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# Identification of a novel *RMST-ALK* rearrangement in advanced lung adenocarcinoma and durable response to ceritinib: A case report

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Next-generation sequencing technology has enabled the identification of fusion partners of anaplastic lymphoma kinase (*ALK*) in non-small cell lung cancer, and various *ALK* fusion partners have been confirmed. Here, a novel rhabdomyosarcoma 2-associated transcript (*RMST-ALK*) rearrangement was identified in an 80-year-old Chinese man with advanced lung adenocarcinoma. The patient was prescribed ceritinib and achieved a partial response, which has been sustained for more than 18 months. This is the first report of the *RMST-ALK* rearrangement, and we showed that a patient with lung adenocarcinoma carrying this rearrangement can benefit from ceritinib treatment; therefore, this is a significant finding in clinical practice.

## KEYWORDS

*RMST-ALK* rearrangement, non-small cell lung cancer, ceritinib, next-generation sequencing, sensitive

## Introduction

Lung cancer is currently the third most common cancer worldwide (12.3% of all cancer diagnoses) and the leading cause of cancer-related mortality (21.4% of all cancer deaths) (1). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of primary lung tumors (2). Molecular typing is the premise for the implementation of targeted therapy in NSCLC. Commonly mutated genes in lung adenocarcinoma in Eastern populations include *EGFR* (~60%), *KRAS* (~11%), and anaplastic lymphoma

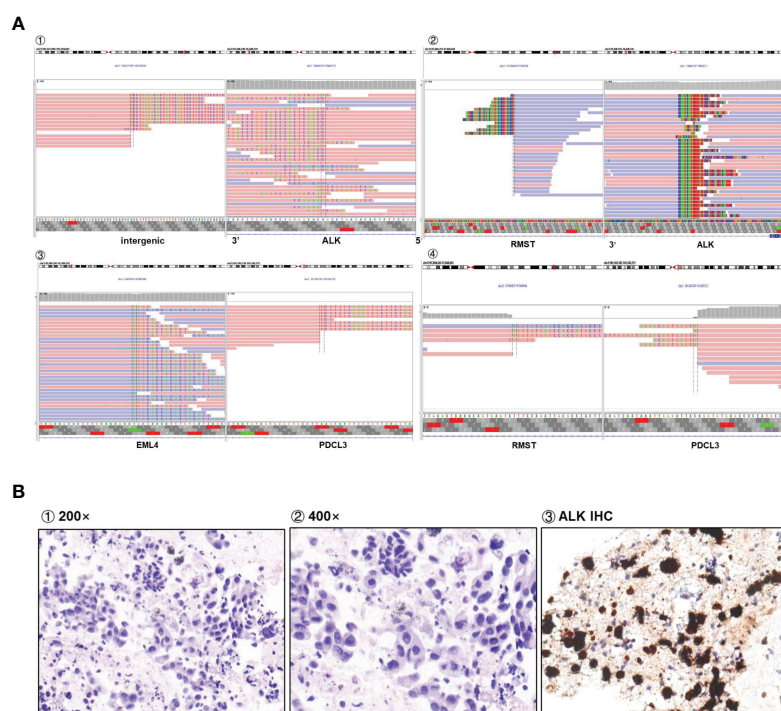
kinase (*ALK*; ~2%), and mutations have also been identified in *MET* (1%), *HER2* (~2%), *BRAF* (~2%), *RET* (1%–4%), and *ROS1* (~2%) (3, 4).

In most *ALK* rearrangements, one breakpoint of *ALK* often occurs at intron 19, which results in dissociation of the 3' end of exons 20–29 from 5' end sequences. The other breakpoint affects a diverse group of genes that contribute to the fusion oncogene, including a different gene promoter and a series of 5' exons of variable lengths and properties, which predominantly share the ability to self-associate (5). Numerous fusion oncoproteins have been identified in various tumor types, of which echinoderm microtubule-binding-like protein 4 (*EML4*)-*ALK* is the primary fusion product (6). The ASCEND-4 and ASCEND-8 trials determined that first-line ceritinib treatment was efficacious in patients with advanced *ALK* fusion-positive NSCLC (7, 8). Here, we present our experience with a patient with lung adenocarcinoma with a rare *ALK* rearrangement who had a remarkable response after ceritinib treatment.

