case reports

Clinical Responses to Crizotinib, Alectinib, and Lorlatinib in a Metastatic Colorectal Carcinoma Patient With ALK Gene Rearrangement: A Case Report

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INTRODUCTION

Colorectal carcinoma (CRC) has the third highest incidence and the second highest mortality across all types of cancer worldwide.[1] In 2015, there were 388,000 new CRC cases and 187,000 deaths in China.[2] With advances in combining chemotherapy with vascular endothelial growth factor or epidermal growth factor receptor inhibitors, the median overall survival for patients with metastatic colorectal carcinoma (mCRC) is approximately 30 months.[3] Recent next-generation sequencing (NGS) has uncovered several novel potential molecular targets in mCRC, such as *RET, ROS1, NTRK*, and *ALK*.[4-11] Based on basket trials that screen for the off-label use of a targeted drug in patients with the same genomic alterations,[12] NGS-guided therapy could yield clinical benefits and provide novel insights into optimal clinical management for intractable mCRC.

ALK gene fusions have been successfully exploited as therapeutic targets in non–small-cell lung cancer (NSCLC) using the *ALK* inhibitors crizotinib and lorlatinib.[13,14] However, knowledge on the efficacy of targeted therapy for *ALK* gene fusion in mCRC remains rare. To our knowledge, only two patients have been described who harbored *ALK* gene fusions and responded to ceritinib and entrectinib, respectively.[8,10]

A diagnosis of leptomeningeal metastasis (LM) carries a poor prognosis with a median survival of only 2-4 months.[15] Few cases of LM caused by CRC have been reported.[16] Recently, it was found that CSF circulating tumor DNA (ctDNA) could better reflect the molecular characteristics than plasma ctDNA in patients with NSCLC harboring *ALK* rearrangement and may be useful in identifying drug targets and guiding treatment.[17]

In this case study, we describe the first instance of *ALK* rearrangement in CRC detected using NGS of CSF ctDNA, as well as a case of lasting objective tumor response to crizotinib, alectinib, and lorlatinib therapy.

CASE REPORT

A 70-year-old female arrived at our clinic with abdominal pain present for 3 months. A computed tomography scan revealed a mass in the ascending colon accompanied by liver, peritoneum, and pleura metastases. Serum tumor markers including carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 125, and CA19-9 significantly increased (Figs 1A and 1B). Colonoscopy pathology reported moderately to poorly differentiated adenocarcinoma (Fig 2A), and immunohistochemistry (IHC) demonstrated positivity for CK20 (Fig 2B). Formalin-fixed paraffin-embedded specimens from colonoscopy biopsy were subjected to NGS using the OncoScreen plus (Burning Rock Dx, Irvine, CA) assay platform, including 520 cancer-related genes and plasma ctDNA. The tissue-based NGS identified 12 genomic alterations: EML4-*ALK* fusion (E21;A20) (Fig 3A) and mutation in *TP53 R157H, AKT1, ANNKRD11, BRAF, DNMT3A, FLT4, GABRA6, NKX2-1, PTPRT, RBM10*, and *SLX4*. No *BRAF V600E* or *KRAS* mutations were identified. The IHC results showing strong D5F3 anti-*ALK* antibody of Ventana staining verified *ALK* overexpression as a result of *EML4-ALK* fusion (Fig 2D). The first XELOX (capecitabine, 1.5g, d1-14 + oxaliplatin, 200mg, d1, q3w) cycle was interrupted because of the patient's intestinal obstruction after she had taken oral capecitabine for 1 week. She was subsequently switched to mFOLFOX6 (oxaliplatin, 130 mg, d1 + 5-fluorouracil, 500 mg, d1 leucovorin 500mg, d1 + maintenance dose of 3g, 5-fluorouracil for 46 hours, q2w) + cetuximab (700mg, d1, q2w), but the regimen was terminated after nine days because of dyspnea resulting from hydrothorax. Because of the presence of EML4-*ALK* fusion, she was treated with oral crizotinib (250 mg, twice a day) on July 10, 2019. The treatment resulted in clinical benefit with the disappearance of tumor-related abdominal pain. After a month, computed tomography

