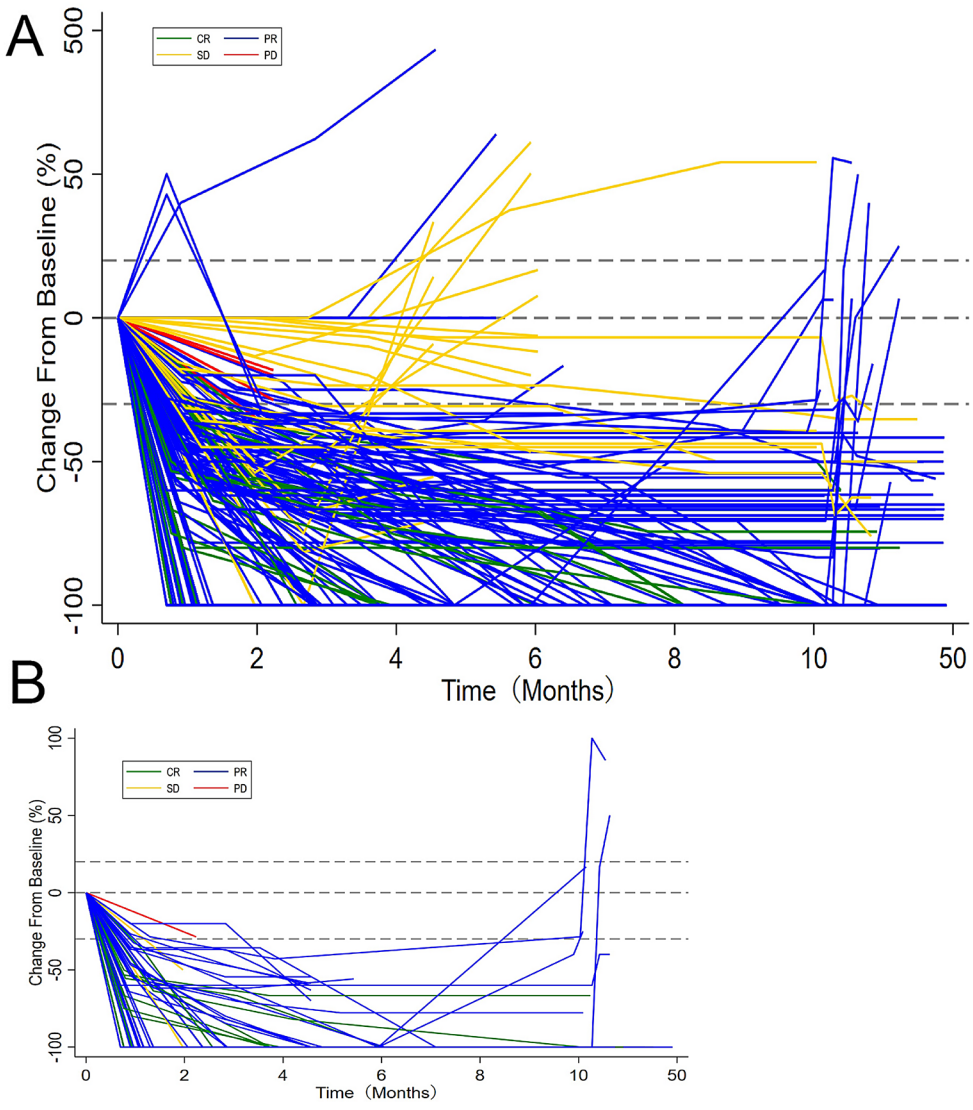

Fig. 3 (**A**) Patterns of response in patients treated with Alectinib. Analysis of changes in tumor burden for all 181 lesions. Tumor burden was considered 0 at baseline, and longitudinal follow-up (x-axis) was captured in percentage of change (y-axis). Complete response (CR; $n=25$), partial response (PR; $n=123$), stable disease (SD; $n=28$), progression of the disease (PD; $n=5$) as their best overall response per RECIST. The time to tumor volume nadir was 4.9 months (range, 1.1-19.2months). (**B**) Analysis of changes in the tumor burden of 65 brain lesions. Complete response (CR; $n=14$), partial response (PR; $n=43$), stable disease (SD; $n=6$), progression of the disease (PD; $n=2$) as their best overall response per mRECIST. The time to nadir in intracranial targets was 4.4 months (range, 0.9–21.3 months)

