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Research Article

JOURNAL OF CANCER SCIENCE AND CLINICAL THERAPEUTICS

ISSN: 2637-5079

Other Driver Genes as Resistance Mechanisms of ALK Inhibitors in *ALK*-Rearranged Lung Adenocarcinoma

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Abstract

Introduction: Other dependent driver genes, including *MET*, *EGFR* and *BRAF*, can cause resistance to the first- and second-generation ALK inhibitors. *In vitro* studies have shown that individualized intervention against these resistance pathways may be an optional treatment. We aimed to explore the clinical characteristics of patients with other dependent driver genes as resistance mechanisms to ALK inhibitors.

Methods: We performed next-generation sequencing on tissue and liquid samples obtained at every treatment milestone from three *ALK*-rearranged patients with advanced lung adenocarcinoma receiving targeted therapy. FISH and IHC were underwent in some tissue samples to verify the existence of *ALK* rearrangement and *MET* amplification

Results: Three patients revealed other driver gene alteration after resistance to the first- and second-generation ALK inhibitors (one *BRAF V600E* mutation, one *EGFR L858R* mutation and one *MET* amplification). Combination targeted therapy could overcome the resistance of acquired other driver gene alteration. When *BRAF V600E*, *EGFR* mutations and *MET* amplification occurred as resistance mechanisms of ALK inhibitors, they performed gene heterogeneity. Pleural effusion only revealed *BRAF V600E* mutation in Patient 1 and *EGFR L858R* mutation only showed up in cerebrospinal fluid and peripheral blood by NGS in Patient 2. *MET* amplification individually occurred in adrenal gland in Patient 3.

Conclusions: *BRAF V600E*, *EGFR* mutations and *MET* amplification could be served as resistance mechanisms of targeted therapy in *ALK*-rearranged lung adenocarcinoma. Dabrafenib and trametinib might overcome such resistance in acquired *BRAF V600E*-mutant patients. Other driver genes as resistance mechanisms of ALK inhibitors may have heterogeneity

Keywords: lung Cancer; *ALK* Rearrangement; ALK TKI; ALK-TKI Resistance

Introduction

Lung cancer is one of the most commonly diagnosed cancer and the leading cause of cancer-related deaths [1]. Rearrangement of the anaplastic lymphoma kinase (*ALK*) occur in 2-7% of lung adenocarcinoma and response to ALK inhibitors [2]. The first- and second-generation ALK inhibitor crizotinib and alectinib are recommended as fist-line treatment for *ALK*-positive advanced non-small-cell lung cancer (NSCLC), as it significantly prolonged the median progression-free survival (PFS) to 10.9 and 34.8 months, respectively [3-5]. And lorlatinib, considered as a third-generation

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Citation: Xiao-Cheng Lin, Qian-Yu Wang, Xu-Hui Guan, Yu-Fa Li, Hai-Yan Tu, Hua-Jun Chen, Jin-Ji Yang. Other Driver Genes as Resistance Mechanisms of ALK Inhibitors in ALK-Rearranged Lung Adenocarcinoma. Journal of Cancer Science and Clinical Therapeutics. 8 (2024): 70-79.

Received: August 31, 2023
Accepted: September 21, 2023
Published: January 12, 2024

Lin X, et al., J Cancer Sci Clin Ther 2024
DOI:10.26502/jcsct.5079226

TKI targeting *ALK* rearrangement, demonstrated a better efficacy. With a median follow-up time of 36.7 months, the 3-year PFS rate was 63.5% for and the median PFS of lorlatinib still has not been reached [6].

However, the patients who derive benefit initially will eventually develop resistance. Secondary mutations and *ALK* gene amplification are known mechanisms of ALK inhibitors resistance [7-9]. Otherwise, a few reports found that adopting another different driver gene, including *MET, EGFR* and *BRAF*, can also cause ALK-TKIs resistance [10-14]. *In vitro* studies have shown that individualized intervention against these resistance pathways may be optional treatment [13-15]. The treatment strategy and the clinical characteristics for patients after resistance to ALK-TKI was unclear, especially the population with other driver gene alteration as the resistance mechanisms of ALK-TKI.

Therefore, we retrospectively analyzed the clinical characteristics of *ALK* rearrangement patients with another driver gene alteration after resistance to ALK-TKI. We reported the clinical evidence of efficacy generated by a combination of alectinib, dabrafenib and trametinib targeting *ALK* and *BRAF V600E*. And we also reported the first clinical case with acquired *EGFR L858R* mutations after the treatment of alectinib and another special case with *MET* amplification.

