**STK11 and KEAP1 Mutations in Lung Adenocarcinoma: Solving the Puzzle Continues**

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**STK11/LKB1** encodes a protein involved in the maintenance of cell metabolism and energy homeostasis. Its inactivation, frequent in lung adenocarcinomas, was found to be associated with reduced density of effector T lymphocytes, diminished response rate, and inferior progression-free survival of patients with co-occurring KRAS mutations, when treated with immune checkpoint inhibitors.1 Tumors with loss of STK11 were also found to have reduced expression of programmed death ligand-1 (PD-L1) protein. These findings prompted physicians to take into account the occurrence of STK11/LKB1 loss when considering the use of programmed cell death protein-1 or PD-L1 inhibitors for the treatment of patients with lung cancer in sequence with other systemic treatment options.

The KEAP1 gene, encoding KEAP1, is a negative regulator of NFE2L2 or NRF2, the key transcriptional regulator of the endogenous antioxidant response. KEAP1 loss-of-function activates the KEAP1-NRF2 axis, leading to dependency on glutaminolysis and promoting KRAS-driven lung adenocarcinomas.2 Although the association of NRF2 activation and chemoresistance or radiation resistance is quite well established,3 association with the lack of activity of immune checkpoint inhibition was so far unknown.

In this issue of the *Journal of Thoracic Oncology*, Ricciuti et al.4 provide us with very important data on clinicogenomic associations of patients with lung adenocarcinoma who received immune checkpoint inhibitors. In a total of 1261 subjects, from two independent retrospective institutional cohorts, the authors revealed that STK11 loss (approximately 20% of patients) or KEAP1 loss (approximately 20% of patients) is associated with reduced efficacy of immunotherapy, but only in those patients whose tumors had co-occurring KRAS mutations. This finding was further supported by transcriptomic data from The Cancer Genome Atlas database, revealing the existence of unique transcriptomic profiles of patients with STK11 loss or KEAP1 loss in KRAS-mutant lung adenocarcinomas, with several down-regulated pathways of antigen presentation and immune response.

Should these data influence clinical practice and how? Well, even if only retrospective, these data are robust (two independent very large cohorts with very similar results) and convincing. It should be kept in mind that true prognostic or predictive nature of biomarkers (STK11 or KEAP1 loss in the presence of mutant versus wild-type KRAS) cannot be determined in the absence of the control group of patients in a retrospective setting. Nevertheless, this series of patients reveals that STK11 or KEAP1 loss should always be interpreted in the context of KRAS mutational status. Given the emerging data on the activity of programmed cell death protein-1 or PD-L1 inhibitors in the adjuvant or neoadjuvant setting, it is tempting to speculate that the above-mentioned associations may also be observed in the adjuvant or neoadjuvant trials, which remains to be established. Finally, as the practical use of several KRAS G12C inhibitors is rapidly entering the lung cancer clinics, the results of clinical trials with KRAS G12C inhibitors should ideally contain the information on the co-occurrence of STK11 or KEAP1 loss, particularly if combination or sequencing with immune checkpoint inhibitor is part of the study. Such information would help physicians to optimally sequence the systemic treatments of patients with KRAS G12C mutation-positive tumors in light of the data presented in the current issue of the *Journal of Thoracic Oncology.*
CRediT Authorship Contribution Statement

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References