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CASE REPORT

Combined Lorlatinib, Dabrafenib, and Trametinib Treatment for *ROS1*-Rearranged Advanced Non-Small-Cell Lung Cancer with a Lorlatinib-Induced *BRAF* V600E Mutation: A Case Report

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Background: Lorlatinib has been suggested as the therapeutic option for patients with *ROS1*-rearranged non-small-cell lung cancer (NSCLC) after ROS1 tyrosine kinase inhibitor (TKI) failure. However, the mechanism mediating lorlatinib resistance has not been well elucidated in *ROS1*-rearranged NSCLC. Post- lorlatinib therapeutic options remain scarce.

Case Presentation: Herein, we describe a 31-year-old female patient with stage IVB *ROS1*-rearranged NSCLC. She received 2nd line treatment with crizotinib after chemotherapy failure and achieved a partial response lasting for 15 months. An *NF1* p.G127Ter mutation emerged as a potential crizotinib resistance mechanism. She subsequently received lorlatinib treatment and achieved a progression-free survival (PFS) of seven months. Based on the emergence of a resistant *BRAF* V600E, the patient was switched to a combinatorial targeted therapy with lorlatinib, dabrafenib, and trametinib and attained stable disease. She continued the treatment with a time-to-treatment failure of 5.5 months. The acquisition of *NRAS* p.Q61R and *NTRK* amplification may confer resistance to the combinatorial targeted therapy.

Conclusion: To the best of our knowledge, we reported the first case demonstrating that *BRAF* p.V600E can mediate the lorlatinib resistance in *ROS1*-rearranged NSCLC and the combinational targeted therapy of ROS1 TKI with dabrafenib and trametinib may serve as an efficient therapeutic option for subsequent treatment.

Keywords: NSCLC, *ROS1* rearrangement, *BRAF* V600E, lorlatinib combined with dabrafenib and trametinib, case report

Introduction

The *ROS-1* rearrangement is an oncogenic driver found in 1–2% of non-small-cell lung cancers (NSCLCs). It defines a clinically and molecularly distinct subset of patients. Several tyrosine kinase inhibitors (TKIs), including crizotinib, ceritinib, and entrectinib, have been approved as first-line treatment for advanced *ROS1*-rearranged NSCLC, with the median progressive-free survival (PFS) ranging from 6 to 20 months.[1,2] Lorlatinib is a brain-penetrant TKI targeting both ALK and ROS-1. It shows a response rate of 35–45% and a median PFS of 7.1–8.5 months in metastatic *ROS1*-rearranged NSCLC after ROS1 TKI failure[3,4] and has been suggested as a subsequent treatment.[5] Therapeutic resistance in *ROS1*-rearranged NSCLC has extensively been investigated in the context of crizotinib. Limited studies described both *ROS1*-dependent and independent mechanisms of resistance to lorlatinib.[4,6] Efficient therapeutic options remain lacking for patients upon lorlatinib failure.

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Herein, we describe the first case with metastatic *ROS1*-rearranged NSCLC who acquired *BRAF* V600E upon lorlatinib progression and subsequently received combinatorial treatment with lorlatinib, dabrafenib, and trametinib. We present the following case in accordance with the CARE reporting checklist.

Case Presentation

A 31-year-old female was referred to our hospital in Sep 2018 with a space-occupying mass on the right lung. She had no smoking history or family cancer history. A chest CT scan revealed a lesion (5.55 cm in diameter) on the right upper lobe and enlarged lymph nodes in the pretracheal retrocaval space. A whole-body bone scanning indicated bone metastases. Brain CT and abdomen MRI revealed no sign of metastasis. A CT-guided percutaneous pneumocentesis was performed for histopathological assessment. The patient was diagnosed with stage IVB (cT3N2M1c) adenocarcinoma with bone and lymph node metastases. Genetic tests on *EGFR* mutations and FISH for *ALK* fusion showed negative results. The immunohistochemical assay showed PD-L1 expression of 10% (TPS) (Figure 1A).

In Oct 2018, the patient started 1st-line treatment with pemetrexed combined with cisplatin (AP), lasting for three cycles, and the disease was stable (Figure 1A). The treatment was subsequently switched to AP combined with bevacizumab for four cycles which yielded a partial response (PR) of the lung lesion. The patient then received maintenance treatment with pemetrexed plus bevacizumab and remained on PR until Nov 2019 with a PFS of 12 months. After a new lymph node lesion was noted, a plasma sample was collected and sent for NGS using a 168-gene panel (Burning Rock Biotech, Guangzhou, China). NGS identified a novel fusion *MED13L-ROS1* (Figure 2A) co-occurring with a common *EZR-ROS1* (Table 1). The patient started the treatment with crizotinib (250mg bid) in Dec 2019 and achieved a PR on both lung and lymph node lesions lasting for 15 months. In March 2021, the patient developed a progressive disease (PD) indicated by a new brain metastatic lesion. Radiotherapy was not recommended because of the patient's poor condition and cerebral edema. NGS with her plasma sample showed the retaining of the two *ROS1* fusions, albeit with lower allele frequencies, and the

