


## CASE REPORT

# Alectinib treatment response in lung adenocarcinoma patient with novel *EML4-ALK* variant

Peng Song<sup>1\*</sup> , Jingcheng Zhang<sup>2\*</sup>, Congcong Shang<sup>3</sup> & Li Zhang<sup>1</sup>

1 Department of Respiratory Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

2 Department of Internal Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

3 Department of Respiratory Medicine, Henan Provincial Peoples Hospital, Zhengzhou, China

## Keywords

Alectinib; crizotinib; *EML4-ALK*; lung cancer.

## Correspondence

Li Zhang, Department of Respiratory Medicine, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, No. 1 Shuaifuyuan, Dongcheng District, Beijing 100730, China.  
Tel: +86 10 6915 8760  
Fax: +86 10 6915 8760  
Email: zhanglipumch@aliyun.com

\*Peng Song and Jingcheng Zhang contributed equally.

Received: 31 May 2018;

Accepted: 14 July 2018.

doi: 10.1111/1759-7714.12834

Thoracic Cancer 9 (2018) 1327–1332

## Introduction

Lung cancer is the leading malignant tumor responsible for morbidity and mortality worldwide. According to the latest published data, 110 000 new cases of lung cancer are diagnosed and approximately 70 000 people die of this disease annually in the United States (US).<sup>1</sup> Non-small cell lung cancer (NSCLC) is the most common type, accounting for 85% of all cases and patients are often in advanced stages when diagnosed. The one-year survival rate after treatment with a doublet platinum-based regimen is < 40%.<sup>2</sup> With developments in research on the tumor signal pathway, targeted therapy has received increasing attention. Approximately 5% of NSCLC patients are reported to have mesenchymal lymphoma gene fusion (*ALK*), with *EML4-ALK* being the most common.<sup>3</sup> Approximately 10 000 *ALK*-

## Abstract

Common gene fusion of the *ALK* gene is fusion of the *ALK* tyrosine kinase area and the 5' end of *EML4*. Seventeen *EML4-ALK* fusion variants have been reported. Herein, we report a novel *EML4-ALK* variant detected by next-generation sequencing in a 36-year-old female lung adenocarcinoma patient who experienced disease progression after six months of alectinib treatment. Second generation sequencing revealed an *EML4-ALK* fusion variant in which intron 19 of *EML4* was fused to exon 20 of *ALK*. This is the first case of *EML4-ALK* (E19: A20) fusion to be reported. Alectinib may show unsatisfactory therapeutic effects for this kind of *ALK* fusion.

positive patients are confirmed annually in the US, particularly non-smoking young women and adenocarcinoma and *EGFR* wild-type patients.<sup>4</sup>

The *ALK* gene inhibitor has been a great breakthrough in recent years, significantly extending the survival period of advanced NSCLC patients with *ALK* (+). Crizotinib, ceritinib, and alectinib have all been approved as first-line-therapy for advanced NSCLC patients harboring *ALK* activating mutations.<sup>5–7</sup> However, almost all patients with *EML4-ALK* fusion mutations initially responsive to *ALK*-tyrosine kinase inhibitors acquire resistance. With the exception of non-*ALK* mutated resistance (*ALK* WT), another major reason for drug resistance of *ALK*-tyrosine kinase inhibitors (TKIs) is that mutations exist in the *ALK* kinase region. The main reasons for crizotinib resistance are *ALK* amplification and L1196M mutation.<sup>8</sup> G1202R

mutation is the main reason for the resistance of second-generation TKIs.<sup>9</sup> Clinically, G1202R mutations are sensitive to lorlatinib, but the sensitivity of other drug resistance sites to lorlatinib requires further study.<sup>10</sup> The choice of subsequent treatments after patients develop resistance to first and second generation TKIs therefore remains a major challenge.