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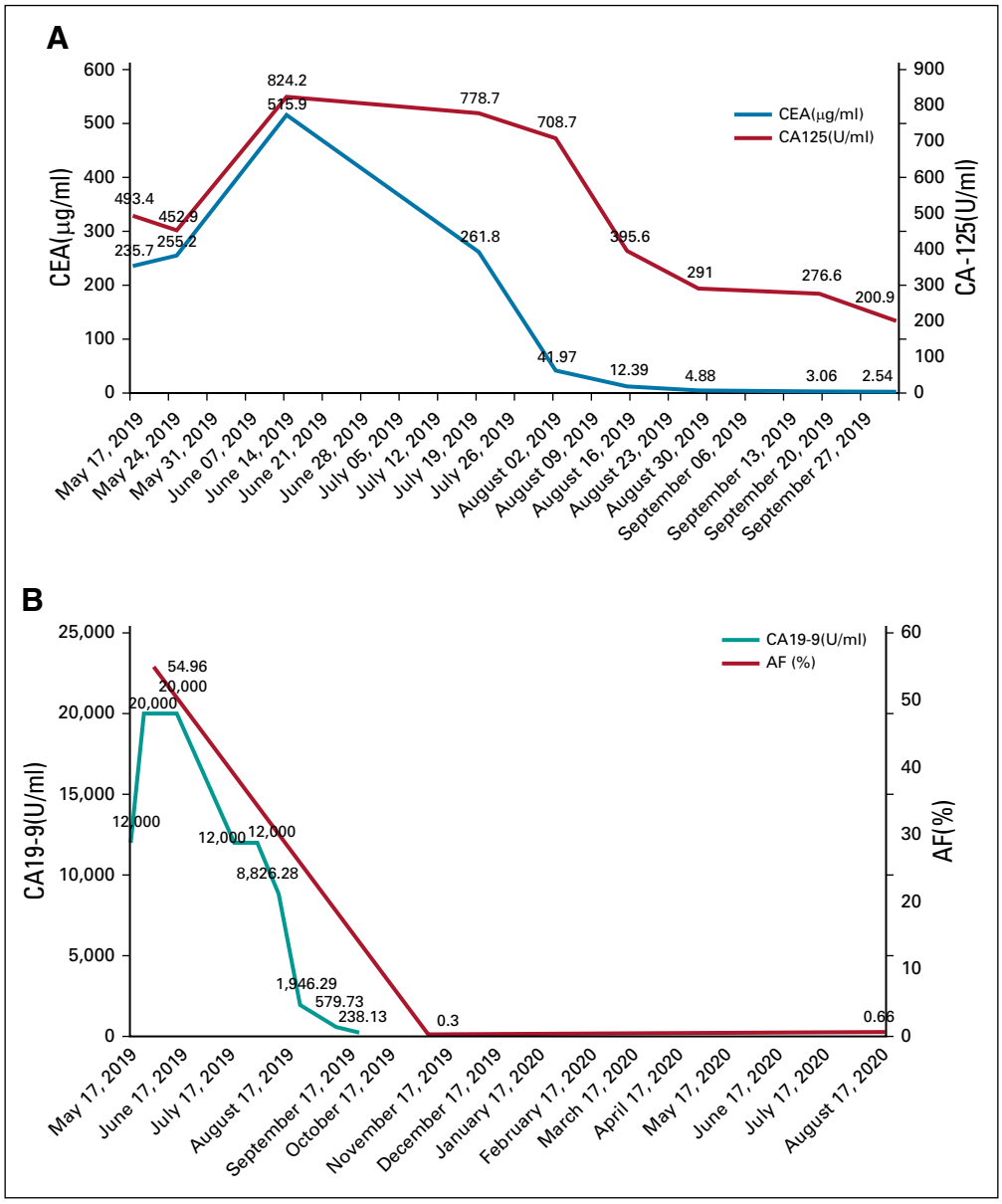

FIG 1. (A) Fluctuation of CEA (normal value: 0-5 μg/L) and CA 125 (normal value: 0-35 U/L) levels in the blood. (B) Fluctuation of CA 19-9 (normal value: 0-39 U/mL) levels and AF of ctDNA ELM4-ALK fusion in the blood. AF, allele frequency; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; ctDNA, circulating tumor DNA.

