

# Squamous Cell Transformation of Primary Lung Adenocarcinoma in a Patient With *EML4-ALK* Fusion Variant 5 Refractory to ALK Inhibitors

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## ABSTRACT

Histologic transformation from adenocarcinoma to squamous cell carcinoma in lung cancer has not been reported as a mechanism of resistance to ALK inhibition. This report describes the clinical course of a female former light smoker with metastatic lung adenocarcinoma whose tumor underwent histologic transformation from a well-differentiated lung adenocarcinoma to a well-differentiated lung squamous cell carcinoma in the same location at the left mainstem bronchus while maintaining the *ALK* fusion oncogene without any resistance mutations. After experiencing disease progression while on crizotinib, the patient participated in clinical trials that provided early access to the novel ALK inhibitors ceritinib and alectinib before they were commercially available. Tumor recurrence occurred at the primary and metastatic central nervous system sites (ie, brain and spine). At tumor progression, liquid biopsy and tumor genomic profiling of plasma cell-free DNA next-generation sequencing (NGS) provided an accurate diagnosis with a short turnaround time compared with the tissue-based targeted capture NGS. The patient received several courses of radiation primarily to the brain and spine during her disease course. Her disease did not respond to the immune checkpoint inhibitor nivolumab, and she died on home hospice approximately 4 years after diagnosis. This case supports the importance of both histopathologic assessment and comprehensive genomic profiling in selecting appropriate treatment for patients with refractory, metastatic, *ALK* oncogene-driven non-small cell lung cancer. Use of symptom-directed radiation in tandem with ALK inhibitors contributed to the disease and symptomatic control and prolonged survival in this patient.

*J Natl Compr Canc Netw* 2019;17(4):297–301  
doi: 10.6004/jnccn.2019.7291

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## Background

Originally discovered in lymphomas,<sup>1</sup> the *ALK* fusion oncogene with gain-of-function cytoplasmic tyrosine kinase activity has since been identified as an oncogenic driver in 3% to 10% of patients with non-small cell lung cancer (NSCLC).<sup>2,3</sup> FDA approval of crizotinib, a small molecule ALK tyrosine kinase inhibitor (TKI), only 3 years after the discovery of the *ALK* fusion oncogene represents one of the most rapid bedside translational advances in the history of targeted cancer therapy.<sup>4</sup> Among the many fusion partners that have been reported, *EML4* is the most common gene partner of *ALK* through a paracentric inversion of chromosome 2 inv(2) (p21;p23). We previously reported that in a cohort of 200 NSCLC specimens, the *EML4-ALK*-positive transcripts included 109 variant 1 (V1; 54.5%), 20 V2 (10.0%), 68 V3 (34.0%), and 3 V5a (1.5%) variants.<sup>5</sup> Most (n = 188; 94.0%) *EML4-ALK*-positive NSCLC tumors had adenocarcinoma histology. *ALK* expression level varied significantly among different *EML4-ALK* variants and individual tumors, with V3 having the lowest *ALK* expression level by reverse transcription polymerase chain reaction (RT-PCR) assay.<sup>5,6</sup> Although *EML4-ALK* V1 has been shown to be most common in Caucasians, V3 has been shown to be most common in the Chinese population.<sup>7</sup> Recent studies have shown that *EML4-ALK* V1 and V3 may have different sensitivity to ALK inhibitors and different resistant mutations.<sup>8,9</sup> Little is known regarding whether rare variants other than *EML4-ALK* V1, V3, or different fusion partners affect the clinical benefit of ALK inhibitors.

Histologic transformation from lung adenocarcinoma (LUAD) to small cell lung carcinoma (SCLC) or large cell neuroendocrine tumor has been associated with resistance to EGFR<sup>10–12</sup> and ALK TKIs.<sup>13</sup> Although histologic transformation from LUAD to lung squamous

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cell carcinoma (LUSC) has been reported as a mechanism of resistance to EGFR inhibition,<sup>14,15</sup> it has not been reported for ALK inhibition. This report describes the clinical course of a female former light smoker with metastatic LUAD whose tumor underwent histologic transformation from a well-differentiated LUAD to a well-differentiated LUSC in the same location in the left mainstem bronchus while maintaining the *ALK* fusion as the driver oncogene without any known resistance mutation detected by clinical next-generation sequencing (NGS) assays.