Methods and Materials

Patients and data collection

We retrospectively reviewed patients with lung cancer who were diagnosed with *ALK* rearrangement of histological specimens at Guangdong Lung Cancer Institute from January 2018 to December 2020 (Figure 1). Three patients were treated and evaluated at our institute; meanwhile informed consent was used to collect tumor tissue, peripheral blood and cerebrospinal fluid. This study was approved by the institutional review board at the Guangdong Provincial People's Hospital. The follow-up time was from January 1st, 2018 to December 31th, 2022.

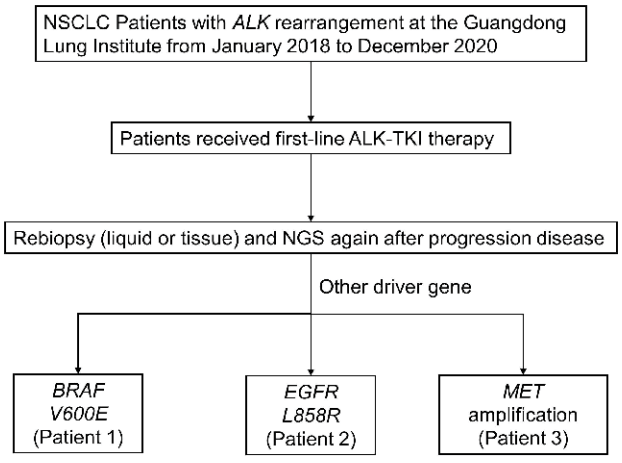

Figure 1: Flow chart of the study.

Abb: NSCLC, non-small cell lung cancer; NGS, next-generation sequencing.

Immunohistochemistry (IHC), Fluorescence in situ hybridization (FISH) and next-generation sequencing (NGS)

ALK rearrangement was performed by IHC using D5F3 (Ventana, Tucson, AZ) and by FISH using Vysis *ALK* Break-Apart FISH Probe (Abbott Molecular, Abbott Park, Illinois, USA) according the manufacturer's instructions, respectively. NGS was performed by a Clinical Laboratory Improvement Amendments (CLIA)-certified testing center (Burning Rock Biotech, Guangzhou, China).

Response evaluation of treatment

Assessments of partial response (PR), stable disease (SD) or progression disease (PD) were according to the efficacy evaluation criteria of solid tumor (RECIST) version 1.1. PFS was defined from the beginning of targeted therapy to the date of tumor progression or the last follow-up.

Results

Characteristics and pathological features of patients

We selected patients with *ALK* rearrangement treated with ALK-TKI in Guangdong Provincial People's Hospital January 2018 to December 2020 and found 3 patients who appear another driver gene alteration after resistance to ALK-TKI (Figure 1). The clinical information is shown in Table 1. All patients (3/3, 100%) are female and never smoked, with a great performance status and low tumor mutation burden. Distant multiple metastasis was found when they were diagnosed or relapsed. The pathology of them was all adenocarcinoma.

Validation of ALK rearrangement and other driver gene

In our study, we performed NGS on tissue and liquid samples obtained at every treatment milestone from three *ALK*-rearranged patients receiving targeted therapy. FISH and IHC were undergone in some tissue samples to verify the existence of *ALK* rearrangement and *MET* amplification (Figure 2).

For patient 1, the tissue of the first lung biopsy performed *ALK* rearrangement positive by IHC, FISH and NGS. The second time lung biopsy showed an acquired *BRAF V600E* mutation was observed by NGS, but *ALK* rearrangement was negative by NGS, FISH or IHC. And the third time lung biopsy identified *ALK* rearrangement again by IHC and FISH, while the NGS analysis of tissue biopsy, peripheral blood, and cerebrospinal fluid re-identified *EML4-ALK* without *BRAF V600E* mutation. About the fourth time biopsy, *ALK* rearrangement disappeared and *BRAF V600E* mutation

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Table 1: Clinicopathologic characteristics of patients.

Patient ID	Age	Gender	Smoking	Pathology	TMN Stage	Metastasis	PD-L1 (%)	TMB
1	74	Female	Never	ADC	cT4N3M1b IVB	pleura, multiple bone	<1%	Low(<10mut/Mb)
2	45	Female	Never	ADC	rT4N0M1b IVA	pleura, meninge	70%	Low(5.0mut/Mb)
3	47	Female	Never	ADC	cT1aN3M1b IVB	adrenal glands, liver, multiple bone, pleural effusion, peritoneal lymph nodes	-	Low(1.6mut/Mb)

