A Novel LINC00478/LINC01549 Intergenic Region-ALK Fusion Responded Well to Alectinib in a Patient With Lung Adenocarcinoma

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Introduction
Approximately 3% to 5% of patients with NSCLC bear ALK rearrangements.1 The administration of ALK tyrosine kinase inhibitors has achieved impressive clinical outcomes. Besides the classic EML4-ALK fusions, emerging ALK fusion variants, including intergenic fusions, were discovered.2,3 Here, we report a novel intergenic region fusion between LINC00478 and LINC01549 with exon 20 of ALK in a patient with NSCLC who responded well to alectinib.

Case Report
A 42-year-old woman who was a smoker was referred to our hospital with a 2-month history of cough in December 2019. A chest computed tomography scan was performed, which revealed a solid nodule in the lateral segment of the middle lobe and a high-density nodular shadow in the anterior segment of the superior lobe of the right lung. Multiple lymph node metastases were also observed in the right lung, right hilum, mediastinum, and right supraclavicular fossa. Immunohistochemical (IHC) staining of the lymph node in right supraclavicular fossa revealed it to be TTF-1-positive, Napsin A-positive, CK-positive, CK7-positive, CK20-negative, CK5/6-positive, Ki67-p (40% positive), P40-negative. The disease was then diagnosed as metastatic low-differentiated peripheral lung adenocarcinoma.

To guide targeted therapy, formalin-fixed and paraffin-embedded specimens were subjected to the DNA-based next-generation sequencing (NGS) analysis (in the College of American Pathologists–certified laboratory). A novel intergenic ALK fusion was detected (Fig. 1A). This fusion included the LINC00478/LINC01549 intergenic region and exons 20 to 29 of ALK, retaining the whole kinase domain. No other driver-gene mutations were discovered except for several concurrent mutations (Table 1). Alectinib (600 mg orally twice daily) was then administrated in January 2020. The patient then achieved partial response within 3 months (Fig. 1B and C), and the progression-free survival (PFS) exceeded 6 months by the time of submission. Informed consent was obtained from the patient and family for the publication of this case.

Discussion
To our knowledge, this is the first report describing the fusion of the intergenic region between LINC00478/LINC01549 and ALK exon 20 in lung adenocarcinoma. The durable response indicated the novel fusion as a potential alectinib-sensitive variant.

Alectinib and crizotinib exhibited great efficacies in ALK-positive NSCLC.4 Noteworthily, heterogenous responses of different ALK fusion variants to ALK tyrosine kinase inhibitors were reported,5 the disease control rate could vary from 63% to 95%, and the median PFS varied from 4.2 to 11.0 months among variants. Hence,
identifying sensitive ALK fusion bears great value for clinical applications of ALK inhibitors. NGS exhibited strengths in identifying a fusion variant than IHC and fluorescence in situ hybridization by providing specific partner genes and the fusion break points and concurrent oncogenic mutations. In the meantime, sensitive ALK fusions usually retained the whole ALK kinase domain that was responsible for ALK activation. Our results from NGS confirmed that this new fusion retained the whole kinase domain (exon 20–29). Owing to the limited sample, the confirmation from fluorescence in situ hybridization or IHC could not be conducted. Because this intergenic fusion was the only driver-gene mutation detected, plus the durable

Table 1. Concurrent Gene Mutations Detected by NGS

| Gene Name | Mutation | Mutation Abundance, % |
|-----------|----------|-----------------------|
| TP53 | Intron10 c.1101-1G>A | 38.38 |
| ACVR2A | Exon7 p.S258fs c.767_773dupGCACCAG | 25.04 |
| CTNNB1 | Exon7 p.K335I c.1004A>T | 20.34 |
| PBRM1 | Exon17 p.R836L c.2507G>T | 36.18 |
| PBRM1 | Exon17 p.Y834C c.2501A>G | 36.47 |
| ENOX1-TYRO3 | ENOX1(Exon2)-TYRO3(Exon1) fusion | 16.97 |

NGS, next-generation sequencing.
response (PFS >6 mo) to alectinib, we, therefore, considered this novel LINC00478/LINC01549-ALK fusion as a sensitive variant.

In recent years, intergenic fusion is attracting attention because it did bring the target clinical benefit for some of the fusion carriers. Our patient exhibited a good response to alectinib, which may enrich the evidence on intergenic ALK fusion as a potential oncogenic mutation. Further studies are needed to determine the oncogenic and molecular mechanisms of this fusion.

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