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Oncogenic Fusions Involving Exon 19 of *ALK*

Anh T. Le, BA, **Marileila Varella-Garcia, PhD**, and **Robert C. Doebele, MD, PhD**
Department of Medicine, Division of Medical Oncology, University of Colorado, Anschutz Medical Campus, Aurora, Colorado

Penzel et al.[1] recently described a lung adenocarcinoma patient with an *EML4-ALK* fusion between exon 6 of echinoderm microtubule associated protein like 4 *(EML4)* and exon 19 of anaplastic lymphoma kinase (*ALK)* (E6;A19) as a novel molecular variant. It should be noted that this *EML4-ALK* (E6;A19) fusion has been previously reported by our group in a 62-year-old woman also with lung adenocarcinoma.[2] The second finding of this atypical *EML4-ALK* breakpoint (the majority of ALK gene fusions occur at exon 20 of *ALK*) suggests that it may not be an isolated event, and highlights the great diversity of fusion events involving this gene. Furthermore, an *FN1-ALK* gene fusion was previously identified in a malignant stromal sarcoma patient, in which the fusion also occurs at exon 19 of *ALK*.[3] The significance of these *ALK* exon 19 fusion variants is currently unknown, but is interesting as it expresses the ALK transmembrane domain. The subcellular localization of these exon 19-containing variants should be further investigated to better understand the implications of this finding; prior evidence suggests *EML4-ALK* (E13;A20) is localized within the cytoplasm.[4] Oncogenic fusions involving *ROS1* and *RET* in lung cancer have been shown previously to also include the transmembrane domain in some instances.[5] The patient described by our group demonstrated a partial response to crizotinib and experienced a progression free survival of approximately 6.5-months, supporting the argument that these patients be considered for *ALK* inhibitor therapy like other patients who are positive for *ALK* rearrangements.[2]

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Address for correspondence: Robert C. Doebele, MD, PhD, Department of Medicine, Division of Medical Oncology, University of Colorado Anschutz Medical Campus, Aurora, CO. robert.doebele@ucdenver.edu.

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