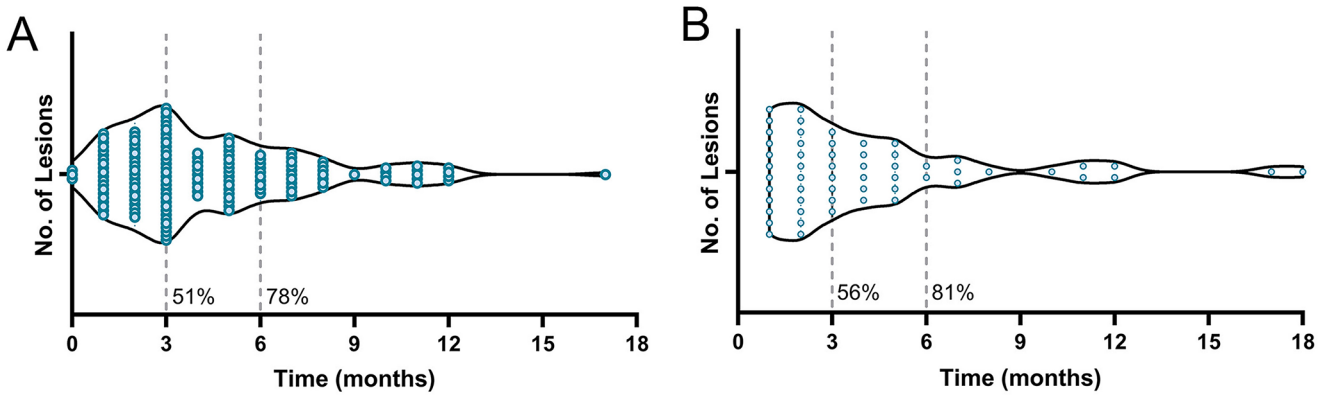

Fig. 4 Violin plots of the timing of response of individual lesions in patients that achieve CR or PR per RECIST or mRECIST. The first time at least one target lesion responded (>30% response) was considered 0; then other target lesions were assessed for relative timing of initial response on the same or subsequent scans. (**A**) Time to achieve response in 148/181 lesions from CR/PR patients patients, indicating that 51% and 80% of lesions ($n=148$) responded within 3 and 6 months, respectively, from the first responding lesion. (**B**) The timing of response of individual intracranial evaluable lesions in CR/PR patients patients with baseline brain metastases. Specifically, 38% and 68% of brain metastases responded within 3 and 6 months, respectively, from the first responding brain metastasis lesion ($n=57$). RECIST, Response Evaluation Criteria in Solid Tumors version; mRECIST, Modified Response Evaluation Criteria in Solid Tumors version

Fig. 5 (**A**) The progression-free survival (PFS) of first-line Alectinib and posterior-line Alectinib (NR vs. 16.3 months, $p<0.001$). (**B**) 50.0% (9/18) consolidative LCT eligible patients developed PD. RR, NR, and RNR were observed in 55.6% (5/9), 33.3% (3/9), and 11.1% (1/9) of patients, respectively. (**C**) 66.7% patients (6/9) with brain lesions at baseline among the PD patients. 33.3% (2/6) with only intracranial oligo-progression. NR, and RNR were observed in 50.0% (3/6), 16.7% (1/6) of patients, respectively. RR, only residual sites; NR, only new sites; RNR, a combination of both. BM, brain metastases

response. The 55.6% of oligo-residual patients with ALK-positive NSCLC treated with Alectinib experienced recurrence within the residual disease at originally involved sites, indicating that residual disease may enable the emergence of acquired resistance. The Prospective study about the value of LCT in ALK-positive NSCLC with ORD was warranted.