scans revealed partial response (PR) for retroperitoneal lymphadenectasis and liver metastases based on RECIST 1.1 (Fig 4) and concomitant decrease in serum CEA and CA 19-9 (Figs 1A and 1B). After four months of treatment, LM symptoms appeared, accompanied by continuous elevation of serum CA 19-9. Brain MRI demonstrated diffuse linear enhancement of the cerebral sulci (Fig 4). The second ctDNA NGS test was implemented, but no resistant mutations were found except for a lower allele frequency of *EML4-ALK* fusion (0.3%) and TP53 mutation (0.3%) (Table 1 and Fig 1A). The patient accepted alectinib (600 mg twice a day), and the LM symptoms were slightly relieved, but did not entirely disappear after 2 weeks. Thus, lorlatinib, a third-generation tyrosine kinase inhibitor, was recommended as fifth-line therapy with a dose of 75 mg qd beginning December 9, 2019. As the patient's LM symptoms gradually improved, we increased the dose to 100 mg qd. The progression-free survival (PFS) on lorlatinib was 11.5 months. Because of the increasing serum CEA and CA 19-9 and stable extracranial lesions, her oncologist opted for a lumbar puncture to obtain her CSF to implement the third ctDNA test with CSF and plasma samples on August 13, 2020. It is surprising that high allele frequency of EML4-*ALK* (99%) and other gene alterations, such as *FGFR2* mutations, *KRAS* amplification, and *PTEN* deletion, appeared in CSF (Table 1). No evidence was confirmed regarding the progressive index related to *ALK* alterations, and thus, lorlatinib was still retained. The patient died on September 17, 2020, because of progression of LM.

DISCUSSION

In this report, we show the clinical efficacy of crizotinib, alectinib, and lorlatinib in an *ALK*-rearrangement mCRC

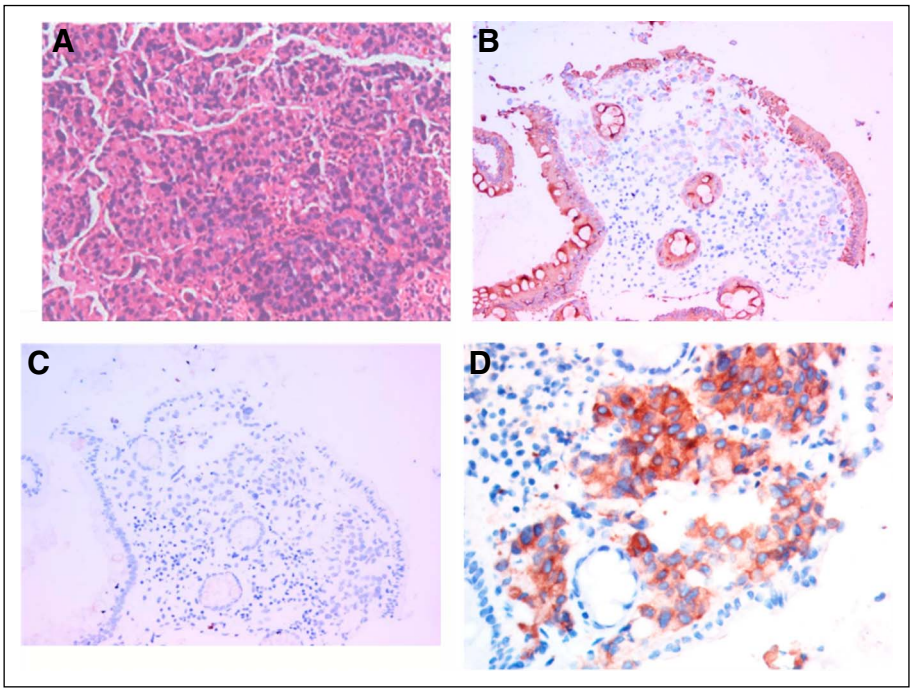

FIG 2. H&E staining (A), 100×, and IHC, (B) for CK20 (+), (C) for Ki-67 (–), and (D) for IHC with D5F3 anti-ALK Ventana antibody showing strong staining and verifying ALK overexpression as a result of EML4-ALK fusion. ALK, anaplastic lymphoma kinase; H&E, hematoxylin and eosin; IHC, immunohistochemistry.

with LM. This case had several uncommon features: the presence of *ALK* fusions that are rarely present in mCRC; the first report of a patient with *ALK*-rearranged mCRC who showed a good response to crizotinib, alectinib, and lorlatinib therapy; and the first case of *ALK* fusion detected in a patient with mCRC through CSF ctDNA.