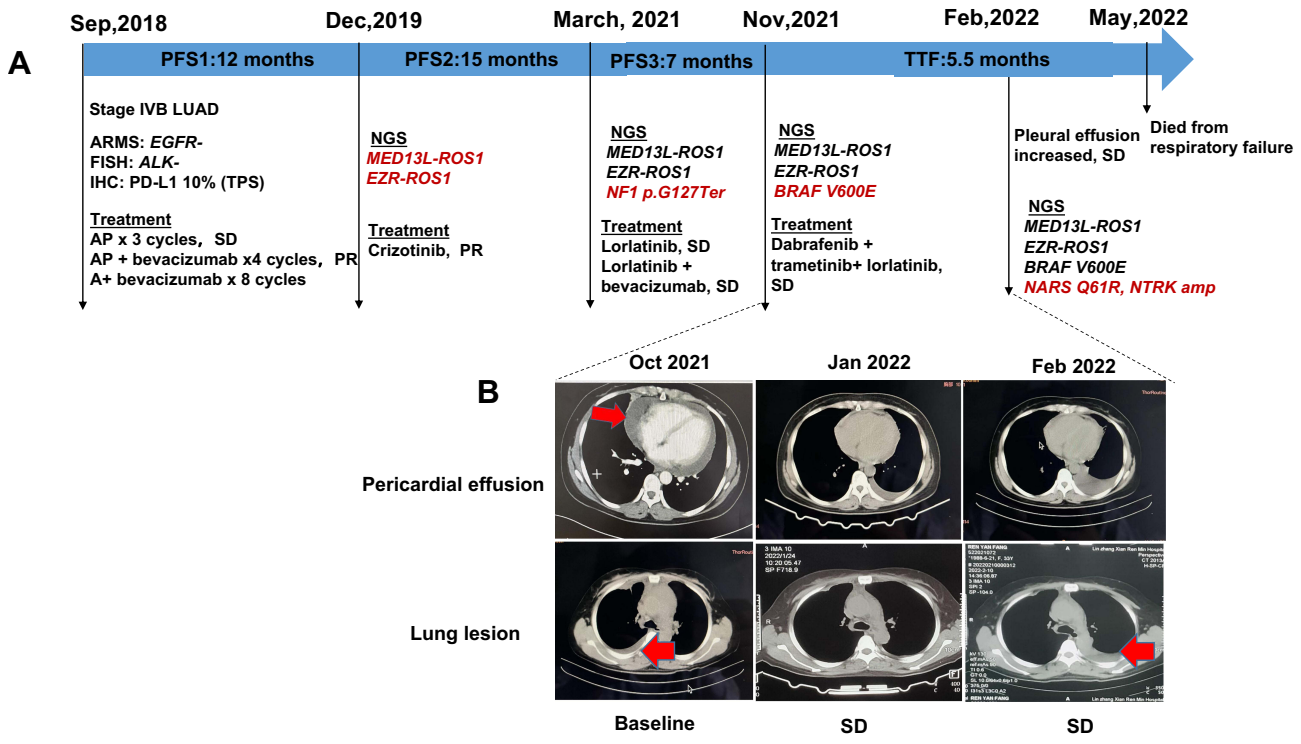

Figure 1 Diagram of patient's treatment history and clinical course. (**A**) Timeline of treatment; (**B**) Change of tumor lesions upon the combined treatment with dabrafenib, trametinib and lorlatinib. The arrow denotes pericardial or pleural effusion; Two months after the treatment beginning, both pericardial and effusions declined; lung lesion remained stable; Three months after the treatment beginning, the arrow denotes the increased pleural effusion, lung lesion remained stable.
Abbreviations: ARMS-PCR, amplification refractory mutation system PCR; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; AP, pemetrexed + cisplatin; PR, partial response; SD, stable disease; PFS, progression-free survival; TTF, time to treatment failure.

