Identification of A Novel *FRK-ROS1* Fusion Variant in Advanced Non-Small Cell Lung Cancer with Brain Metastases and Remarkable Response to Crizotinib

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Research Article

Keywords: non-small cell lung cancer, ROS1, fusion, TKI, crizotinib

Posted Date: October 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-989538/v1

Abstract

ROS1-rearranged non-small cell lung cancer (NSCLC) is a subset of NSCLC patients with unique malignant behavior and clinical course. Crizotinib, a multi-targeted *ALK*/ *ROS1*/ *MET* tyrosine kinase inhibitor (TKI), has promising significant activity in NSCLC with *ROS1*-rearrangement. The next-generation sequencing (NGS) is commonly used to identify the “druggable” genetic alterations in clinical practice. We identified a novel *ROS1* fusion variant (FRK-ROS1) in a de novo stage IV NSCLC patient by NGS testing. This novel *ROS1*-rearrangement is generated by the fusion *FRK* to *ROS1*. The patient was remarkably responsive to crizotinib including the brain metastasis. A 29-year-old male never-smoker with chief complaints of back pain with a lumpy and flaky soft tissue mass in the upper right lobe of the lung and diffuse ground-glass shadow in both lungs e IV ($cT_4N_3M_{1b}$). A CT-guided biopsy revealed the predominant adenocarcinoma and partial mucinous adenocarcinoma. By using next-generation sequencing (NGS) assay, we found that the tumor had *FRK-ROS1* fusion rather than other actionable mutations. In that case, the patient took the first-line crizotinib and experienced a remarkable tumor response to it and tolerance well until written. *FRK-ROS1* is a novel *ROS1* fusion variant in NSCLC identified by NGS testing and the first-line crizotinib showed excellent performance in all lesions including the brain metastasis.

Full Text

Nowadays, *ROS1* rearrangement represented a unique pattern in about 1%-2% of patients with NSCLC [1]. Crizotinib, a tyrosine kinase inhibitor targeting *ROS1*, *ALK*, and *MET*, has become the standard first-line therapy in this population [5]. Other ROS1 targeted drugs are emerging but varying levels of effectiveness, such as entrectinib, lorlatinib, ceritinib, TPX-0005, DS-6051b, and cabozantinib [6–11]. However, brain metastasis has been found not very sensitive to crizotinib treatment probably due to its poor penetration of the blood-brain barrier (BBB) [12–13]. Here, we reported *FRK-ROS1* fusion as a novel *ROS1* fusion variant in non-small lung cancer (NSCLC). Meanwhile, the excellent well-control of all lesions including BM by crizotinib and the response lasted at least 8.0 months in this de novo stage IV NSCLC patient with *ROS1* fusion.

The patient is a 29-year-old male never-smoker with chief complaints of back pain for 3 days and cough for 1 day charged in hospital on Sep 20th, 2019. No family history of cancer or any other special disease has been tract. Physical examination revealed the reduced respiratory sound of the right lung. The levels of serum tumor markers of CEA and NSE were elevated to 25.46 ng/ml and 18.56 ng/ml, respectively. Chest computed tomography (CT) revealed a lumpy and flaky soft tissue mass in the upper right lobe of the lung and diffuse ground-glass shadow in both lungs **(Figure 1A)**. MR-PET found the suspicious pulmonary lesion as above, multiple metastatic lesions in the lungs, and lumbar spine. A CT-guided biopsy revealed the predominant adenocarcinoma and partial mucinous adenocarcinoma **(Figure 2)**. The contrast-enhanced MR images depicted a metastatic lesion in his left frontal lobe. No evidence of the superficial lymphadenopathy or adrenal glands metastasis by ultrasound examination. The primary tumor tissue biopsy has been delivered for NGS testing that the *FRK-ROS1* fusion and abnormal

alterations of *CDKN2A*, *CDKN2B*, and *BCL2L11* were found **(Figure 3)**. The initial diagnosis was stage IV ($cT_4N_3M_{1b}$) NSCLC with multiple metastases in the lungs, brain, lymph nodes, and lumbar spines. This patient was treated with crizotinib (250 mg/twice daily) as first-line therapy from Oct 8th, 2019 until now (July 2020). After administration of crizotinib for 1.0 month, his primary tumor achieved partial response (PR) confirmed by CT scans **(Figure 1B)** according to Response Evaluation Criteria in Solid Tumors (RECIST) standard (version 1.1) [14]. Of note, the BM lesion was also detected remarkably shrink just after 2.0 months of crizotinib treatment and BM is controlled until now without radiation intervention. Meanwhile, he tolerated crizotinib well and no severe adverse event has been reported, including abnormal hepatic and renal dysfunction, visual disorders, gastrointestinal disturbances, cardiac and endocrine abnormalities. Until recently, his disease has no clinical sign of progress and remained as PR for almost 8.0 months and tolerated well with crizotinib as the first-line therapy.

