Association Between KRAS Variant Status and Outcomes With First-line ImmuneCheckpoint Inhibitor-Based Therapy in Patients With Advanced Non–Small-Cell Lung Cancer

For patients with advanced non–small-cell lung cancer (NSCLC) without a driver alteration and programmed cell death ligand 1 (PD-L1) expression of 50% or greater, immune checkpoint inhibition (ICI) monotherapy or in combination with chemotherapy is standard first-line therapy. When deciding between these options, clinicians consider disease burden and comorbidities; however, to our knowledge, no biomarkers have been shown to predict differential benefit or harm.

KRAS variants in NSCLC are associated with smoking history, higher PD-L1 expression, and responsiveness to ICI monotherapy.

The KEYNOTE-042 study demonstrated an overall survival (OS) benefit for first-line pembrolizumab over chemotherapy in patients with PD-L1 expression of 1% or greater. In an exploratory analysis, this benefit was seen regardless of KRAS status, but was more pronounced in patients with KRAS variants (median OS [mOS], 28 vs 11 months; hazard ratio [HR], 0.42; 95% CI, 0.22–0.81) than those without KRAS variants (mOS, 15 vs 12 months; HR, 0.86; 95% CI, 0.63–1.18). However, to our knowledge, no prior studies have evaluated the association of KRAS status with outcomes following ICI monotherapy versus chemoimmunotherapy in patients with PD-L1 of 50% or greater.

Methods | Using the Flatiron Health database, comprising 280 cancer clinics across the US, we analyzed patients with advanced nonsquamous NSCLC with PD-L1 expression of 30% or greater, known KRASv status, and no alteration in EGFR, ALK, or ROS1 who were treated with first-line ICI monotherapy or chemoimmunotherapy between January 2016 and May 2020. Institutional review board exemption was granted by the University of Pennsylvania after determination that the proposal met eligibility criteria for institutional review board review exemption. Kaplan-Meier methods compared OS (from first-line systemic therapy initiation to death from any cause) between groups stratified by treatment type and KRAS status (variant [v] or wild type [wt]). Cox proportional hazards models estimated adjusted HRs and 95% CIs for death associated with KRAS status and treatment regimen. Analyses were performed using Stata, version 15 (StataCorp). Statistical significance was set at 2-sided P < .05 for all tests.

Results | Among 1127 patients with advanced nonsquamous NSCLC with PD-L1 expression of 50% or greater, 573 (50.8%) had KRASv status and 554 (49.2%) had KRASwt status. Patients with KRASv status were more likely to be female (58.7%...
chemoimmunotherapy might be favored over ICI monotherapy for patients with KRASv with high PD-L1 expression. While the specific prevalence of KRASv in the PD-L1-high subset is not definitively known, the 50% prevalence observed in our cohort is similar to that reported by others. The limitations of this analysis include unknown KRASv subtype and covariant status, including TP53 and STK11, as well as residual confounding despite adjustment for multiple covariates. Further investigation is needed to optimize selection between multiple available treatment strategies for patients with PD-L1-high NSCLC.

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COMMENT & RESPONSE

Patient Willingness to Enroll in Cancer Clinical Trials When Sites Return to Prepandemic Status

To the Editor In their Research Letter published in JAMA Oncology, Fleury et al1 suggest that patients with cancer will be less likely to consider trial participation even when sites return to prepandemic status. Nevertheless, we would like to point out that this conclusion should be interpreted cautiously because this study has several limitations, and mechanistic factors to support these findings are missing.

In the first place, this study1 was conducted in a US cancer survivor population with only 30% of responses and without specifying whether the patients were in remission or not. However, a patient’s decision is based on a benefit-risk ratio in which the more benefit they expect, the more risk (even due to COVID-19) they are willing to take. Moreover, it is important to emphasize that among 907 respondents, the majority of patients (743 [81.9%]) indicated no difference in their willingness (or were even more likely for 22 of them) to participate in a clinical trial.

It is also necessary to highlight that the authors sent the questionnaire very early in the US epidemic (between May and June 2020).1 Therefore, there is a risk of biased results—on the one hand, because of the relative ignorance of certain characteristics of the epidemic and therapeutic options at that time, and on the other hand, because hospitals had not yet put in place all procedures that now exist to pursue their activities despite the health crisis. Recent data2,3 show that organizational innovations (eg, telemedicine, drug distribution) have since been implemented by all stakeholders to overcome these difficulties and enable patients to access therapeutic innovation.

Hence, we wonder whether the association observed between the COVID-19 pandemic and patient willingness to enroll in cancer clinical trials is relevant. Indeed, many patients with cancer want to participate in a clinical trial because it is often either their last or their best option (eg, access to innovative drugs or combinations, especially in the field of precision medicine). Therefore, the reopening of trials is a hope that they do not want to miss, even if enrollments were halted for several months.

Our clinical experience, in particular in phase I trials,4 suggests that enrollment in clinical trials was more affected by availability of sites and investigators than by patients’ willingness to enroll. This is underlined by optimistic figures5 regarding the restarting or the completion of clinical trials interrupted because of the COVID-19 crisis. In addition, promising announcements regarding the arrival of vaccines will certainly confirm this trend.

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