See Article page e73.

Commentary: KRAS-mutant lung adenocarcinomas—a work in progress

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In this article, Ma and colleagues¹ aim to evaluate the prevalence and prognostic significance of KRAS-mutant lung adenocarcinomas among a variety of subgroups. As the authors note, our understanding of the prognostic role is evolving. Although this report fills in some of the gaps, the utility of Ma and colleagues' findings remains indeterminate, given this marker was prognostic in some subgroups but not in others.

The International Association for the Study of Lung Cancer and the American Joint Committee on Cancer have called upon collaborators to submit data on eligible patients to inform the ninth edition of the tumor–node–metastasis classification for lung cancer, which includes potential biomarkers and mutations.² Although Ma and colleagues have amassed a respectable cohort and investigated a novel and potentially useful genomic marker, KRAS, the application of these data is yet unproven. To date, phase I clinical investigations have shown promise in KRAS-G12C mutant advanced solid tumors, including non–small cell lung cancer.^{3,4} Furthermore, additional phase I/II studies are currently underway to evaluate the KRAS-targeted compound (AMG510; Amgen, Thousand Oaks, Calif) in combination with other chemotherapeutic or targeted therapies, including anti-PD-1/PD-L1 agents (NCT03600883, NCT04185883). However, so far, no randomized, phase III data yet exist, which may guide clinical decision-making.

One challenge with the findings by Ma and colleagues is that that no recurrences occurred among patients with adenocarcinoma in situ, minimally invasive adenocarcinoma, or

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CENTRAL MESSAGE

Ma and colleagues highlight the prognostic importance of KRAS-mutant lung adenocarcinomas. They found KRAS to be prognostic in partially solid tumors but not once nodal metastases developed.

lepidic-predominant adenocarcinoma. In addition, although the International Association for the Study of Lung Cancer has endorsed this subclassification, the utility of these histologic classifications remains an area of academic exploration, given that they have not been fully integrated into the majority of clinical practices.⁵ In their subgroup analysis, the authors identified the prognostic importance of KRAS-mutant disease among patients with part-solid nodules. Interestingly, an additional subgroup analysis suggested that such mutations may drive disease biology for stage I disease primarily, whereas nodal and micrometastatic disease dominate over tumor genomics for more advanced cancers. Most biomarker-driven therapy is used in the metastatic setting, so the findings that the mutation is less important once nodal disease occurs is interesting. Hopefully, additional studies will examine this question to explore this finding in an additional dataset.

Nonetheless, Ma and colleagues' report is timely, as recent work has identified challenges in treating this common subset of lung adenocarcinomas. Given the prevalence of this disease, particularly among smokers, this work will help clarify the relative importance of KRAS as biomarker-driven therapy becomes more prevalent.^{6–8} Although this arena remains a field of active investigation, additional work is needed to best determine the optimal treatment algorithm for these patients. Whether such KRAS-specific paradigms will be included in the forthcoming ninth edition of the tumor–node–metastasis staging criteria remains

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uncertain, given the current status of this field. However, the efforts by Ma and colleagues will certainly contribute to a growing body of literature that will eventually guide management of this disease.

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See Article page e73.

Commentary: Every detail matters—Understanding the impact of KRAS mutations

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CENTRAL MESSAGE

The presence of certain *KRAS* mutations in early-stage lung adenocarcinoma may portend a worse clinical prognosis.

Despite surgical resection, 30% to 60% of patients with early-stage non-small cell lung cancer (NSCLC) develop recurrent disease.^{1,2} Adjuvant chemotherapy has shown survival benefit in stages Ib and II NSCLC, but several genetic mutations have been identified in the pathogenesis of lung cancer that affect both prognosis and response to treatment.^{2,3} Moreover, some of these genetic modifications serve as potential targets for therapy in certain patients. Thus, genetic mutation mapping has the potential to guide the staging and treatment of lung cancer. As such, some centers perform mapping on all

adenocarcinomas and in up to three-quarters of patients with early-stage disease.¹

Two of the most clinically significant markers identified in NSCLC, specifically adenocarcinomas, are the *p53* tumor suppressor gene and the Kirsten rat sarcoma viral (*KRAS*) oncogene. These genes regulate cell growth, differentiation, and death.^{1,2,4,5} Overexpression of *p53*, but not a mutation in *p53*, is a known prognostic marker of poor outcome, and studies have shown that these patients benefit from adjuvant chemotherapy. On the other hand, *KRAS* mutations, which are found in approximately

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