In patients with NSCLC, *ROS1* fusion is featured by mutually exclusive to *ALK*-rearranged and patients tend to be younger, never-smokers, and histology of adenocarcinoma [2]. Identification of the fusion partners to *ROS1* is the key to locating NSCLC patients for effective target therapy. More than 50 fusion partners have been reported for *ROS1* in NSCLC, including *CD74*, *EZR*, *SLC34A2*, *GOPC*, *TMEM106B*, *ADGRG6*, and others [16–18]. The protein encoded by the FRK gene belongs to the tyrosine kinase receptor family of protein kinases which is a nuclear protein [2]. Functionally FRK has played a role as a tumor suppressor by negatively regulating cell proliferation and positively regulating PTEN protein stability [19]. So far, the *FRK-ROS1* fusion has not been reported in NSCLC but as the potential oncogenic activating the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway causing the occurrence of the inflammatory hepatocellular adenomas (IHCAs) [20].

About 60-80% of advanced *ROS1* fusion NSCLC patients respond to crizotinib as the first-line therapy [20], but 23.3% of patients will develop brain metastasis as the most frequent site of initial crizotinib failure [12, 21]. The mechanism of crizotinib resistance in BM is considered as the poor penetration of crizotinib into the central nervous system [13]. By now, some of *ROS1* fusion targeted drugs may have shown intracranial activities, such as entrectinib, lorlatinib, and repotrectinib (TPX-0005) [22]. One recent study compared the crizotinib or pemetrexed-based chemotherapy in ROS1 fusion NSCLC patients with BM and chemotherapy seemed to have better BM control than crizotinib for unknown reason [20]. Active surveillance of brain imaging during crizotinib treatment and exploration of next-generation ROS1 inhibitors featured by higher BBB penetration is warranted.

Altogether, this case provided the clinical evidence for *FRK-ROS1* as a novel *ROS1* fusion variant with a remarkable response to crizotinib in de novo advanced *ROS1* fusion patients with brain metastasis.

Declarations

Acknowledgments We thank Yan-fang Guan from Geneplus-Beijing for his kindly assistance.

Availability of data and material Not applicable.

Authors' contributions Conception/Design: Wen-xian Wang, Chun-wei Xu, Lei Lei.

Provision of study material or patients: Li-xin Wu, Wei-hu Huang, Xiao-jie Chen.

Collection of data: Wei-hu Huang, Xiao-jie Chen.

Data analysis and interpretation: Chun-wei Xu, Wen-xian Wang.

Manuscript writing: Lei Lei, Chun-wei.

Final approval of manuscript: All authors.

Data availability All data generated or analysed during this study are included in this published article.

Code availability Not applicable.

Funding This study was supported in part by grants from the Science and Technology Planning project of Zhejiang Province (LGF19H160002), the Medical Scientific Research Foundation of Zhejiang Province of China (2019RC027), Zhejiang Traditional Chinese Medicine Science Fund Project (2020ZB037), Scientific Research Foundation of Zhejiang Medical Association (2018ZYC-B5, 2019ZYC-A76), Science and Technology Bureau Project of Jiaxing City of Zhejiang Province (2018AD32163), and Xisike-Hanson Cancer Research Foundation (Y-HS2019-20).

Ethics approval and consent to participate All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the patient for participating this case.

Consent to publication Informed consent was obtained from the patient for publication of this case.

Research involving human participants and/or animals YES, Research involving Human Participants. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient for participating and publication of this case.

Competing interests The authors declare that they have no conflict of interest.