ADC, adenocarcinoma; TMB, tumor mutation burden

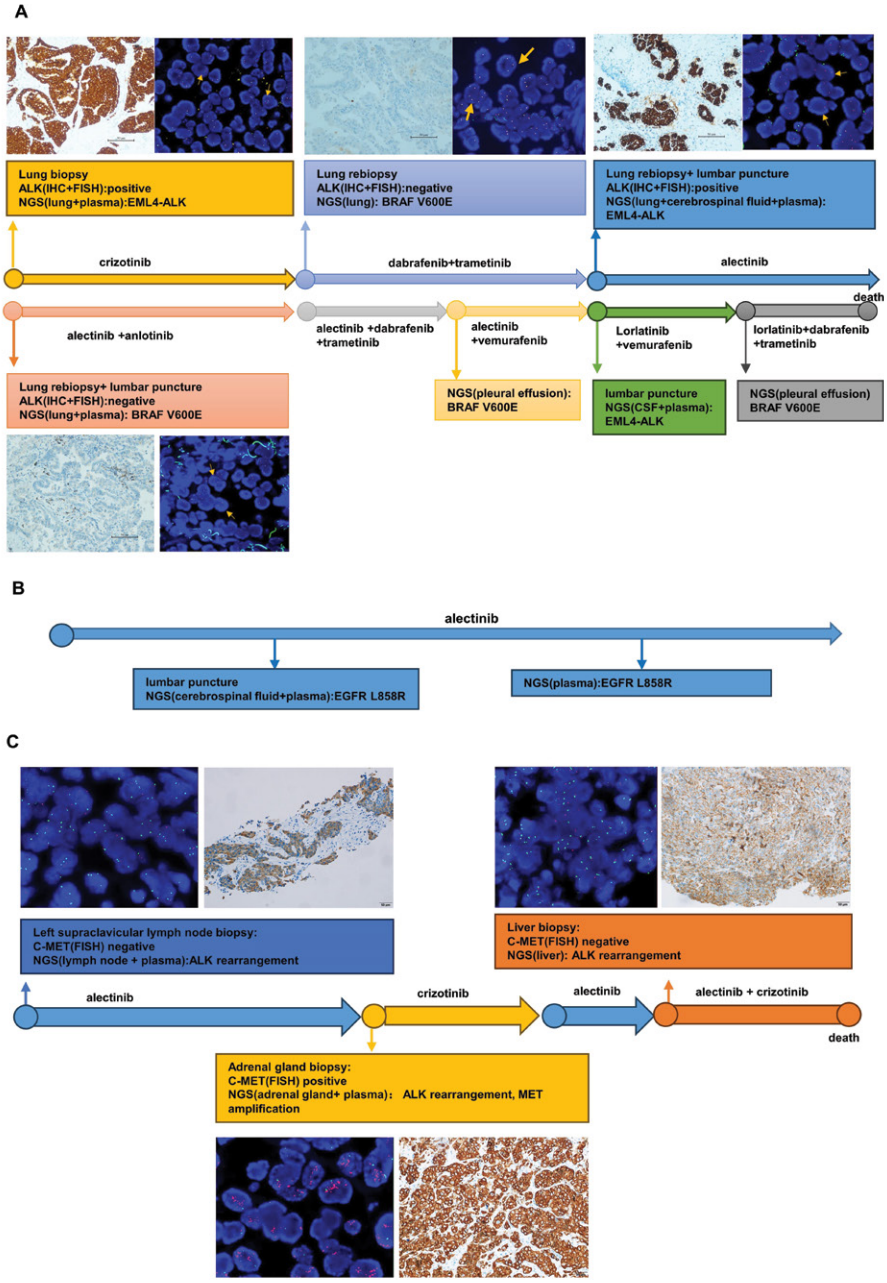

Figure 2: Validation of other driver gene and ALK rearrangement. (A) Treatment line of patient 1 and validation of BRAF V600E and ALK rearrangement by IHC, FISH and NGS. (B) Treatment line of patient 2 and validation of EGFR L858R by NGS of Patient 2. (C) Treatment line of patient 3 and validation of MET amplification by IHC, FISH and NGS of Patient 3. Abb: IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; NGS, next-generation sequencing.

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showed again. Then we found *BRAF V600E* mutation from pleural effusion and *EML4-ALK* from peripheral blood and cerebrospinal fluid by NGS.

For patient 2, after 9 months therapy of alectinib, *EGFR L858R* mutation was found in peripheral blood and cerebrospinal fluid by NGS. Then we found it again in peripheral blood by NGS 4 months later. And it disappeared in next time NGS of peripheral blood. In baseline, Patient 3 showed *MET* amplification negative by IHC and FISH using left supraclavicular lymph node. After resistance to alectinib, IHC, FISH and NGS all validated *MET* amplification positive by adrenal gland tissue. But *MET* amplification negative again in liver tissue in subsequent resistance.