## Materials and Methods

The patient provided consent to participate in an Institutional Review Board–approved study (University of California, Davis, #226210), as well as consent for publication. The clinical history, radiographic images, and histologic and immunohistochemistry stains were performed as standard of care clinical tests at our institution. Fluorescence in situ hybridization (FISH) assay was performed using the Vysis ALK Break Apart FISH Probe Kit (Abbott Laboratories) at a commercial CLIA-certified laboratory. A board-certified radiologist (E.H.M) and pathologists (J.P.G., Y.Z.) selected the images. Plasma cell-free DNA (cfDNA) and tumor specimens were subjected to the hybridization capture–based NGS (FoundationACT for blood and FoundationOne for tissue) assays performed at a CLIA-certified, College of American Pathologists (CAP)–accredited, New York State–approved laboratory (Foundation Medicine, Inc).<sup>16,17</sup>

## Case Presentation

In January 2013, a 60-year-old Hispanic female former light smoker (4 pack-year history who quit 33 years prior to diagnosis) was diagnosed with LUAD with a lingular primary, at least 9 subcentimeter metastases to the brain, and with additional lesions in the liver, spleen, and bones. The patient underwent bronchoscopy, which revealed diffuse submucosal hemorrhage in the left mainstem bronchus and a tumor obstructing approximately 30% to 50% of the left upper lobe which corresponded to the chest CT findings (Figure 1A). The diagnostic tumor specimen tested negative for *EGFR* L858R, exon 19 deletion, and T790M mutations by RT-PCR, but positive for *ALK* gene rearrangement by FISH, without any information on the fusion partner. Figure 2 and supplemental eTable 1 (available with this article at JNCCN.org) summarize the major diagnostic and treatment course of this patient over almost 4 years (in order): 30 Gy of palliative whole-brain radiation therapy (WBRT) in 10 daily fractions; crizotinib for 13 months; 30 Gy of palliative external-beam RT (EBRT) to T11–L1 in 10 daily fractions; ceritinib for 10 months; alectinib for 7 months; 30 Gy of palliative EBRT to T4–T9 in 10 fractions. The patient also received zoledronic acid first and then

denosumab for approximately 2 years to prevent fracture, spinal cord compression, or the need for RT.

In July 2016, the patient presented with chest and back pain and dyspnea. Chest CT showed disease progression with confluent soft tissue attenuation and adenopathy within the subcarinal space that invaded and occluded the left mainstem bronchus and extended into the left upper and lower lobes with postobstructive consolidation (Figure 1B), small left pleural effusion, right-sided mediastinal adenopathy, and new pleural nodularity along the medial aspect of the right hemithorax. A bronchoscopy on August 2, 2016, revealed that the left mainstem bronchus was completely obliterated by friable tissue. Cryoablation was performed with restoration of approximately 50% patency. Pathology showed invasive well-differentiated LUSC (Figure 1D) that was TTF-1–negative (Figure 1F) and P40–positive (data not shown) compared with the original LUAD (Figure 1C) that was TTF-1–positive (Figure 1E). Tumor genomic profiling assay of this tumor and plasma cfDNA revealed a rare driver oncogene, *EML4-ALK* V5 (supplemental eTable 2). Other notable genomic alterations in the tumor specimen included *PTEN* loss of exon 1, *CDKN2A* and *CDKN2B* loss, and *FAS* loss. The tumor had high tumor mutational burden (TMB) of 15.17 mutations per megabase (Muts/Mb), and positive PD-L1 expression with a tumor proportion score of 3% by PD-L1 IHC 22C3 pharmDx assay (Agilent).