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Figures

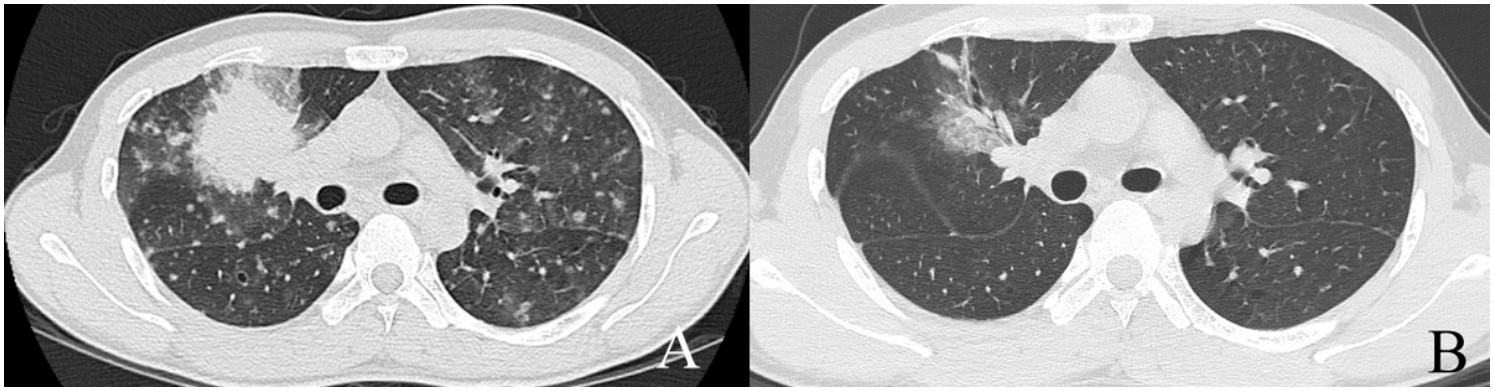

Figure 1

Computed tomography (CT) scans show: before crizotinib therapy (A); CT of the chest showed partial response after one months of crizotinib (B).

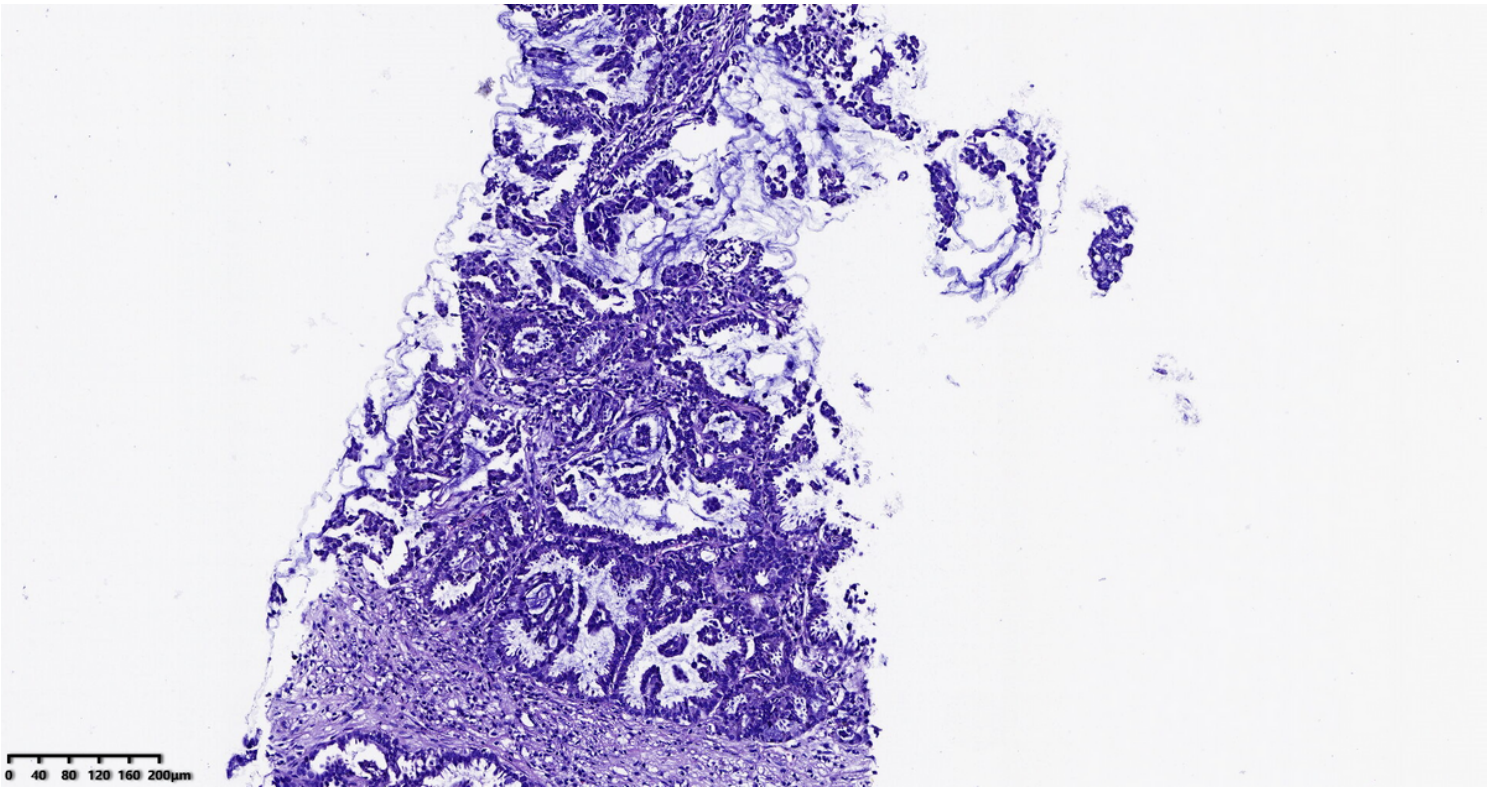

Figure 2

Histology of the FRK-ROS1 rearranged the NSCLC biopsy sample (HE ×100).