ALK fusion activates downstream signaling pathways without ligand binding, including phospholipase Cγ, Janus kinase-signal transducer and activator of transcription, and *PI3K-AKT-mTOR* signaling cascades, which regulate proliferation, growth, invasion, and antiapoptotic signaling. In epithelial tumors, *ALK* gene rearrangements are most common in lung carcinomas, with an incidence rate varying from 3% to 7%, and are rare in CRCs.[18]The oncogenic *ALK* rearrangements were reported to have frequencies varying from 0.04% to 2.5% and in 23 cases of CRC with various fusion partners (Table 2). Sheng et al[19] reported more than 40,000 Chinese cancer tissue or blood sample subjected to NGS for *ALK* rearrangement. The frequency of *ALK* fusion in CRC is 0.99%. Based on the data available from The Cancer Genome Atlas and Burning Rock datasets, the rates of *ALK* fusion in CRC cases are estimated to be 0.17% and 0.16%, respectively.

Several studies have investigated the effects of *ALK* inhibitors on CRC in vitro. It was shown that crizotinib or entrectinib could inhibit the phosphorylation of *ALK* protein tumor cell line derived from *EML4-ALK* fusion CRC.[6] It was noted that C10 cells, harboring the *ALK* rearrangement, were sensitive to crizotinib, which downregulates *MAPK*

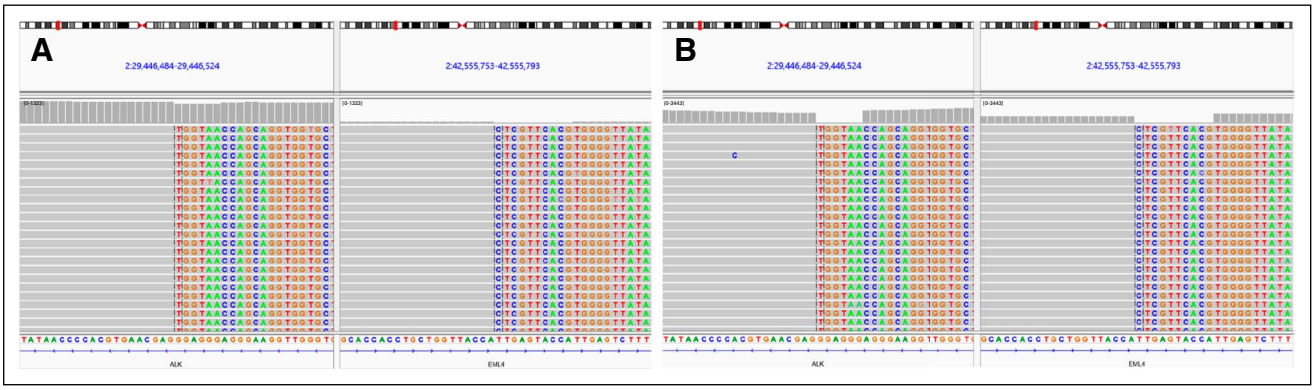

FIG 3. NGS showing EML4-ALK fusion (E21;A20) on (A) FFP and (B) CSF, in which the AF is 21.5% and 99%, respectively. AF, allele frequency; ctDNA, circulating tumor DNA; FFP, fresh frozen plasma; NGS, next-generation sequencing; PR, partial response.