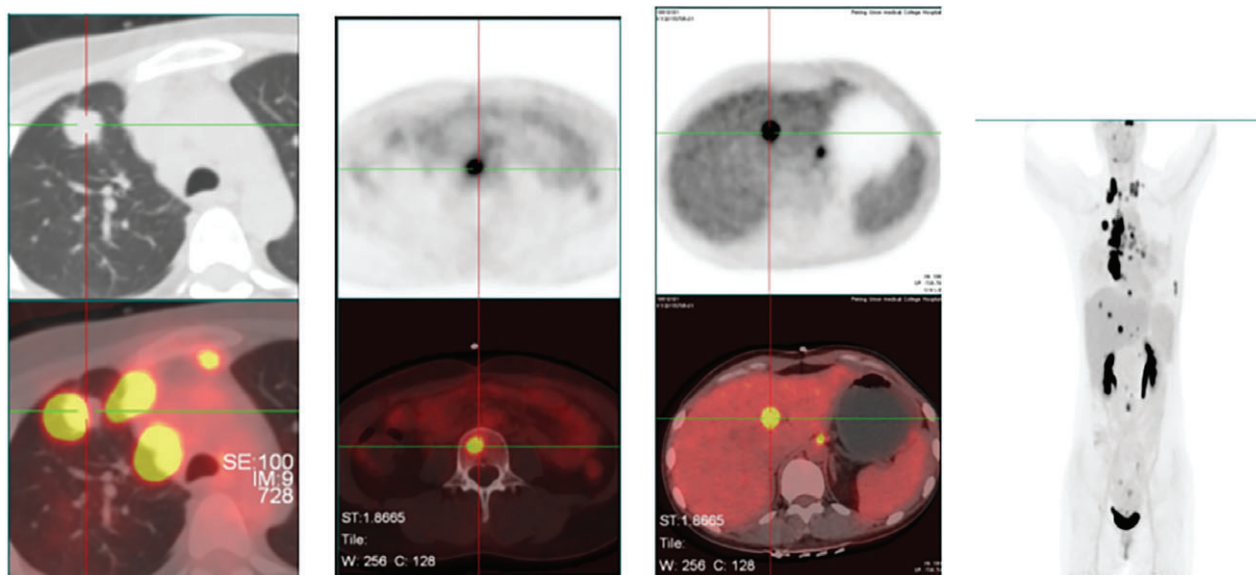
## Case report

A 36-year-old woman was admitted to our hospital in June 2017 because of right cervical lymph node enlargement, which had been present for a month. Positron emission tomography-computed tomography (PET-CT) showed right upper lobe lung cancer with multiple lymph node, liver, and bone metastases (Fig 1). A biopsy was performed on 7 July. The immunohistochemical markers were: TTF-1(+), Ventana ALK (D5F3) (+), HER-2(+), PMS-2(+). Lymph node metastatic lung adenocarcinoma was confirmed and right upper lobe adenocarcinoma (cT4N3M1c, IVb) was diagnosed. The results of cervical lymph node tissue gene detection (second-generation sequencing technology) showed fusion of intron 19 of *EML4* and exon 20 of *ALK* (*EML4-ALK* [E19: A20]) (Fig 2), abundance 15.6%, which was confirmed by Sanger sequencing of *EML4-ALK* fusion (Fig 3).

The patient was administered crizotinib 250 mg orally twice a day (b.i.d. per os) from 7 July 2017, but developed uncontrollable diarrhea after a week of treatment. Thus, alectinib 300 mg b.i.d. per os was administered instead, with no apparent adverse effects. On 16 August, PET-CT revealed that the lesions in the upper lobe had significantly