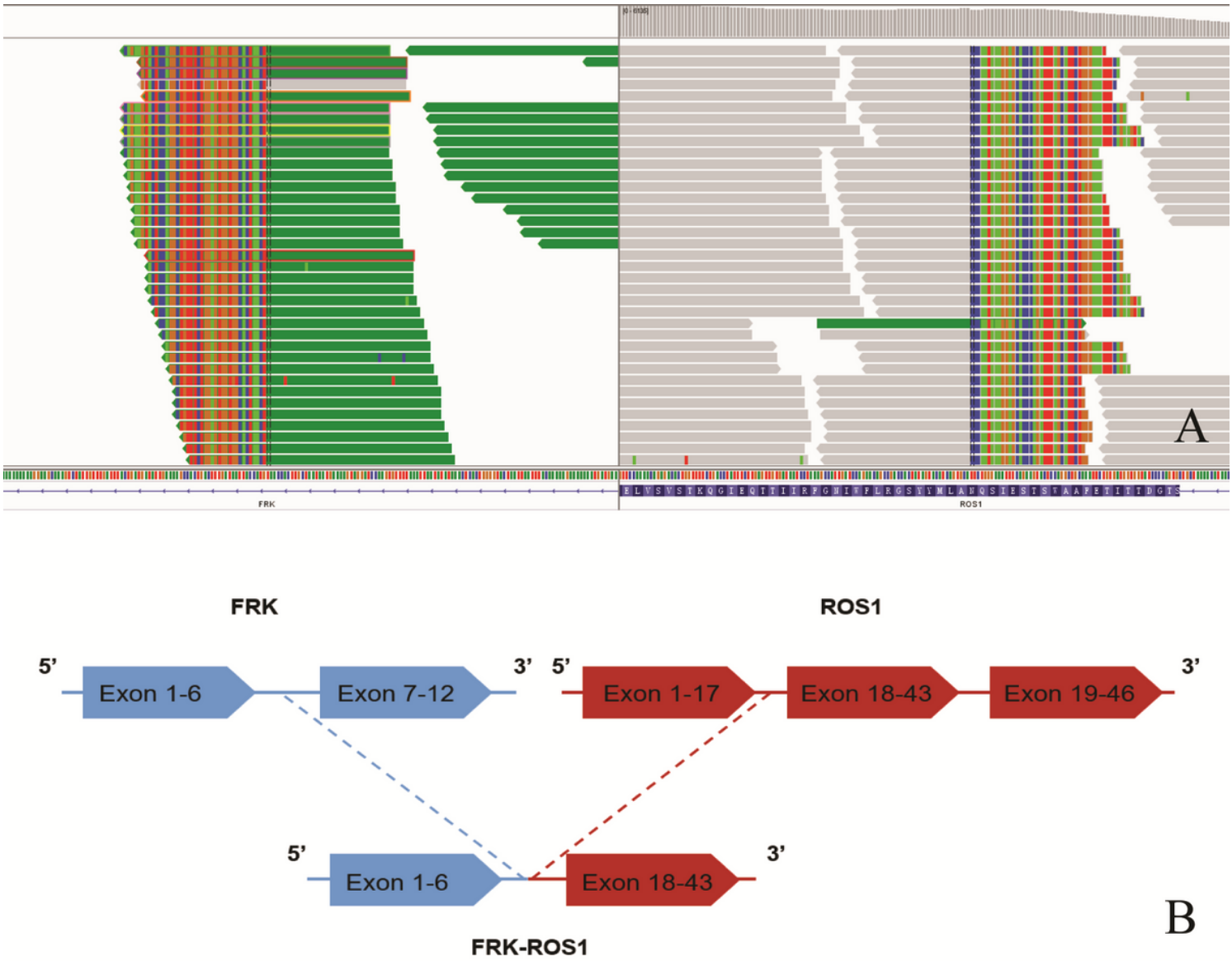

Figure 3

(A) Paired-end sequencing data indicated a somatic intrachromosomal FRK-ROS1 fusion as demonstrated by the Integrative Genomics Viewer program. (B) Schematic representation of the translocation involving FRK and ROS1. Schematic figure of the predicted domains of the FRK-ROS1 fusion protein.