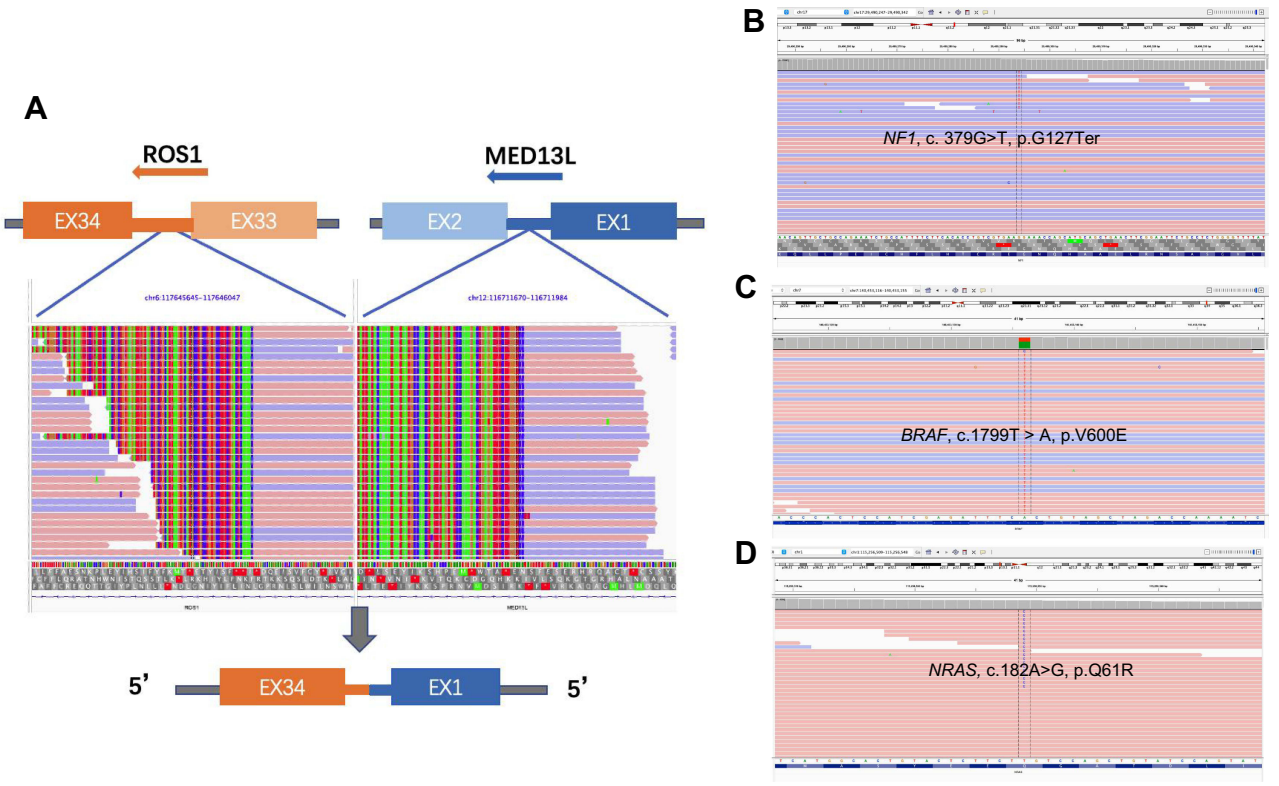

Figure 2 IGV illustration of ROS1 novel fusion and potential drug-resistant mutations. **(A)** *MED13L-ROS1*(M1:R34); **(B)** *NF1* p.G127Ter; **(C)** *BRAF*, c.1799T > A, p.V600E; **(D)** *NRAS*, c.182A>G, p.Q61R.

emergence of *NF1* p.G127Ter (Figure 2B, Table 1). The patient subsequently received 3rd-line treatment with lorlatinib ((100mg qd) and achieved stable disease (SD). In June 2021, the brain lesion enlarged, while the imaging evaluation (RECIST 1.1) indicated SD. The treatment was switched to lorlatinib (100mg qd) combined with bevacizumab (400mg triweekly), and the disease was stable After a PFS of 7 months on 3rd-line treatment, the patient was detected with pericardial and pleural effusions (Figure 1B), and a PD was determined in Oct. 2021. NGS with her pericardial effusion

Table 1 List of Alterations Detected by NGS

Sample Collection Time	**PD on 1st Line (Dec. 2019)**	**PD on 2nd Line (Mar. 2021)**	**PD on 3rd Line (Nov. 2021)**	**4th Line SD (Mar. 2022)**
Sample type	Plasma	Plasma	Pericardial effusion	Pleural effusion
Alterations/Features	**Allele frequency**			
MED13L-ROS1 (M1:R34)	20.51%	4.08%	40.85%	48.46%
EZR-ROS1 (E11:R34)	4.19%	1.23%	14.64%	15.29%
ARID1A c.1921-2A>T	0.69%	/	48.23%	51.58%
NF1 p.G127Ter	/	1.26%	/	/
BRAF p.V600E	/	/	37.27%	29.12%
NFE2L2 p.T80A	/	/	22.40%	34.03%
FGF19 amp	/	/	CN:3.4	/
FGF4 amp	/	/	CN:3.7	/
FGF3 amp	/	/	CN:3.7	/
NRAS p.Q61R	/	/	/	9.16%
NTRK amp	/	/	/	CN:4.2
CDKN2A del	/	/	/	CN:0.9

sample revealed the emergence of *BRAF* p.V600E mutation (Figure 2C), retention of the two *ROS1* fusions, and the disappearance of *NF1* p.G127Ter. Other alterations were also identified, such as amplifications in *FGF19, FGF4*, and *FGF3* (Table 1).