Efficacy of combined targeted therapy after resistance to ALK-TKI

Patient 1 was treated with first-line crizotinib and received PR but brain metastases were found after 8.8 months (Figure 3A). An acquired *BRAF V600E* mutation was observed by NGS, but *ALK* rearrangement was negative by NGS, FISH or IHC. The patient was then switched to the combination therapy of dabrafenib and trametinib for 4.0 months, with the efficacy of SD. NGS analysis of tissue biopsy, peripheral blood, and cerebrospinal fluid re-identified *EML4-ALK* without *BRAF V600E* mutation. She started treatment with alectinib as third-line setting and achieved PR. After a PFS of 13.7 months, CT scan revealed an increase in the size of pulmonary lesions. The lung biopsy was performed again and NGS revealed *BRAF V600E* without *EML4-ALK*. Due to poor performance status, the patient was then received the combination therapy of alectinib and anlotinib before the molecular analysis came out, but progressed in 2.0 months. According to the latest NGS result, the patient was switched to the combination therapy of alectinib, dabrafenib and trametinib, and received PR after one month. However, she suffered from vomiting, nausea, and decreased appetite, therefore she discontinued alectinib from the second month. The patient benefitted from dabrafenib and trametinib about 3 months until the new lesion was found in brain finally. However, the patient refused to receive more biopsy, we recommended intercalated combination of alectinib and dabrafinib plus trametinib according to her previous NGS results. After intercalated therapy, lung lesion enlarged slowly and brain lesion shrank gradually, with the comprehensive evaluation of stable disease. After using combination therapy of alectinib, dabrafenib and trametinib for 19.1 months, she was evaluated as PD again because of the enlarged lung lesion, new pleural effusion and new brain metastases. NGS of pleural effusion and peripheral blood identified *BRAF V600E* mutation without *EML4-ALK*. According to the failure and side effect of dabrafenib and trametinib, she received alectinib and vemurafenib together and the CT scan showed lung lesion shrank obviously after one month of sixth-line treatment. But disease quickly progressed after 2.6 months and she started to take lorlatinib plus vemurafenib on the basis of the NGS result of peripheral blood and cerebrospinal fluid (*EML4-ALK*). Though PR again, pleural effusion became more and NGS showed *BRAF V600E* mutation again and no *EML4-ALK*. After taking lorlatinib, dabrafenib and trametinib about only 0.67 months, patient 1 dead because of the tumor progression (Figure 3B).

Patient 2 underwent radical surgical resection at other hospital and diagnosed with pT1N2M0 stage IIIA adenocarcinoma. Without any adjuvant treatment, after a disease-free survival of 28.0 months, new lesions were found in the left upper lobe, left lower pleura and leptomeningeal metastasis. Thus, she was diagnosed with a recurrence. Then, she underwent the wedge section of left upper lobe and pleural node biopsy and NGS revealed *EML4-ALK*. The patient was treated with alectinib and experienced significant improvement in headache and dizzy. After 8 months of treatment, magnetic resonance (MR) showed enhanced signal at cerebellar vermis. Molecular analysis of cerebrospinal fluid and peripheral blood revealed *EGFR L858R* mutation. However, the patient continued alectinib because she still had clinical benefit. We did lumber puncture again 4 months later, *EGFR L858R* was confirmed in peripheral blood but missed in cerebrospinal fluid. Then she continued alectinib, and new pulmonary nodule was showed in CT after 6 months. Considering the NGS of peripheral blood was negative and the patient was asymptomatic, she continued the treatment of alectinb. The disease was stable until follow-up time (Figure 4A).

Patient 3 was diagnosed with advanced lung cancer, with metastases of adrenal glands, liver, multiple bone, pleural effusion, peritoneal lymph nodes. IHC and FISH of supraclavicular lymph node and NGS of lymph node and peripheral blood all identified *ALK* rearrangement. She received alectinb as first-line treatment with the best therapeutic evaluation of partial response. CT indicated lesion of left adrenal gland enlarged after alectinib therapy for 25.4 months. Then she underwent biopsy of left adrenal gland. NGS of left adrenal gland showed not only *ALK* rearrangement but also *MET* amplification, which was identified again by IHC and FISH. Targeting to *ALK* rearrangement and *MET* amplification, crizotinib was selected as second-line therapy to her. Fortunately, the lesion of left adrenal gland shrank obviously and she obtain PR. About 5 months later, new lesions were found in lung, bones and brain. She underwent lumber puncture and the NGS of cerebrospinal fluid revealed *ALK* rearrangement and *MET* amplification while the peripheral blood just showed *ALK* rearrangement, without *MET* amplification. While waiting for the result of NGS, she refused to take chemotherapy and tried alectinib again. But PD quickly because of the liver lesion. The gene testing of the liver revealed *ALK* rearrangement and *MET* amplification