## Case presentation

An 80-year-old Chinese man who had a more than 50-year smoking history and occasionally consumed alcohol was admitted to the local hospital in October 2020 because of hoarseness,

shortness of breath after activity, decreased activity endurance, and chest tightness. The patient was otherwise in good health and did not have a history of hypertension, diabetes, coronary heart disease, pneumonia, tuberculosis, or other infectious disease. In 2007, he had undergone cystectomy for bladder cancer, and a percutaneous urine bag was indwelled for a long period after the operation. The patient underwent a physical examination and a series of auxiliary examinations. Enhanced computed tomography (CT) showed a mass in the middle and lower lobes of the right lung (57 × 35 mm), which was considered central lung cancer with obstructive inflammation and segmental atelectasis, and pericardial metastasis. The pathological report of the puncture effusion smear of the lung tumor under the fiberoptic bronchoscope indicated adenocarcinoma. Therefore, the patient was diagnosed with stage IVA non-small cell lung cancer (T3N2M1), ECOG PS 2. Next-generation sequencing (NGS) targeting 1,267 genes identified a rare novel rhabdomyosarcoma 2-associated transcript (*RMST*)-*ALK* translocation (R5'UTR: A20) and an *ALK*-intergenic (A19: intergenic) rearrangement (Figure 1A). The immunohistochemical (IHC) results confirmed that the tumor was *ALK* fusion positive (Figure 1B). Besides, no *EGFR* mutations and *ROS1* rearrangements were found. Based on the genetic test results, the patient was administered ceritinib treatment (450 mg P.O QD) in November 2020. After treatment, his CEA declined from 13.38 to 4.2 μg/l, and his CA 125 declined