Starting from November 2021, the patients received a combinatorial treatment with lorlatinib (100mg qd), dabrafenib (150mg bid), and trametinib (2mg qd). A CT scan in Jan 2022 showed reduced pericardial and pleural effusions and a stable lung lesion (Figure 1B). In Feb 2022, a repeated CT scan revealed increased pleural effusions and a stable lung lesion. Due to the COVID-19 pandemic, the patient continued receiving the same therapy and undergoing repeated imaging examinations in a local hospital. The primary lung lesion remained stable, but pleural effusion increased repeatedly. The patient underwent pleural puncture and drainage in March 2022, and the pleural effusion sample was sent for NGS. The result showed the acquisition of *NRAS* p.Q61R (Figure 2D), *NTRK* amplification, and *CDKN2A* deletion, as well as the disappearance of *FGF19, FGF4*, and *FGF3* amplifications (Table 1). The patients remained on the combined targeted therapy until April 2022, with a time to treatment failure (TTF) of 5.5 months. On May 2022, she died from respiratory failure, with an overall survival of 44 months.

Discussion

Our case showed the acquisition of *NF1* p.G127Ter upon crizotinib progression and *BRAF* p.V600E after lorlatinib failure through longitudinal tumor genomic profiling. *NF1* alterations were reported in 5/47 crizotinib-resistant *ROS1*-rearranged NSCLCs, while the prior-crizotinib status of these alterations was unknown in these cases.[6] Our finding further supports the crizotinib resistance mechanism mediated by *NF1* alteration. On the other hand, ROS-1 resistance mechanisms have not been thoroughly examined in the context of TKIs other than crizotinib. In 32 post-lorlatinib NSCLCs with *ROS1*-fusion, 46% were identified with a *ROS1* mutation. ROS1-independent alterations were also noted, including *MET* amplification (4%), *KRAS* G12C (4%), *KRAS* amplification (4%), *NRAS* mutation (4%), and *MAP2K1* mutation (4%).[6]

Here, we reported the first case acquiring *BRAF* p.V600E as the mechanism of lorlatinib resistance. She achieved an SD on the post-lorlatinib treatment with lorlatinib, dabrafenib, and trametinib with a TTF of 5.5 months. The combined therapy with dabrafenib and trametinib has been approved for *BRAF* V600E-mutant NSCLC. *BRAF* p.V600E has only been reported to mediate crizotinib resistance in three *ROS1*-rearranged NSCLC cases. One case acquired *BRAF* V600E lost ROS1 fusion after crizotinib failure and achieved a durable PR on the dabrafenib and trametinib combination.[7] The other two cases retained *ROS1* fusion when acquiring *BRAF* V600E. One was subsequently treated with dabrafenib and the other with dabrafenib and trametinib, but both died shortly.[8,9] Our patient also retained *ROS1* fusion after lorlatinib resistance. Our case indicates that combinatorial targeted therapy of ROS1 TKI, dabrafenib, and trametinib may serve as a therapeutic option for NSCLC in the context of *ROS1* fusion and *BRAF* p.V600E. Similarly, Meng et al reported the effectiveness of EGFR TKI combined with dabrafenib and trametinib in an *EGFR*-mutant NSCLC case with an acquired resistance mutation of *BRAF* V600E (10). It should be noted that the lack of regression on the targeted lung lesion may weaken the strength of the effectiveness of the combinatorial treatment in our case. More solid evidence from cohort studies is needed to translate our observation into clinical decision-making.

Another finding was the emergence of *NRAS* p.Q61R and *NTRK* amplification coupled with the increased pleural effusion four months after the combined targeted therapy. The observation suggests the patient required a resistance mediated by the activation of bypass signaling pathways, despite the lung lesion remaining stable.

Conclusions

To the best of our knowledge, we provide the first clinical evidence on the effectiveness of treatment with lorlatinib, dabrafenib, and trametinib in NSCLC harboring *ROS1* fusion and *BRAF* p.V600E. Our case suggests the combinatorial targeted treatment may serve as an efficient therapeutic option for late-line treatment for patients who develop bypass resistance to TKI.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). This study was conducted with Fourth Hospital of Hebei Medical University Research Ethics Board approval ((2021KS005). Written informed consent was obtained from the patient's family for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors have no conflicts of interest to declare for this work.

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