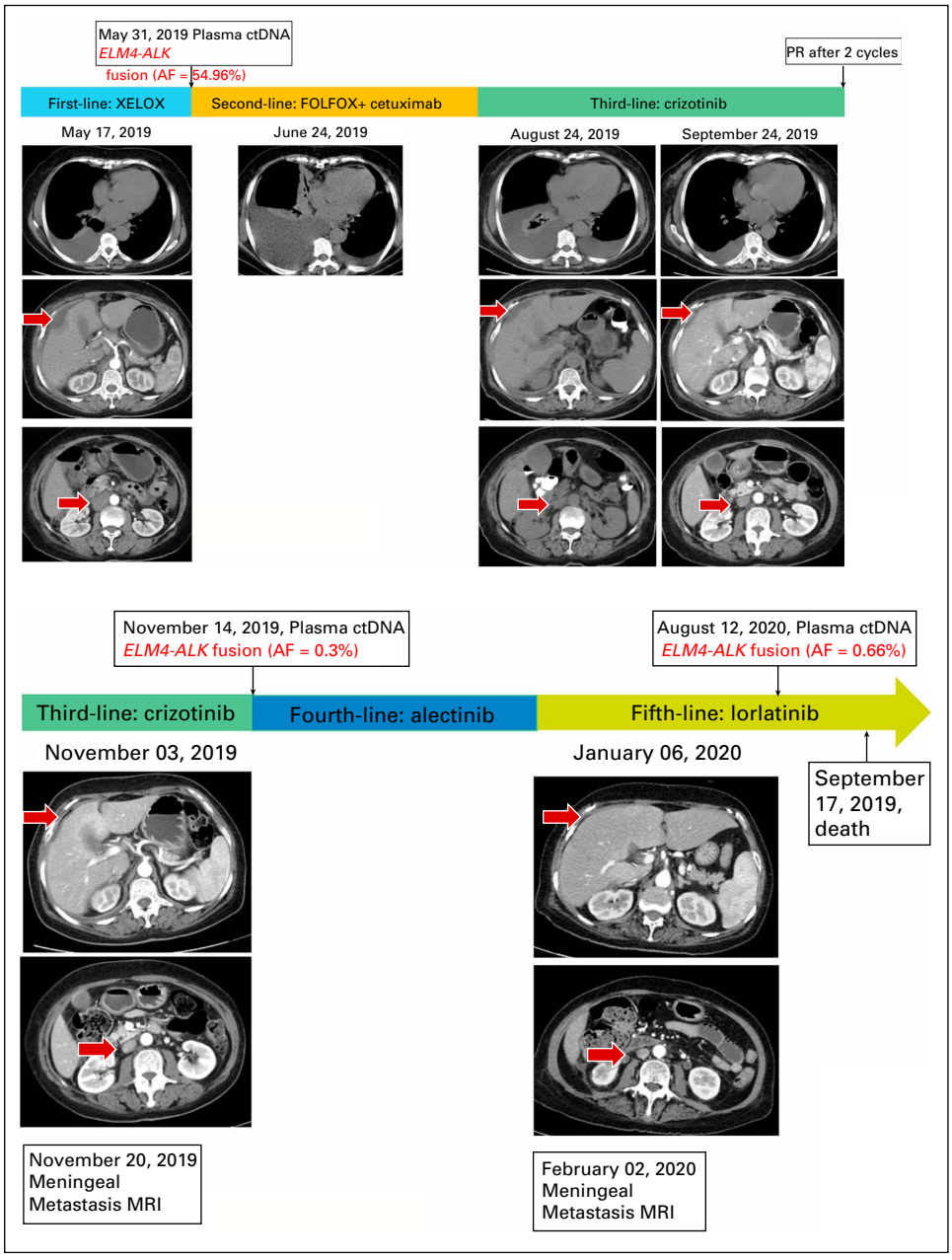

FIG 4. mCRC treatment using different regimens and results of NGS ctDNA monitoring in plasma. AF, allele frequency; ctDNA, circulating tumor DNA; mCRC, metastatic colorectal carcinoma; MRI, magnetic resonance imaging; NGS, next-generation sequencing; PR, partial response.