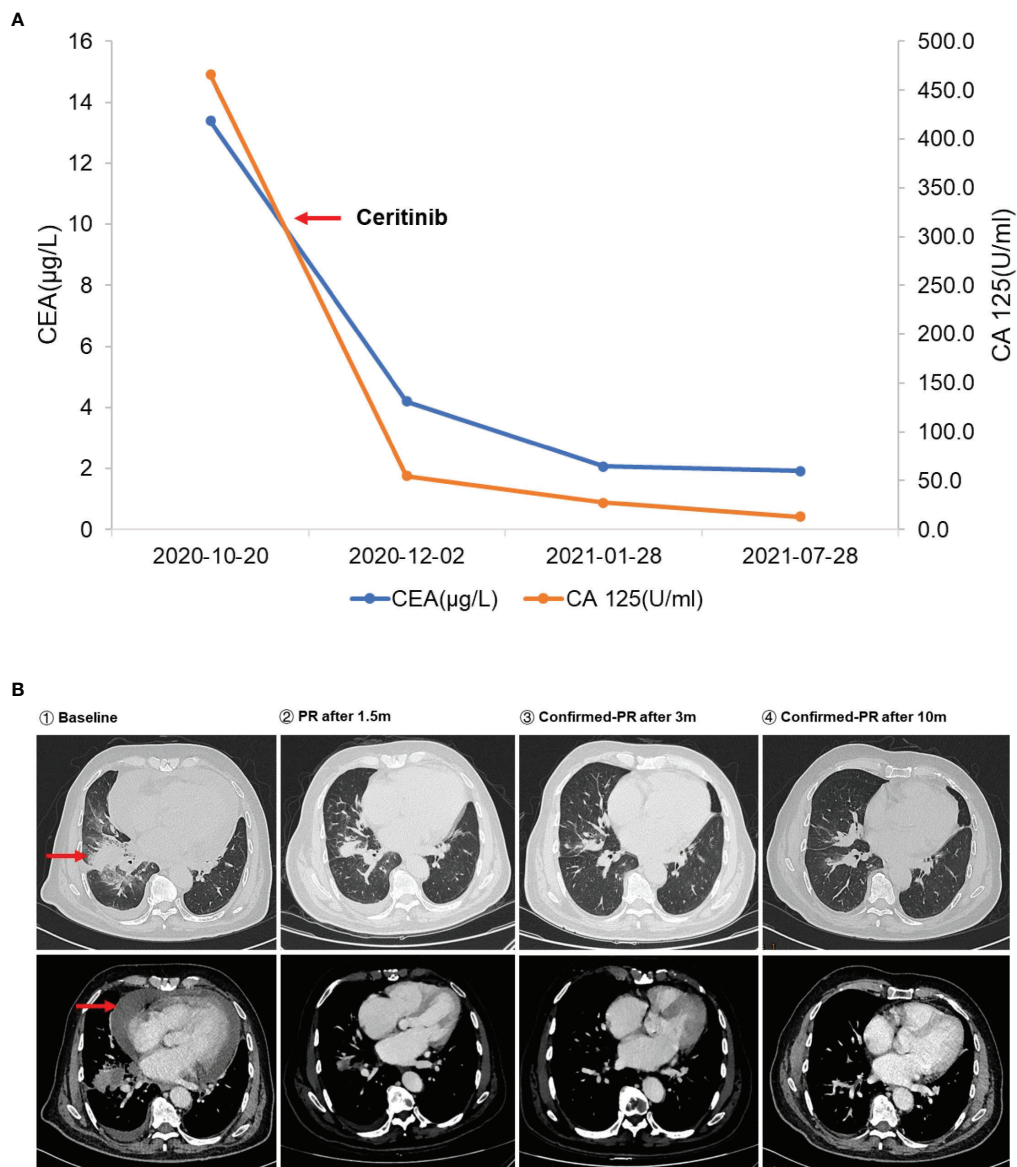
**FIGURE 1**  
(A) Sequencing reads of multiple rearrangements are shown by the Integrative Genomics Viewer. (B) Positive ALK expression detected by IHC assay.

from 465.7 to 54.6 U/ml (Figure 2A). Chest CT demonstrated significantly reduced hydropericardium 1.5 months later, confirming a partial response (Figure 2B). As of July 2022, the patient has retained a partial response to ceritinib treatment.

## Discussion

To our knowledge, this is the first case of an *RMST-ALK* rearrangement based on the fusion of the 5' UTR of *RMST* and

exon 20 of *ALK*. *RMST*, a long non-coding RNA, regulates mRNA and protein expression in the cytoplasm and is expressed in cervical cancer and triple-negative breast cancer (9). The *RMST-ALK* fusion is not currently documented in the COSMIC fusion database (<https://cancer.sanger.ac.uk/cosmic/fusion>) or the Quiver fusion database (<http://quiver.archerdx.com/>). The IVG view suggests that the *RMST-ALK* rearrangement may be transcribed in the opposite direction (“antisense rearrangement”). “Non-functional rearrangements” involving the *ALK* locus have been described, in which the reading frame of one or both genes is disrupted, *ALK*



**FIGURE 2**  
**(A)** The changes in serum carcinoembryonic antigen (CEA) and CA 125 level during ceritinib treatment. The left red arrow means initiation of ceritinib. **(B)** Dynamic imaging of lung lesions at different stages of treatment. The red arrows indicate the baseline lesion and pericardial effusion.