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DOI:10.26502/jcsct.5079226

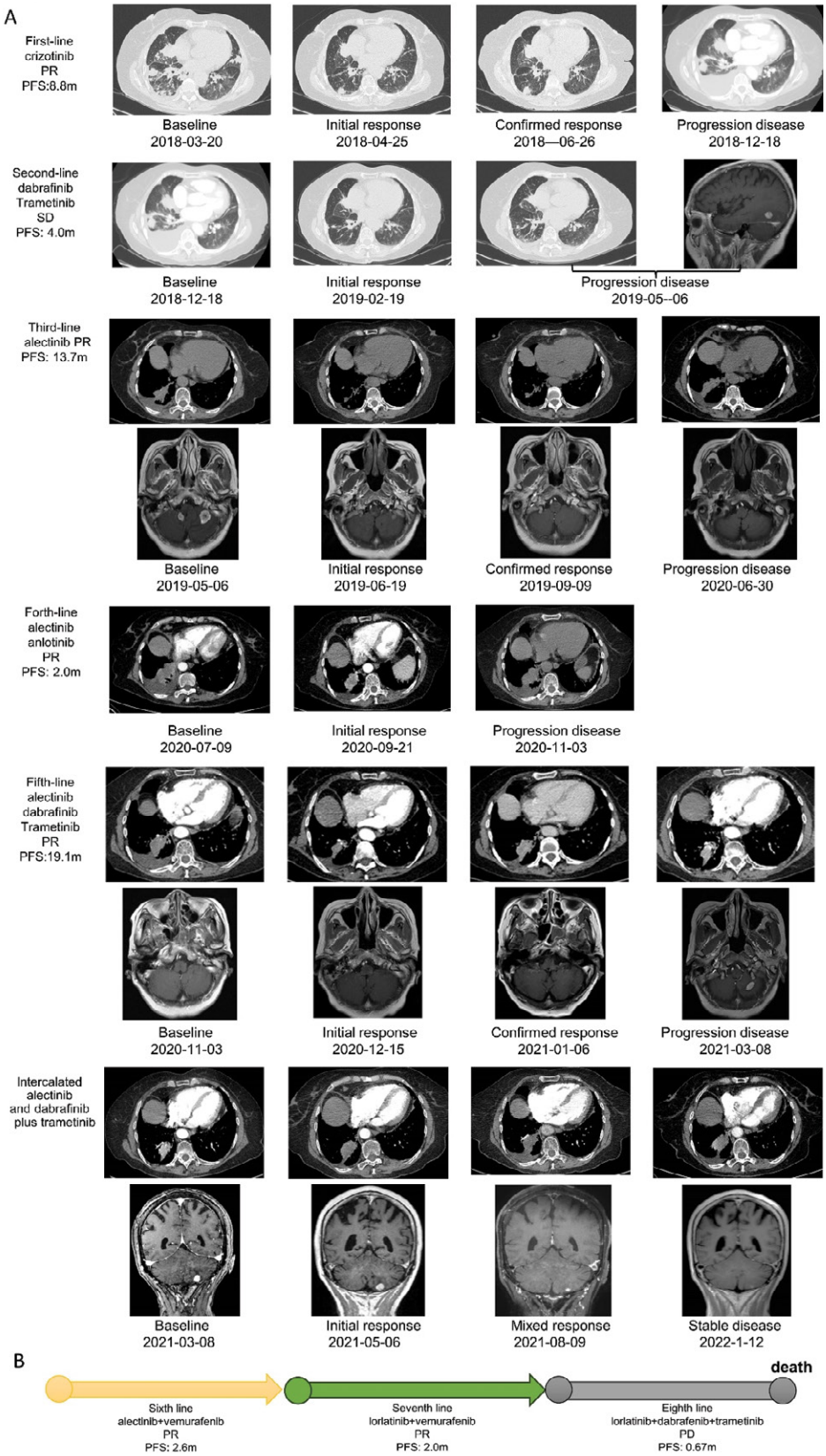

Figure 3: Treatment and efficacy of patient 1. (A) Response evaluation of treatment and radiographic imaging of patient 1. (B) Sixth to eighth line treatment and efficacy of patient 1.

Abb: PR, partial response; SD, stable disease; PD, progression disease; PFS, progression-free survival.

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was disappeared. She received crizotinib plus alectinb as fourth-line therapy but dead 3.8 months later because of the tumor progression. (Figure 4B)

Gene heterogeneity and dynamic changes of gene alteration

In our study, we found some gene heterogeneity and special dynamic changes of gene alteration. The dynamic gene alteration of patient 1 was that *EML4-ALK* and *BRAF V600E* appeared alternately, both in tissue or blood by NGS. (Figure 5A and B) When *EML4-ALK* rearrangement occurred, *BRAF V600E* mutation was disappeared. The same phenomenon showed up when they switched. And for patient 1, the dynamics changes of gene are consistent between tissue and blood. Otherwise, pleural effusion only showed *BRAF V600E* mutation while cerebrospinal fluid was only found *EML4-ALK*. *EGFR L858R* mutation was only occurred in liquid biopsy (peripheral blood and cerebrospinal fluid) but not in tissue for patient 2, which showed a situation of gene heterogeneity. Patient 3 identified *MET* amplification only in adrenal gland, not in lung and liver lesion (Table 2).