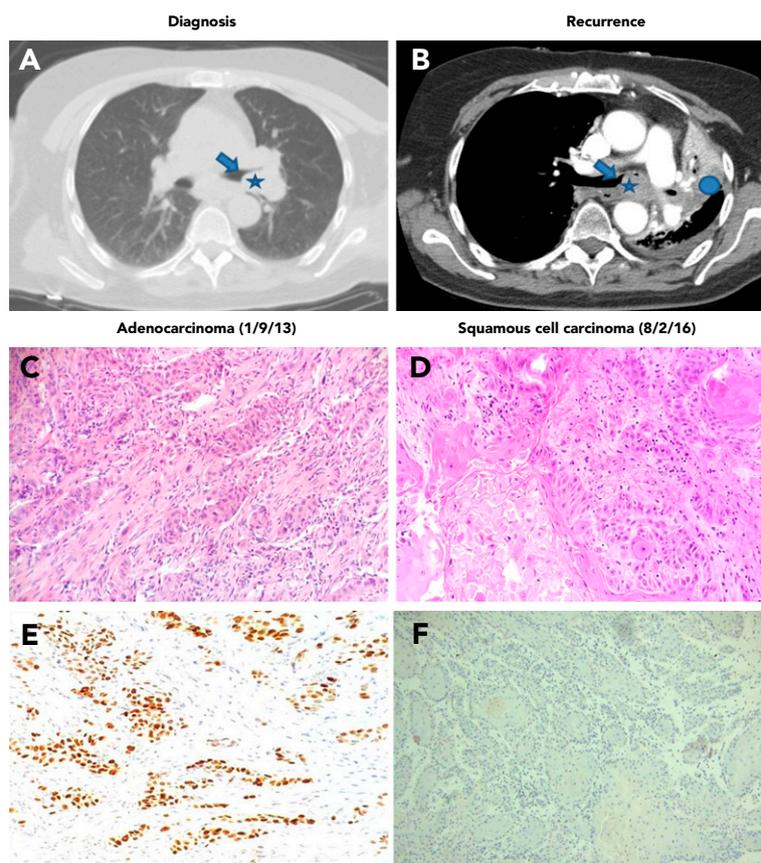
Due to her poor performance status, the patient was deemed not a candidate for chemotherapy. Instead, she received 30 Gy of EBRT to the left hilum in 10 daily fractions, and showed symptomatic improvement. Shortly thereafter, brain MRI revealed diffuse progression of intracranial metastases. After extensive discussion, an additional course of WBRT to 25 Gy in 10 fractions was performed. She received pembrolizumab for 2 cycles without any significant clinical improvement, and died after enrolling in home hospice care several weeks later.

## Discussion

### NGS for Detecting Rare Variants of *EML4-ALK* Fusion Oncogene in Tissue and Blood

Histology assessment of lung cancer at diagnosis is important for selecting chemotherapy and molecularly targeted therapy.<sup>18</sup> Currently, testing for *ALK* rearrangements is recommended for patients diagnosed with adenocarcinoma and mixed lung cancers with an adenocarcinoma component, regardless of clinical characteristics.<sup>19</sup> At initial diagnosis in early 2013, our patient was found to have *ALK*-rearranged LUAD by the *ALK* break-apart FISH assay. However, FISH is less sensitive or unable to detect the fusion variants and partners compared with NGS.<sup>20</sup>

Despite exceptional tumor response rates and improved survivals, almost all patients with *ALK*-rearranged NSCLC eventually develop acquired resistance to the



