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.

See Article page 441.

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

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It is good to have hair-splitters and lumpers.

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

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References

1. Yang P, Kulig K, Boland JM, Erickson-Johnson MR, Oliveira AM, Wampfler J, et al. Worse disease-free survival in never-smokers with ALK+ lung adenocarcinoma. *J Thorac Oncol*. 2012;7:90-7.
2. Kim MH, Shim HS, Kang DR, Jung JY, Lee CY, Kim DJ, et al. Clinical and prognostic implications of ALK and ROS1 rearrangements in never-smokers with surgically resected lung adenocarcinoma. *Lung Cancer*. 2014;83:389-95.
3. Serritell AV, Bestvina CM. Anaplastic lymphoma kinase mutation-positive non-small cell lung cancer. *Thorac Surg Clin*. 2020;30:137-47.
4. Chaft JE, Dagogo-Jack I, Santini FC, Eng J, Yeap BY, Izar B, et al. Clinical outcomes of patients with resected, early stage ALK-positive lung cancer. *Lung Cancer*. 2018;122:67-71.
5. Golding B, Luu A, Jones R, Vilorio-Petit AM. The function and therapeutic targeting of anaplastic lymphoma kinase (ALK) in non-small cell lung cancer. *Mol Cancer*. 2018;17:1-15.
6. Blackhall FH, Peters S, Bubendorf L, Dafni U, Kerr KM, Hager H, et al. Prevalence and clinical outcomes for patient with ALK-positive resected stage I to III adenocarcinoma: results from the European thoracic oncology platform lungscape project. *J Clin Oncol*. 2014;32:2780-7.
7. Matsuura Y, Ninomiya H, Ichinose J, Nakao M, Okumura S, Nishio M, et al. Prognostic impact and distinctive characteristics of surgically resected anaplastic lymphoma kinase-rearranged lung adenocarcinoma. *J Thorac Cardiovasc Surg*. 2022;163:441-51.e1.

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.

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

kinase (*ALK*) rearrangements in lung cancer in 2007. These prototypical targetable mutations are now joined by actionable driver mutations in ROS proto-oncogene 1 (*ROS1*), B-Raf proto-oncogene (*BRAF*), neurotrophin receptor tyrosine kinase (*NTRK*), human epidermal growth factor receptor (*HER2*), rearranged during transfection gene (*RET*), Kirsten rat sarcoma viral oncogene homolog (*KRAS*), and gene amplification in mesenchymal-to-epithelial transition factor (*MET*). About one-half of all lung adenocarcinomas harbor a driver mutation targetable by approved or investigational drugs. Although clinical applicability of targetable mutations has primarily been in the metastatic setting, the surgeon wonders if she may use targeted therapy to increase cure rates and prolong survival in patients undergoing resection for early-stage lung cancer.

In this issue of the *Journal*, Matsuura and colleagues¹ present one of the largest single-center cohorts of resected *ALK*-positive lung cancer. Their main observation is that patients with resected *ALK*-mutant lung cancer exhibit improved overall and cancer-specific survival compared with patients with non-*ALK* mutant lung cancer. Most previous reports indicated that *ALK* did not alter prognosis or was associated with decreased survival after surgical resection. The explanation for improved outcomes in *ALK*-positive resected cancers in Matsuura and colleagues' study may lie in the intriguing observation that recurrence in these patients tended to be oligometastatic, which permitted a greater use of local ablative therapies in concert with systemic tyrosine kinase inhibitor therapy.

Could the remarkable efficacy of targeted therapy in the metastatic setting be harnessed for surgically resected early-stage lung cancer before recurrence? In the recent ADAURA (AZD9291 Versus Placebo in Patients With Stage IB-IIIa Non-Small Cell Lung Carcinoma, Following Complete Tumor Resection With or Without Adjuvant Chemotherapy) trial, investigators found that osimertinib administered to patients with surgically resected stage II to IIIa epidermal growth factor receptor-mutant lung cancer dramatically improved disease-free survival.² One wonders if adjuvant tyrosine kinase inhibitor administration in patients positive for *ALK*, such as those in Matsuura and colleague's study, would have led

to even better survival than observed. The phase III ALINA (Adjuvant Alectinib Versus Adjuvant Platinum-Based Chemotherapy in Patients With *ALK* Positive Non-Small Cell Lung Cancer) study will seek to answer this very question.³ Another avenue for research is to assess whether neoadjuvant targeted therapy of lung cancer improves resectability and survival, as studied by the Lung Cancer Mutation Consortium (LCMC4 trial).

The "splitters" are winning, as lung cancer subtypes based on molecular alterations, protein expression, and many other patient and tumor phenotypes distinguish variations in prognosis and therapeutic options. The 9th edition of lung cancer staging will likely incorporate mutational status as a data element for the first time. Amid all this compartmentalization, do the "lumpers" have any hope? Immunotherapy, which arguably may benefit the largest number of patients as it is not predicated on a specific and relatively infrequent mutation, is a broadly applicable therapy that has already revolutionized the treatment of advanced lung cancer. Immunotherapy is now making inroads in earlier stages of resectable lung cancer. The promising strategy of induction chemo-immunotherapy for IIIa lung cancer was recently demonstrated in the successful phase II NADIM (Neoadjuvant Chemotherapy and Nivolumab in Resectable Non-Small Cell Lung Cancer) study, which showed dramatic complete and major pathologic response rates and a very encouraging 77% progression-free survival at 24 months.⁴ Perhaps there is room for both the "hair-splitters and lumpers" in the future of lung cancer treatment.

References

1. Matsuura Y, Ninomiya H, Ichinose J, Nakao M, Okumura S, Nishio M, et al. Prognostic impact and distinctive characteristics of surgically resected anaplastic lymphoma kinase-rearranged lung adenocarcinoma. *J Thorac Cardiovasc Surg*. 2022;163:441-51.e1.
2. Wu Y-L, Tsuboi M, He J, John T, Grohe C, Majem M, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. *N Engl J Med*. 2020;383:1711-23.
3. A Study Comparing Adjuvant Alectinib Versus Adjuvant Platinum-Based Chemotherapy in Patients With *ALK* Positive Non-Small Cell Lung Cancer. Available at: <https://clinicaltrials.gov/ct2/show/NCT03456076>. Accessed November 8, 2020.
4. Provencio M, Nadal E, Insa A, García-Campelo MR, Casal-Rubio J, Dómine M, et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2020;21:1413-22.