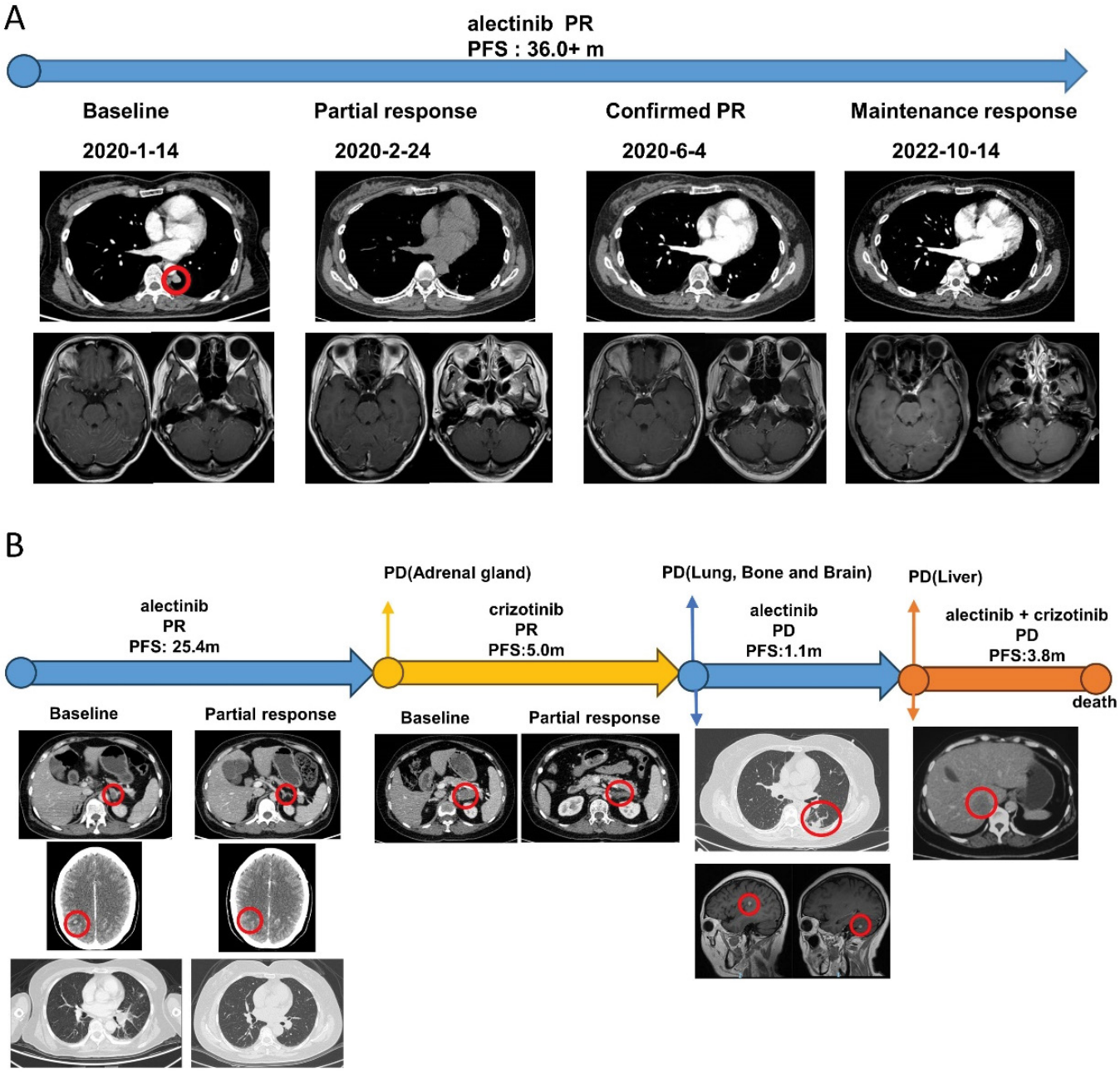

Figure 4: Treatment and efficacy of patient 2 and patient 3. (A) Response evaluation of treatment and radiographic imaging of patient 2. (B) Response evaluation of treatment and radiographic imaging of patient 3. Abb: PR, partial response; PD, progression disease; PFS, progression-free survival.