and *PI3K* pathways.[20] To date, only three patients have been responsive to *ALK* inhibitor, including our patient. Yakirevich et al[8] reported an 84-year-old male presenting with an *STRN-ALK* fusion who achieved clinical benefit for 9 months after treatment with ceritinib, a second-generation *ALK*/*ROS1* inhibitor. Another case study also reported an objective response to the *ALK*/ROS1/NTRK inhibitor entrectinib in a patient with CRC harboring a *CAD-ALK* fusion.[10] Interestingly, nivolumab, a PD-1 inhibitor, also remained PR in a patient with dMMR and high PD-L1 (> 50%) CRC harboring *EML4-ALK* fusion more than 9 months.[21] The most common *ALK*-dependent resistance mechanisms of crizotinib are *L1196M* and of alectinib and ceritinib are *G1269A* and *G1202R*,[22] yet no secondary resistant mutations were found in our second ctDNA NGS. Lorlatinib was designed to cross the blood-brain barrier and had potent antitumor activity in preclinical study[23] result in durable control of LMs in our case (Table 3).

Sample diversity makes ctDNA-based liquid biopsies not less limited to plasma, such as urine. Based on the urine sample of patient who has objective response to entrectinib,[10] Siravegna et al[24] showed that detection of the *CAD-ALK* gene fusion in urine trans-renal DNA anticipated CRC response to entrectinib.

TABLE 1. Results of Molecular Diagnostic Assays

Tissue Assay May 31, 2019	Plasma ctDNA Assay May 31, 2019	Plasma ctDNA Assay November 14, 2019	CSF ctDNA Assay August 12, 2020	Plasma ctDNA Assay August 18, 2020
II class alteration				
EML4-ALK fusion (AF = 21.05%)	*EML4-ALK* fusion (AF = 54.96%)	*EML4-ALK* fusion (AF = 0.3%)	*EML4-ALK* fusion (AF = 99%)	*EML4-ALK* fusion (AF = 0.66%)
TP53 R175H	*TP53 R175H*	*TP53 R175H*	*TP53 R175H*	*TP53 R175H*
			FGFR2-ETV6	
			FGFR2-DUSP16	
			FGFR2 amplification	
			KRAS amplification	
			PTEN del	
III class alteration				
AKT1	*AKT1*		*AKT1*	
ANNKRD11	*ANNKRD11*			
BRAF splice site c.240+1G>A	*BRAF* splice site c.240+1G>A	*BRAF* splice site c.240+1G>A	*BRAF* splice site c.240+1G>A	
			FANCA	
			FAT1	
DNMT3A	*DNMT3A*			
FLT4	*FLT4*		*FLT4*	
GABRA6	*GABRA6*		*GABRA6*	
NKX2-1	*NKX2-1*		*NKX2-1*	*NKX2-1*
PTPRT splice site c.685-10T>G	*PTPRT* splice site c.685-10T>G	*PTPRT* splice site c.685-10T>G	*PTPRT* splice site c.685-10T>G	*PTPRT* splice site c.685-10T>G
RBM10	*RBM10*		*RBM10*	*RBM10*
SLX4	*SLX4*	*SLX4*	*SLX4*	*SLX4*
	EHPHA5		*ARAF, BCOR, EIF1AX, GATA1, KDM5C*, and *KDM6A*	
	XPO1 amplification		*RBM10* amplification	
Additional findings				
TMB-intermediate (11.11 mut/Mb)	TMB-intermediate (12.70 mut/Mb)	TMB-low (3.22 mut/Mb)	TMB-intermediate (8.97 mut/Mb)	TMB-low (2.99 mut/Mb)
MSS	NA	NA	MSS	NA

Abbreviations: AF, allele frequency; ctDNA, circulating tumor DNA; MSS, microsatellite stability; mut, mutation; NA, not available; TMB, tumor mutation burden.

