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Commentary: Using the entire toolbox for improved survival in anaplastic lymphoma kinase-positive non-small cell lung cancer: The next normal?

Staci Beamer, MD, and Jonathan D'Cunha, MD, PhD

Anaplastic lymphoma kinase (ALK) rearrangement is a clinically relevant transforming fusion gene detected in non-small cell lung cancer (NSCLC). Several studies have shown ALK gene rearrangement to correlate with adenocarcinoma histology, younger patients, and never or light smokers.¹ ALK rearrangement is present in approximately 3% to 7% of NSCLC and is mutually exclusive from tumors with EGFR and KRAS mutations.² Tyrosine kinase inhibitors (TKIs) developed to target this rearrangement include crizotinib, ceritinib, alectinib, and most recently Brigatinib.³ The majority of research to date in the ALK rearrangement population is focused in the metastatic setting, analyzing the success of targeted therapies. More recently, analysis of the prognostic impact of ALK rearrangement status on earlier stage, surgically treated cases has produced conflicting results.⁴⁻⁶

The article in this issue of the *Journal* by Matsuura and colleagues⁷ adds to the literature by examining both the prognostic impact of ALK rearrangement in surgically treated patients and postrecurrence survival rates in patients with ALK rearrangement who developed recurrence. It is a single-center retrospective study over an 11-year period from 1996 to 2007. In total, 1925 surgically treated patients were reviewed. ALK immunohistochemistry was positive for the ALK rearrangement in 75 patients who were then propensity matched with 75 patients without ALK rearrangement. Propensity score matching was unsuccessful in controlling for smoking status, as the

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CENTRAL MESSAGE

Improved survival was seen in ALK-rearranged lung cancer using available methods, including surgery, targeted therapy, and local ablative therapy for recurrence. Is this the next normal for precision?

ALK+ group had a high percentage of never or light former smokers. Four EGFR-positive patients were included in the non-ALK-rearranged group. The majority of patients studied were stage Ia (71%) or Ib (12%), but stage II (12%) and stage III (5%) disease were also included. Five-year overall survival (OS), cancer-specific survival (CSS), and time to recurrence were reported. Multivariable analysis revealed that ALK rearrangement was a prognostic factor for improved OS and SCC independent of clinicopathologic factors or treatment era. 5-year OS and CSS were 95% and 97% in patients positive for ALK compared with 75% and 77% in patients negative for ALK ($P = .007$, $P = .003$). A total of 53 cases developed postoperative recurrences (21 ALK rearranged, 31 non-ALK). Five-year postrecurrence survival was significantly greater in the ALK-rearranged group (65% vs 25%). These results were directly affected by TKI administration and greater rates of local ablative therapy in the ALK-rearranged group. Matsuura and colleagues concluded that surgically resected ALK-rearranged NSCLC was associated with better long-term outcomes. Interestingly, for cases with recurrence, greater rates of oligo-metastatic disease allowed for increased use of local ablative therapy, translating to an increased survival. The survival advantage seen with TKI administration was consistent with previous studies comparing TKI with cytotoxic chemotherapy in this population.

NSCLC treatment is increasingly focused on molecular targets and personalized therapy, making information about

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prognosis and therapy response for genetically altered tumors across all stages of disease essential to our progress. Current literature on the prognostic implications of the surgically treated ALK-rearrangement population suffers from lack of consistency in the comparison populations. Studies including the one by Matsuura and colleagues⁷ showing ALK-rearrangement as a positive indicator have included both nonsmoking and heavy smoking populations. The genetic phenotype of NSCLC may be inherently different in the never/light smoker population and possibly explains the conflicting prognostic reports. The findings in this large study support the use of TKIs following surgical resection of ALK-rearrangement. Close follow-up for oligometastatic recurrence was a major message with the attention to local ablative therapies when aiming to improve cancer-specific survival. They advocate for using the whole toolbox: surgery, systemic therapy (TKIs), and local ablative therapy.

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Commentary: One size does not fit *ALK*—targeted therapy, local ablation of recurrence, and improved outcomes after resection of *ALK*-positive lung cancer

Ashok Muniappan, MD

It is good to have hair-splitters and lumpers.

—Charles Darwin, in a letter to J.D. Hooker (1857)

The sole illustration in *The Origin of Species* (1859), Charles Darwin (1809-1882).

CENTRAL MESSAGE

ALK mutation in resected lung cancer is associated with improved survival compared with non-mutant lung cancer. Oligometastasis may be managed effectively with ablation and tyrosine kinase inhibition.

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The first reports of targeting epidermal growth factor receptor-mutant lung cancer with gefitinib in 2004 were quickly followed by the discovery of anaplastic lymphoma