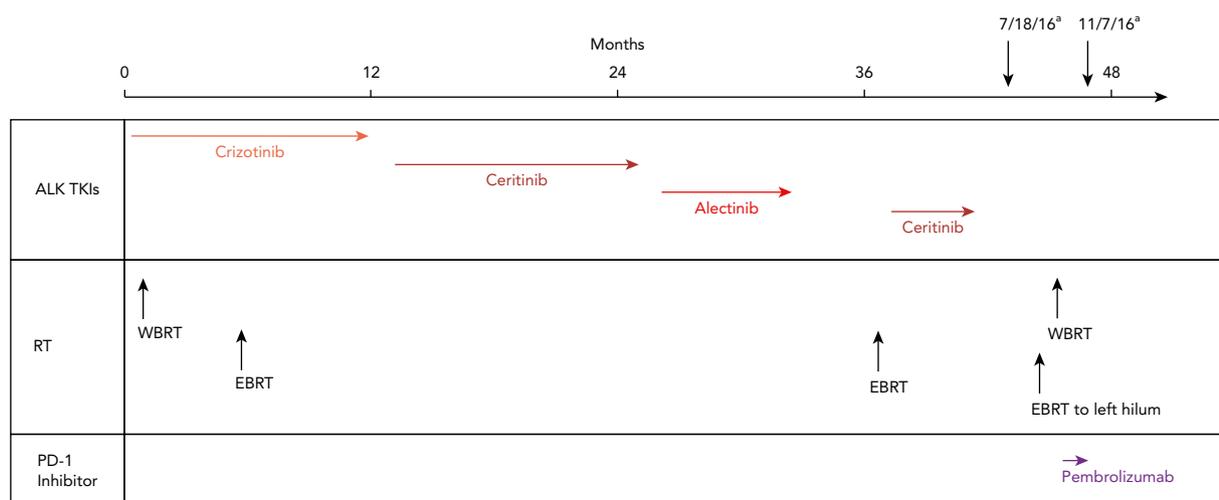
**Figure 1.** Radiographic imaging, histomorphology, and immunohistochemical staining of the initial lung adenocarcinoma (LUAD) and lung squamous cell transformation at the same tumor site. (A) Chest CT showed the tumor at the left upper mainstem (star) obstructing the left mainstem bronchus (arrow), causing (B) left upper lobe collapse (solid circle). (C–F) Histologic assessment of different lung pathologies. (C) Hematoxylin-eosin staining revealed LUAD at diagnosis and (D) invasive, well-differentiated, squamous cell carcinoma approximately 3.5 years later at the same location. (E) TTF-1 immunohistochemical staining was positive in LUAD and (E) negative in lung squamous cell carcinoma. The adenocarcinoma also stained positive for CK7 and negative for CK20 and synaptophysin (data not shown). The squamous cell cancer stains were positive for P40 (data not shown) (original magnification,  $\times 20$  for all).

ALK TKIs.<sup>21</sup> Both ALK-dependent and -independent mechanisms can contribute to the development of resistance mechanisms to ALK inhibitors, which include the presence of a second-site mutation in the tyrosine kinase domain of *ALK* gene in 20% to 30% of cases, *ALK* amplification, *MET* proto-oncogene amplification, activation of bypass pathways, and, rarely, histologic transformation.<sup>22</sup> In the present case, we found histologic transformation from well-differentiated LUAD to well-differentiated keratinizing LUSC in the same location of the left main bronchus site in August 2016. We could not determine the *ALK* fusion partner and variant of the original tumor, because there was insufficient tumor specimen remaining from the initial diagnosis. Detection of the oncogenic *EML4-ALKV5* without any known molecular resistance mutations in both the tumor and blood after disease had progressed on 3 ALK inhibitors suggests histologic transformation might be a resistance mechanism to the ALK inhibitors.

### Potential Mechanisms and Clinical Implication of Histologic Transformation

Histologic transformation from LUAD to SCLC has been reported in *EGFR*-mutant and *ALK*-rearranged LUAD.<sup>23–25</sup> Recent reports suggest the transformation occurs from early clonal evolution and coexpression of molecular markers (such as loss of RB and P53) found in the transformed histology (ie, SCLC).<sup>26,27</sup> These transformed tumors behave biologically like SCLC and have a treatment response and survival comparable to those of typical SCLC.<sup>28</sup>

We do not know the timing and the mechanism controlling the histologic transformation at the same tumor site after ALK inhibitors and RT. Similar to our reported results, FoundationOne identified several genomic alterations, including *PTEN* loss, *CDKN2A* and *CDKN2B* loss, *FAS* loss, and *FBXW7* E113D – subclonal (supplemental eTable 2), that are frequently reported in LUSC but not LUAD. In addition, the tumor had a high TMB of 15.17 Muts/Mb. LUSC shows a higher TMB



**Figure 2.** Summary of the patient's clinical course for both extracranial and central nervous system tumors. The patient was diagnosed in January 2013 and passed away in December 2016. Arrowheads indicate time points for each intervention.

Abbreviations: EBRT, external-beam radiation therapy; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiation therapy.