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Table 2: Dynamic gene testing of patients

NGS Times	Patient 1		Patient 2		Patient 3	
	Gene alteration (Sample)	Frequency	Gene alteration (Sample)	Frequency	Gene alteration (Sample)	Frequency
1	EML4-ALK (T/P)	26.94%/0.92%	EML4-ALK (T)	2.66%	FOXN2-ALK (T/P)	23.06%/16.74%
					SYT16-ALK (T/P)	17.57%/10.34%
					EML4-ALK (T)	3.24%
2	BRAF V600E (T/P)	21.7%/1.70%	EGFR L858R (P/CSF)	0.11%/0.10%	SYT16-ALK (T/P)	24.54%/5.83%
					ALK-intergenic (T/P)	21.97%/6.59%
					EML4-ALK (T/P)	0.59%/8%
					MET amp (T/P)	CN:13.0/3.8
3	EML4-ALK (T/P/CSF)	19.79%/0.02% /20.18%	EGFR L858R (P)	0.29%	SYT16-ALK (P/CSF)	0.19%/2.21%
					ALK-intergenic (CSF)	11.69%
					MET amp (CSF)	CN:3
4	BRAF V600E (T/P)	19.00%/1.14%	Negative (P)	-	EML4-ALK (T)	1.44%
					ALK-intergenic (T)	30.74%
					SYT16-ALK (T)	34.50%
5	Negative (P)	-				
6	BRAF V600E (PE)	16.97%				
7	EML4-ALK (CSF)	41.89%				
8	BRAF V600E (PE)	4.64%				

NGS, next-generation sequencing; T, tissue; P, plasma; CSF, cerebrospinal fluid; PE, pleural effusion; CN, copy number; amp, amplification.

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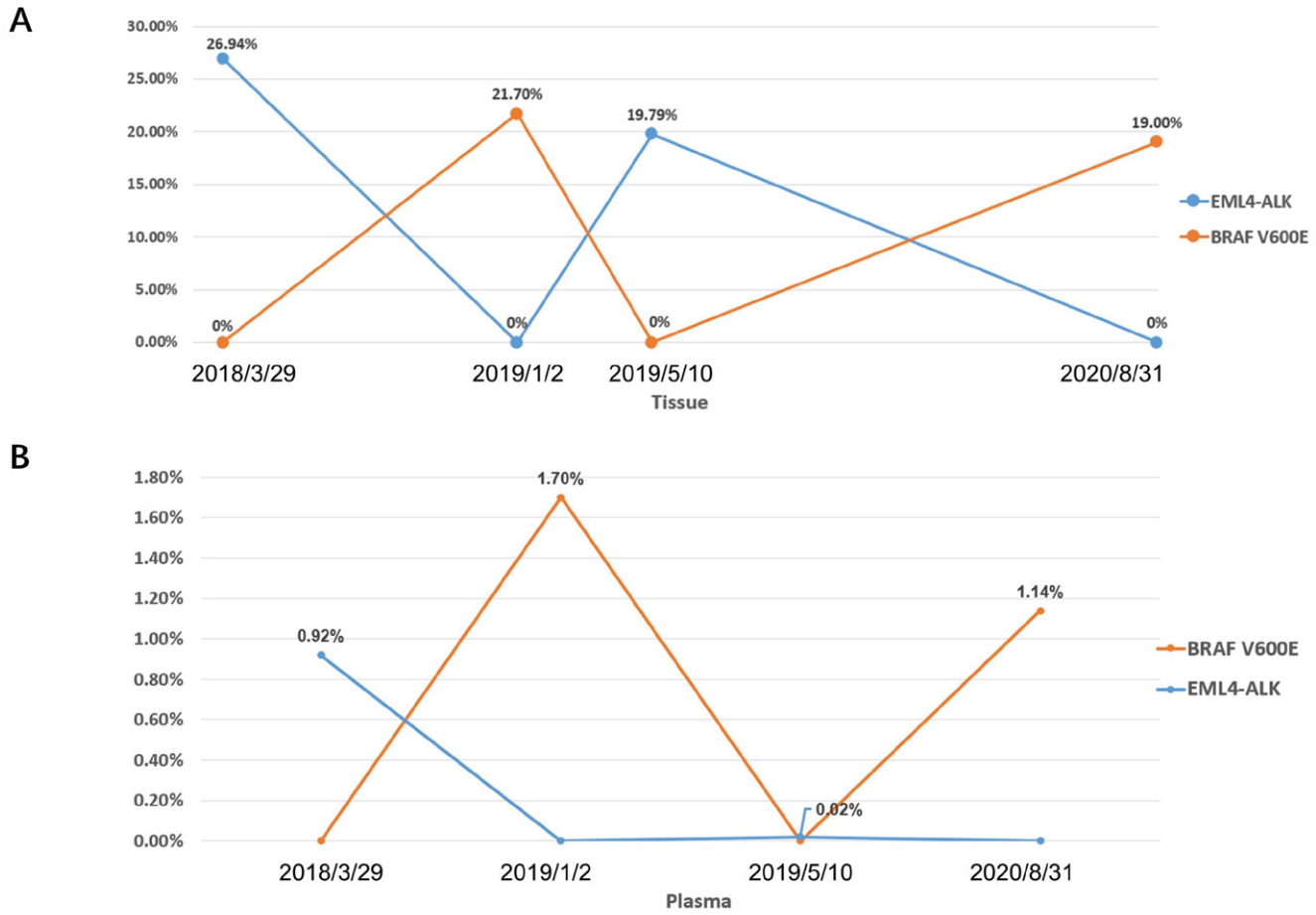

Figure 5: Dynamic changes of genes of patient 1. (A) Dynamic changes of genes in tissue by NGS. (B) Dynamic changes of genes in peripheral blood by NGS.