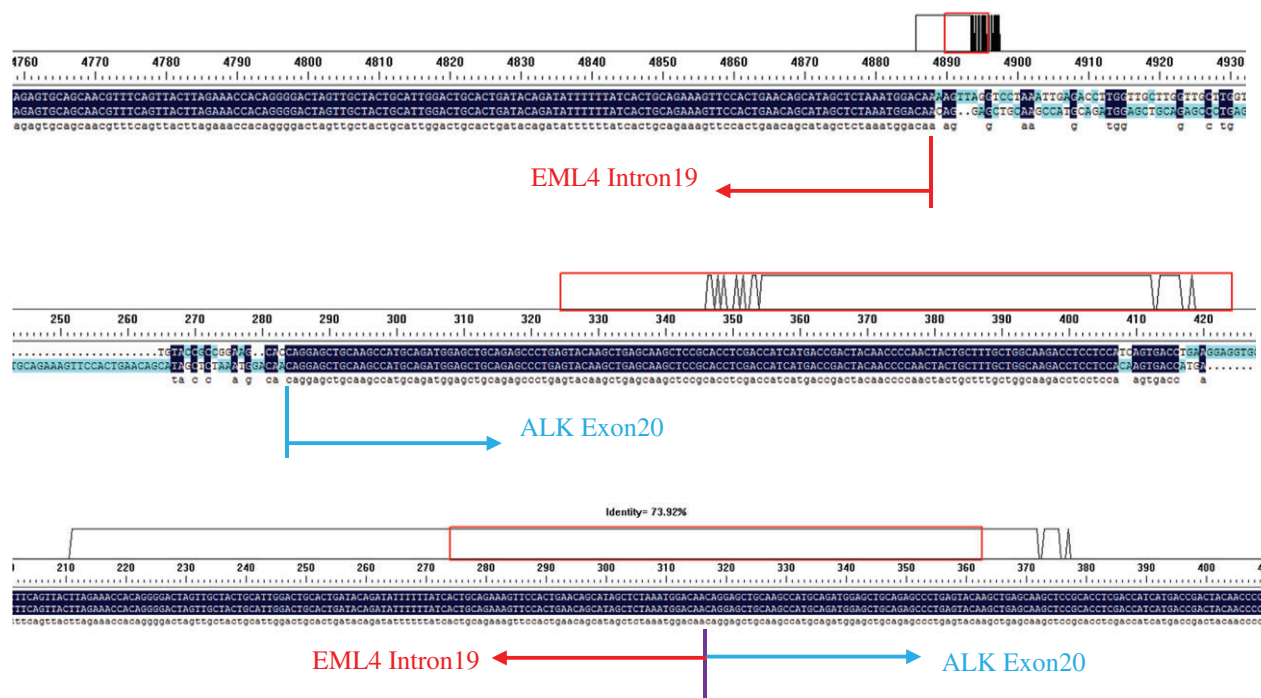
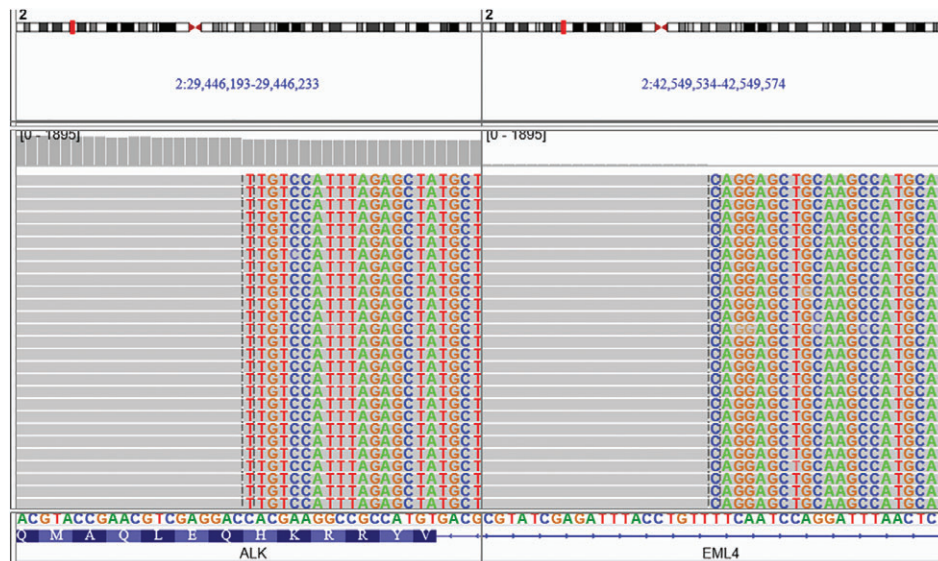
reduced. The metabolism had reduced and the liver and bone metastatic lesions had almost disappeared (Fig 4). The therapeutic efficacy was evaluated as a partial response (PR). We continued to use alectinib 300 mg b.i.d. per os. The PET-CT examination on 20 October (after 3 months of alectinib treatment) indicated that metabolism in the upper lobe of the right lung was low and the liver and bone metastases were not obvious. The therapeutic efficacy was again evaluated as PR.