In the CNS, Alectinib has demonstrated impressive intracranial activity in patients with ALK-positive NSCLC, with encouraging response rates and protective effects [2–5]. Previous retrospective studies investigating the combination of upfront cranial radiotherapy and TKIs in patients with EGFR-mutant NSCLC support this notion, suggesting that combining EGFR-TKIs with upfront cranial radiotherapy may provide additional survival benefits, particularly in subsets of patients with favorable intracranial oligometastatic tumor burden [17–21]. The secondary analysis of the phase III ALEX study found that patients with baseline BMs and prior radiotherapy had a lower 12-month cumulative incidence of CNS progression compared to those without prior radiotherapy [22]. Preliminary findings suggest that the addition of cranial radiotherapy to Alectinib treatment may result in superior intracranial control compared to Alectinib alone. Administering upfront cranial radiotherapy before disease progression occurs could potentially delay the time to intracranial progression and improve overall survival outcomes.

Our study also revealed a high CNS-ORR for both first-line Alectinib and posterior-line Alectinib treating brain-metastatic ALK-positive NSCLC patients. Among PD patients with baseline BMs, half was involved in only brain residual sites. This raised important questions regarding the use of cranial radiotherapy in patients with brain-metastatic ALK-positive NSCLC who are being treated with Alectinib. Unfortunately, there is limited data on the use of upfront cranial radiotherapy in combination with ALK-TKIs for ALK-positive NSCLC. A retrospective study showed that administering upfront cranial radiotherapy before crizotinib treatment altered recurrence patterns and improved PFS in patients with BMs [18]. Additional clinical studies are

needed to establish the potential benefits of upfront cranial radiotherapy for patients with BMs receiving Alectinib.

Given the limitations of our study, which include its retrospective design and relatively small sample size with non-continuous data. In our study, no patients with ORD have received LCT and without relative overall survival data, our findings should be considered as hypothesis-generating and potential feasibility. Therefore, the potential benefits of LCT in metastatic ALK-positive NSCLC patients treated with Alectinib, and the combination of upfront cranial radiotherapy and Alectinib for ORD patients with baseline BMs, should be evaluated in large-scale and well-controlled prospective trials. Nevertheless, our study still provides valuable insights for future trials in this area.

Conclusions

Our study found that ORD is not rare in ALK-positive NSCLC treated with Alectinib, the 55.6% of whom would have their initial PD developed at originally involved sites. Similar recurrence pattern is also observed in PD patients with baseline BMs, in which half of them progressed only in original brain sites. These findings indicate that residual disease may enable the emergence of acquired resistance in both CNS and other organs, thus supporting potential clinical benefits for LCT in these ORD patients.

Author contributions X.Y. and X.C. were responsible for the design of this study and finished the work of revising the paper. R.Y. and J.N. were responsible for the data collection and completed the first draft. Y.Z. and Y.Z. and Q.X. collected and analyzed the data and and revised the manuscript. S.W. and Q.L. and S.L. was involved in helping to collect data. Z.Z. and L.C. participated in the design and data analysis of this studyand finished the work of revising the paper..

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate Ethical approval was obtained from the institutional ethical committees of Fudan University Shanghai Cancer Center (NO. 1612167-18). The study was conducted according to the principles of the Declaration of Helsinki.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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Authors and Affiliations

Xi Yang[1,2,3,4] · Xiao Chu[1,2,3,4] · Ruiting Ye[1,2,3,4] · Jianjiao Ni[1,2,3,4] · Ya Zeng[5] · Yue Zhou[1,2,3,4] · Qing Xia[6] · Shengping Wang[2,7] · Qiao Li[2,7] · Shuai Liu[2,8] · Zhengfei Zhu[1,2,3,4] · Li Chu[1,2,3,4]

✉ Zhengfei Zhu
fusczzf@163.com

✉ Li Chu
fdcl@fudan.edu.cn

[1] Department of Radiation Oncology, Fudan University Shanghai Cancer Center, 270 Dong An Road, Shanghai 200032, China

[2] Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China

[3] Shanghai Clinical Research Center for Radiation Oncology, Shanghai 200032, China

[4] Shanghai Key Laboratory of Radiation Oncology, Shanghai 200032, China

[5] Department of Radiation Oncology, Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200032, China

[6] Department of Oncology, Shanghai Jiaotong University Renji Hospital, Shanghai 200032, China

[7] Department of Radiology, Fudan University Shanghai Cancer Center, Shanghai 200032, China

[8] Department of Nuclear Medicine, Fudan University Shanghai Cancer Center, Shanghai 200032, China