Discussion

In this study, we confirm that *EML4-ALK* lung cancer acquired resistance to crizotinib and alectinib due to other driver gene activation. We performed molecular analysis on tissue, plasma, pleura effusion or cerebrospinal fluid sample obtained at various treatment milestones of these three *ALK* positive NSCLC. At disease progression after treating with crizotinib or alectinib, our sequencing data revealed *BRAF V600E*, *EGFR L858R* and *MET* amplification in samples of 3 patients respectively.

Mechanisms of resistance to ALK TKI include *ALK* dependent secondary mutations and bypass signaling pathway activation [7]. Previous studies have demonstrated that *BRAF* mutation, including *V600E*, *G15V* and *D587A* mutations, could be a resistance mechanism in *ALK* positive NSCLC [7, 13]. It has been reported that acquired *BRAF V600E in vitro* responded to the triple combination of alectinib/dabrafenib/trametinib. A few cases have been reported in previous studies that *BRAF V600E* mutation was showed after resistance to ALK-TKI [16, 17]. But these cases do not try the combined targeted therapy clinically. In our study, although no *ALK* mutation was detected after resistance to alectinib, the patient 1 continued alectinib in combination of dabrafenib and trametinib due to the efficacy of alectinib in central nervous system. Our case suggests triple combination might be an optional treatment of post-alectinib *ALK* positive patient with acquired *BRAF V600E* mutation, but the side effect should be paid more attention. Further investigations are needed to study the efficacy and safety of combination therapy.

Additionally, *EGFR* pathway activation also have been reported as a mechanism of resistance to ALK-TKI[12]. Sachiko et al. suggested that osimertinib combined with alectinib may be suitable treatment for post-alectinib patients with acquired *EGFR* mutation in cell experiment [12]. Otherwise, previous study indicated that *EGFR 19del* mutation was one of the resistance mechanisms to ALK-TKI [18, 19], and it seems not play the leading role. In our study, we first reported a case that *EGFR L858R* mutation showed up after resistance to ALK-TKI. Patient 2 had detectable *EGFR L858R* mutation by NGS after enhanced signal showed at cerebellar vermis.

We also found that other driver genes as resistance mechanisms of ALK inhibitors may have heterogeneity. Pleural effusion only showed *BRAF V600E* mutation while cerebrospinal fluid was only found *EML4-ALK* in Patient 1. *EGFR L858R* mutation was only occurred in liquid biopsy (peripheral blood and cerebrospinal fluid) but not in tissue for patient 2. For Patient 3, *MET* amplification only occurred in adrenal gland, not in lung and liver lesion. This appearance may indicate that when other driver genes mutate after resistance to ALK inhibitors, they may play a secondary role or less and these mutations may only occur in local tissues, showing heterogeneity.

Nevertheless, our study has some limitations. As a single-center retrospective study, there was a recall bias in our study. Limited by the low frequency and sample size, only 3 patients in our study had enough tissue samples to conduct NGS/IHC/FISH, hence, it was difficult to clarify the mechanism of how *BRAF V600E, EGFR L858R* and *MET* amplification affects the resistance to ALK inhibitors. Therefore, further explorations with a larger population to verify our conclusion and identify the main mechanisms from multidimension are warranted.

In a word, resistance to ALK-TKI is inevitable. With further research on the resistance mechanisms, especially other driver genes, the study for follow-up treatment are necessary. We present the first clinical evidence of sequential use of dabrafenib and trametinib in combination with alectinib and report the first clinical case that *EGFR L858R* mutation showed up after resistance to ALK-TKI. Furthermore, we also reveal other driver genes as resistance mechanisms of ALK inhibitors may have heterogeneity.

Acknowledgement

We thanks to all patients and family. We thank the staff at Pulmonary Oncology Division, Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences.

Declaration of Competing Interest

The authors have declared no conflicts of interest.

Funding

This work was supported by National Natural Science Foundation of China [Grant No. 81972164, JJ Yang], Guangdong Provincial Key Lab of Translational Medicine in Lung Cancer (Grant No. 2017B03031412) and High-level Hospital Construction Project [Grant No. DFJH201809, JJ Yang].

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