On 8 February 2018 (after 6 months of alectinib), PET-CT indicated soft tissue masses on both sides of the right second rib (2.1\*1.6\*1.6 cm and 2.1\*1.9\*2.1 cm) with significantly elevated metabolism (maximum standardized uptake value 23.4/21.4). Although the right lung lesion and the liver and bone metastases were no longer obvious, new tumor metastasis was considered (Fig 5). The therapeutic efficacy was evaluated as progressive disease (PD). We believed that the patient acquired drug resistance to alectinib and therefore performed another cervical lymph node biopsy on 16 February 2018. Gene sequencing showed a high abundance of *EML4-ALK* (E19: A20) rearrangement (mutation abundance: 45.6%) and *c-MET* copy amplification (CN = 2.9). We altered the targeted drug to crizotinib 250mg b.i.d. combined with local radiotherapy. No apparent side effects were observed in two months of treatment. On 19 April 2018, PET-CT indicated that the intercostal soft tissue mass on the right side second rib was significantly smaller and the metabolism had decreased. Primary right upper lobe lesions and liver and bone metastases were no longer obvious (Fig 6). The therapeutic efficacy was evaluated as PR and the patient continues to be treated with crizotinib.



**Figure 1** Positron emission tomography-computed tomography baseline results 6 July 2017.

**Figure 2** IGV screenshots (*EML419-ALK20*) of the fusion sample.

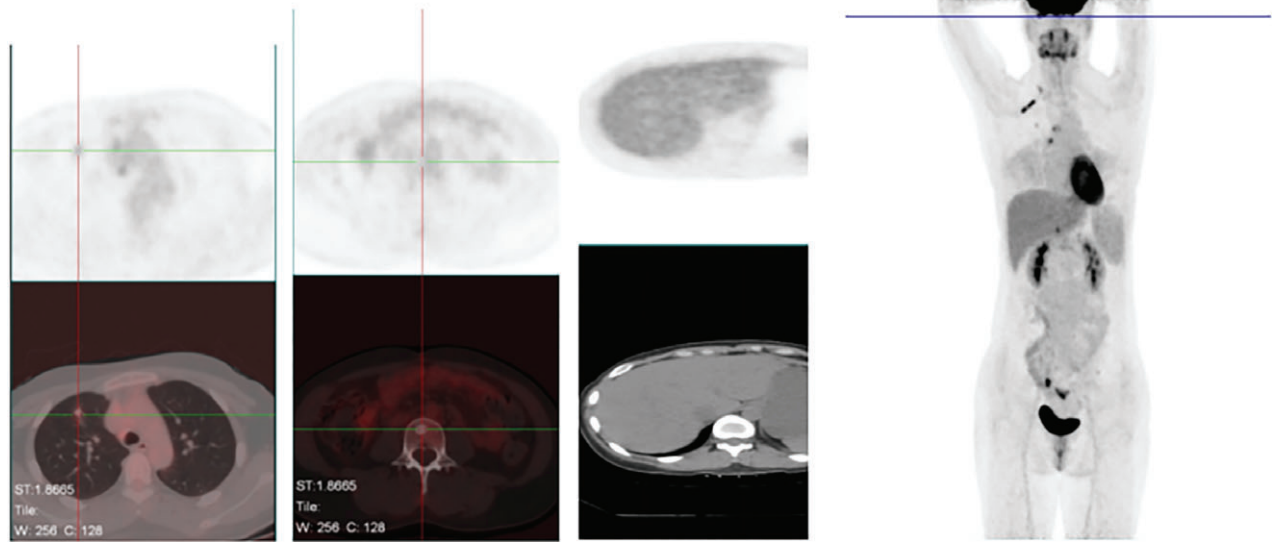


**Figure 3** DNA Sanger sequencing results.

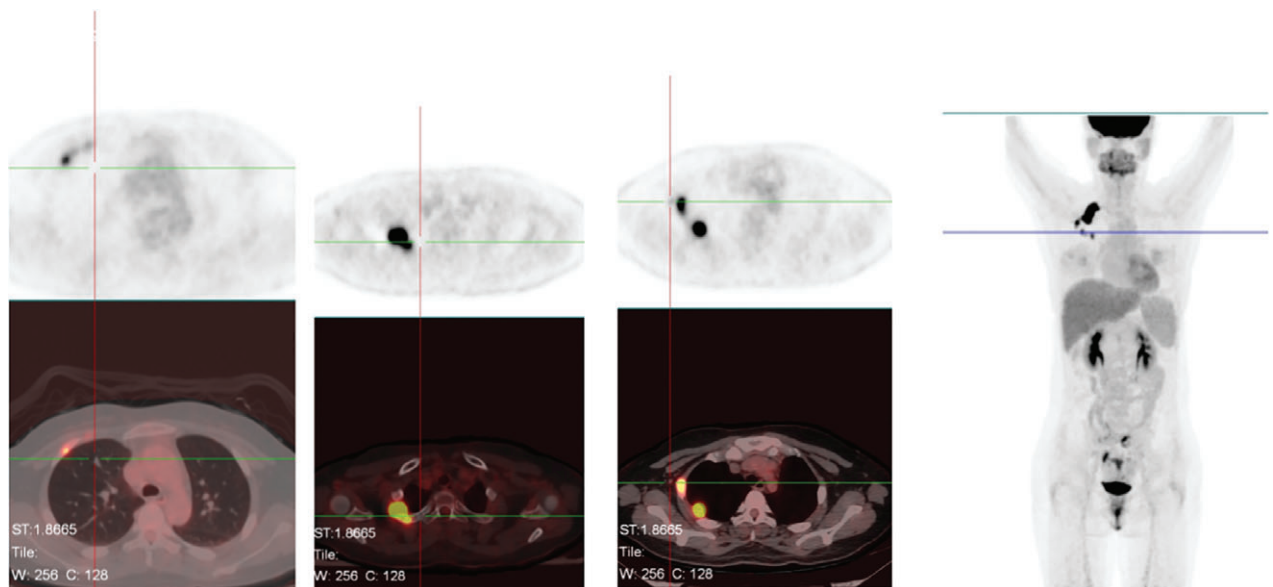
**Discussion**

Our patient is the first reported case of *EML4-ALK* (E19: A20) fusion worldwide. No relevant reports were found in a database search including PubMed, Ovid, and Web of Science. This fusion variant is also not included in the Catalogue of Somatic Mutations in Cancer database (COSMIC v85, 8 May 2018).<sup>11</sup> Since Soda *et al.* first discovered the

*ALK* gene mutation *EML4-ALK* (E13: A20) in lung adenocarcinoma tumor tissues through proteomics in 2007,<sup>12</sup> at least 28 kinds of *EML4-ALK* fusion variants have been reported.<sup>11</sup> The most common are *EML4* variant 1 (v1: exon 13 and *ALK* exon 20 fusion [E13: A20]) and variant 3 (v3a/b: exon 6 a/b and *ALK* exon 20 fusion [E6a/b: A20]), with incidence of > 60%. All variants retain the