TABLE 2. Known ALK Fusions in Colorectal Cancer Cases

Case No.	Sample	*ALK* Fusion	Frequency, No. (%)	Methodology
1 and 2[25]	Tissue	*EML4-ALK* (E20;A20)	2/83 (2.4)	Exon array, PCR
		EML4-ALK (E21;A20)		
3[5]	Tissue	*C2orf44-ALK* (C4:A20)	1/40 (2.5)	NGS
4[26]	Tissue	*EML4-ALK* (E6;A20)	1/236 (0.4)	FISH, PCR
5[4]	Tissue	*SMEK2-ALK*	1/377 (0.26)	RNA-seq
6[27]	Tissue	NA	1/1,889 (0.05)	IHC
7[20]	Tissue	NA	1/742 (0.13)	IHC
8 and 9[6]	Tissue	*CAD-ALK* (C35;A20)	1/172 (0.6)	IHC, NGS
		EML4-ALK (E21;A20)	1/50 (2)	
10[7]	Plasma	*STRN-ALK* (S3:A20)	NA	NGS ctDNA
11 to 16[8]	Tissue	*STRN-ALK* (S3:A20)	6/3,157 (0.19)	NGS
		SENPF-ALK (S11:A20)		
		MAPRE3-ALK (M7:A20)		
		EML4-ALK (E2:A20)		
		PRKAR1B-ALK (P4:A20)		
		PPP1R21-ALK (P17:A20)		
17[9]	Tissue	NA	1/123 (0.08)	NGS
18[10,24]	Tissue	*CAD-ALK* (C35;A20)	1/487 (0.21)	IHC
	Plasma, urine			ctDNA, rt-DNA
19-20[11]	Tissue	*SPTBN1-ALK* (S7;A20)	2/457 (0.43)	IHC, FISH, NGS
		EML4-ALK		IHC, FISH, PCR
21[28]	Tissue	*SPTBN1-ALK*	1/2309(0.043)	NGS
22-26[19]	Tissue and plasma	*EML4*	6/6,045(0.99)	NGS
		EML4		
		NPM1		
		PPFIBP1		
		GPHN		
		TPM4		
21 to 22[11]	Tissue	*SPTBN1-ALK* (S7;A20)	2/457 (0.43)	IHC, FISH, NGS
		EML4-ALK		IHC, FISH, PCR
23[28]	Tissue	*SPTBN1-ALK*	1/2,309 (0.043)	NGS
24-28[19]	Tissue and plasma	*EML4*	6/6,045 (0.99)	NGS
		EML4		
		NPM1		
		PPFIBP1		
		GPHN		
		TPM4		

Abbreviations: ctDNA, circulating tumor DNA; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NA, not available; NGS, next-generation sequencing; PCR, polymerase chain reaction; rtDNA, trans-renal DNA.

In conclusion, we have reported on an elderly patient with *ALK*-fusion mCRC who was treated with crizotinib, alectinib, and lorlatinib and achieved PR with the PFS of 3, 0.5, and 11.5 months, respectively. The case provides a new potential treatment strategy for patients with CRC who did not respond to standard treatment with *ALK* rearrangement but still poses a few questions. Are there any other targetable *ALK*-fusion partners in patients with mCRC? What are the biological characteristics in such patients harboring *ALK* fusions? Translational studies and the establishment of a database will be instrumental for addressing many of these unanswered questions.

TABLE 3. Clinical Characteristics and Prognosis of Patients With CRC Harboring the ALK Fusions

Age/Sex	Partner	Primary Site	Surgery	Stage	Metastases	Sample	Assay	Treatment	PFS (months)	OS (months)
84/female[8]	*STRN*	Cecum	Radical	IV	Lung and umbilicus	Tissue	NGS	Ceritinib (third-line)	9	> 12
53/female[10]	*CAD*	Right colon	Palliative	IV	Brain, cerebellum, and liver	Tissue	IHC	Entrectinib (third-line)	4.5	5
84/female	*EML4*	Ascending	None	IV	Meningeal, liver, pleural, and peritoneum	Tissue, plasma, CSF	IHC, NGS	Crizotinib (third-line)	4	16
								Alectinib (fourth-line)	0.5	
								Lorlatinib (fifth-line)	11.5	

Abbreviations: ALK, anaplastic lymphoma kinase; CRC, colorectal carcinoma; IHC, immunohistochemistry; NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival.

The patient provided written informed consent and gave permission for the use of biopsies and the publication of case details. This study was approved by the Ethical Committee of the Changzheng Hospital of Naval Medical University. Data and materials in the current study are not available to any readers as they contain the patient's personal details.

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Manuscript writing: All authors
Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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