<sup>a</sup>Blood draws were performed, and *EML4-ALK* variant 5 was the only genomic alteration detected in the plasma cell-free DNA by FACT (supplemental eTable 2).

than LUAD (9.6 vs 6.3 Muts/Mb, respectively) in a large human genomic database.<sup>29</sup> Unfortunately, our patient was paralyzed from spine metastasis and had significant physical deconditioning, rendering her unsuitable for chemotherapy. Although no adenocarcinoma or small cell component was identified in the resistant tumor with squamous cell transition, intertumor heterogeneity or sampling artifacts cannot be completely ruled out. Tumor genomic profiling identified the rare *EML4-ALKV5* as the only genomic alteration in plasma cfDNA at the time of tumor sampling of the squamous cell transition and 4 months later, and did not reveal any other resistant mutations to ALK inhibitors or other alterations (supplemental eTable 2), suggesting that the *ALK*-rearranged gene was the dominant oncogenic driver. In support of this, we recently observed that mice bearing xenografts established from the tumor biopsy performed at the time of the squamous cell transformation have significant tumor shrinkage in response to a newer ALK inhibitor brigatinib (data not shown).

### Multidisciplinary Management for Patients With NSCLC and ALK Fusion Oncogenes

Patients with *ALK*-rearranged NSCLC have been found to have a higher incidence of brain metastasis either at initial diagnosis or after control of systemic disease with crizotinib.<sup>21,30</sup> In approximately half of the patients treated with crizotinib, brain metastases develop or progress. Our patient was diagnosed with LUAD with a lingular primary with high TMB in both central nervous system and extracranial sites. After experiencing disease progression on crizotinib, our patient was enrolled in

clinical trials which enabled her to receive the second-generation ALK inhibitors ceritinib and alectinib before FDA approval. RT has been increasingly integrated into the clinical management of patients with metastatic NSCLC, both for symptom relief and for local disease control of oligometastatic progression while on otherwise successful systemic therapy, particularly in patients with oncogene-driven NSCLC on molecularly targeted therapy.<sup>31,32</sup> Our patient received 5 courses of palliative RT during her disease course. Use of symptom-directed RT in this patient in tandem with ALK inhibitors offered disease and symptom control that may have improved her survival. Although ICIs have revolutionized the treatment of patients with advanced NSCLC, and consistent with previous reports,<sup>33,34</sup> we did not observe any clinical response to pembrolizumab despite squamous cell transformation, positive PD-L1 immunohistochemical expression, and high TMB. Further study is needed to define the role of ICIs in *ALK*-rearranged NSCLC.

### Conclusions

To our knowledge, this is the first report of histologic transformation from LUAD to LUSC at the same tumor location while maintaining the *ALK*-rearranged driver oncogene. Tumor genomic profiling using NGS can identify the rare *EML4-ALKV5* fusion gene. Liquid biopsy and plasma cfDNA offer a quick and reliable alternative to invasive tissue biopsy to detect the rare driver oncogene and explore the resistance mechanisms. There are unmet needs to delineate the molecular mechanisms underlying historical transformation from LUAD to LUSC, to develop novel strategies to overcome the resistance to

## ALK TKIs with activity for both extracranial and intracranial metastases, and to develop effective cancer immunotherapy strategies for *ALK*-rearranged lung cancer.

Submitted September 29, 2018; accepted for publication February 26, 2019.

**Disclosures:** Dr. Gregg has disclosed that he is a consultant for Foundation Medicine; receives honoraria from and serves on a scientific advisory board for AstraZeneca; and is a consultant for Bristol-Myers Squibb. Dr. Yoneda has

disclosed that he is a scientific advisor for AstraZeneca and Guardant Health. Dr. Daly has disclosed that she receives research funding from EMD Serono. Dr. Li has disclosed that she is a scientific advisor for Foundation Medicine, Takeda, and PUMA, and receives grant/research support from Foundation Medicine, Pfizer, AstraZeneca, Hengrui, and Eureka. The remaining authors have disclosed that they have not received any financial consideration from any person or organization to support the preparation, analysis, results, or discussion of this article.

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