**Figure 4** Results after one month of alectinib 300 mg orally twice per day, 16 Aug 2017.

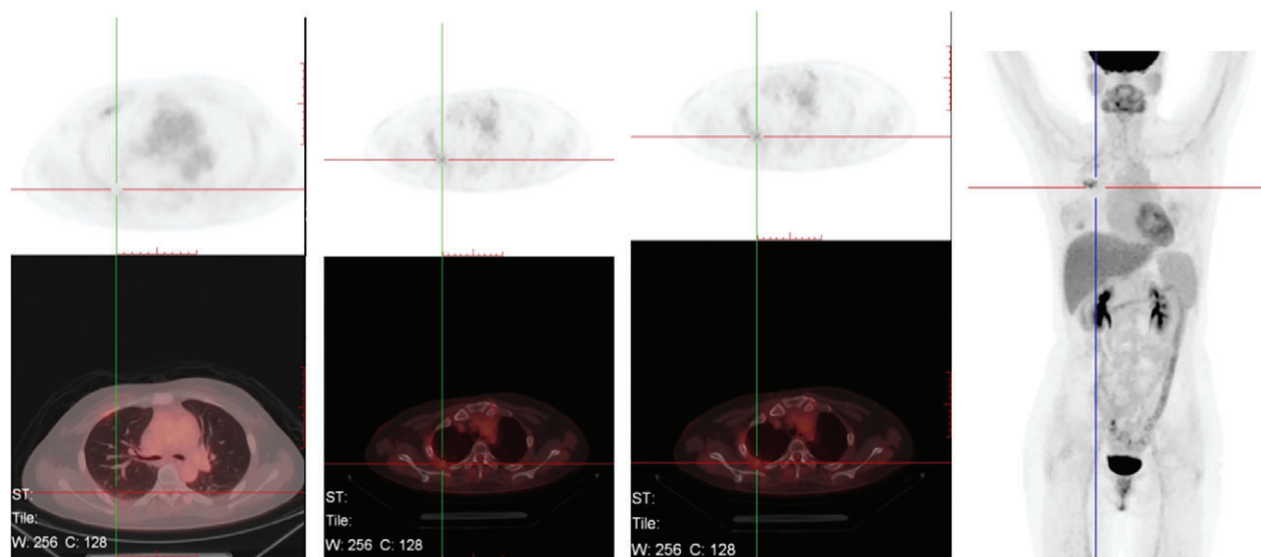


**Figure 5** Results after six months alectinib 300 mg orally twice per day, 8 Feb 2018.

entire tyrosine kinase domain of *ALK* and the N-terminal curly helix region of *EML4*, which is essential for the dimerization and constitutive activation of *ALK*.<sup>13</sup>

The results of the ALEX study were published in 2017: the median progression-free survival (mPFS) period after alectinib treatment is 25.7 months, which is the longest mPFS of current first-line treatment.<sup>7</sup> In our case, PFS on

alectinib treatment was only six months, far lower than the average data. The biopsy showed a significant increase in the abundance of *EML4-ALK* mutations and activation of the MET bypass, which is consistent with research on the resistance mechanisms of alectinib, which include point mutations (including G1202R, I1171, V1180L<sup>10</sup> and activation of hepatocyte growth factor-MET bypass.<sup>14</sup> In this



**Figure 6** Results after two months of crizotinib 250 mg twice per day, 19 Apr 2018.

case, the patient showed resistance to alectinib after a short time, but exhibited a good response to crizotinib, which can be explained MET bypass activation.<sup>14</sup> Lin *et al.* studied the relationship between *EML4-ALK* variant subtypes V1 and V3 and drug resistance and found that compared to the V1 variant, the V3 variant is more likely to develop drug resistance and to produce a G1202R drug-resistant mutation, suggesting that the *EML4-ALK* variant subtype may be related to the efficacy of targeted drugs.<sup>15</sup> *ALK* expression at the protein level indicates functional and thus potential therapeutic relevance.<sup>16</sup> Interestingly, our patient showed a significant increase in the abundance of *EML4-ALK* fusion mutations, which may indicate that the *EML4-ALK* (E19: A20) variant may show an unsatisfactory response specifically to alectinib. Although ours is presently the only reported case of *EML4-ALK* (E19: A20), our experience shows that it is necessary to explicitly identify the subtype of variants in *ALK*-positive patients, which may subsequently identify the patients who will benefit from treatment with *ALK* inhibitors.

## Acknowledgment

We thank the patient and her family for providing their information for this study.

## Disclosure

No authors report any conflict of interest.

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