fuses with non-coding intergenic DNA, or genes are transcribed in the opposite orientation. These “non-functional” rearrangements might indicate *ALK* fusions by fluorescence *in situ* hybridization (FISH) (10). There are also some guidelines and expert consensus that DNA-seq NGS may identify atypical or intergenic fusions (11). Another case of an antisense rearrangement of *ALK* was previously reported, in which a complex tripartite rearrangement involving multiple DNA fusion junctions was formed between *YY1P2* downstream, *EML4*, and *ALK*. This fusion was detected by both FISH and IHC. The authors speculated that a complex structural mutation may have occurred in this region, ultimately producing a codable RNA sequence that generates a functional fusion transcript (12). Through bioinformatics mining and analysis of the raw data, we found that the sample in our case also had other genetic rearrangements: *EML4* and *RMST* fragments were fused to *PDCL3* (Figure 1A). This was validated by D5F3 IHC (Figure 1B), indicating that this *ALK* rearrangement could activate the self-phosphorylation of *ALK* and trigger its downstream signaling pathways, although the exact mechanism remains to be determined.

The gold standard for detecting *ALK* rearrangements is FISH or IHC, but neither method can identify a specific fusion form. Therefore, the detection of *ALK* rearrangements by targeted next-generation sequencing, such as DNA-based and RNA-based NGS, may be a good complementary approach to precisely identify rare or novel *ALK* fusion variants to guide targeted therapy with *ALK* inhibitors in patients with NSCLC (13–15). Crizotinib, which was approved by the US Food and Drug Administration (FDA) in 2011, was the first *ALK*-TKI approved for patients with *ALK*-positive NSCLC. The second-generation *ALK* TKI alectinib obtained expedited approval as first-line medication based on the results of the ALEX trial. Ceritinib is also a second-generation *ALK* TKI and is 20 times as potent as crizotinib against *ALK*-positive NSCLC, has significant antitumor activity against both crizotinib-sensitive and crizotinib-resistant tumors, and has better efficacy in the Asian population (16). Based on the results of ASCEND-4 and ASCEND-8 studies, the FDA and China National Medical Products Administration approved ceritinib as first-line treatment for patients with advanced NSCLC with *ALK* fusions in May 2017 and May 2020, respectively. Exploratory analysis of the ASCEND-1 study found that ceritinib was effective in *ALK*-rearranged NSCLC, including common *EML4-ALK* V3 and V1 variants, and novel *ALK* rearrangements, such as *CRIM1-ALK* and *CLTC-ALK*. Ceritinib is active against almost all *ALK*-resistant mutations found in patients pretreated with *ALK* inhibitors (17). Furthermore, ceritinib was found to be more effective and safe and to comply with treatment when administered with meals at 450 mg. Compared to patients receiving crizotinib, patients receiving ceritinib or alectinib showed better efficacy and had significantly longer progression-free survival (8, 18). Because ceritinib was more economically eligible than alectinib, the patient chose ceritinib for treatment. After 1.5 months of treatment, the CT scan showed that the right

lung mass was slightly smaller than before, confirming a partial response. During more than 18 months of follow-up, the patient had no gastrointestinal adverse reactions such as diarrhea, nausea, vomiting, or abdominal pain and was in good living condition. Since *RMST-ALK* is a novel rearrangement, the mechanism of activation of *RMST* for this novel *ALK* rearrangement remains unclear, as dose has its ability to confer drug resistance. Further functional studies and clinical follow-up are required.

In conclusion, we report a novel case of *RMST-ALK* rearrangement in NSCLC with a durable response to ceritinib. This case may provide valuable information on the reaction to ceritinib of NSCLC patients with *RMST-ALK* rearrangement.

## Data availability statement

The datasets presented in this article are not readily available because of ethical and privacy restrictions. Requests to access the datasets should be directed to the corresponding author/s.

## Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

GL and QL: supervision, funding acquisition. HL, YD, and BC: conceptualization, methodology, writing—original draft preparation, writing—review and editing. YX and JY: formal analysis. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

Authors YD, YX and JY are employed by YuceBio Technology Co., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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