What is the significance of TP53 and KRAS mutation for immunotherapy in non-small cell lung cancer?

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Increasing evidences including PD-L1 expression (1,2), tumor mutation burden (TMB) (3,4), and the intensity of CD8+ T cell infiltrates (5-7) have been respectively certified as predictive biomarkers of response to immunotherapy. More recently, our study identified TP53/KRAS mutation may be another applicable factor to predict response to PD-1 blockade in non-small cell lung cancer (NSCLC) (8). This result has aroused some discussions. Dr. Taweew Tanvetyanon (9) raises a question of when is KRAS or TP53 mutation predictive of response to immunotherapy for lung cancer? He points out that it is not adequate enough to demonstrate the predictive value of KRAS mutation independently from TMB and that TP53 or KRAS mutation may be served as a predictive biomarker along with high TMB.

As the editorial mentioned, a number of genetic alternation, such as POLE, mismatch repair genes, BRCA1/2, and EGFR, strongly correlated with TMB, either positively or negatively, have been identified (10). In our study, we demonstrated tumor with TP53 and/or KRAS mutation showed significantly increased TMB and transversion mutation. We agree with that KRAS mutation cannot be separated from TMB in the prediction. We also haven’t enough data right now to verify the superiority of KRAS or TP53 mutation in those with a low TMB. One of the advantages in our study may be that TP53 or KRAS mutation could be routinely detected in the laboratory as a qualitative index. However, by comparison, it is relatively difficult to acquire the TMB and define a rational cut-off value. Even the PD-L1 protein detection still faced the perplexity of different antibody clones and cut-off values. Specific gene alteration might be available to substitute the TMB before which we can easily and precisely evaluate.

Apart from the convenient detection, the prediction of efficacy should be the leading consideration. Recent studies have explored the impact of co-mutations on the immune contexture and response of KRAS-mutant lung cancer to immunotherapy. Skoulidis et al. identified inactivation of STK11 is associated with establishment of “immune desert” in KRAS-mutant lung adenocarcinoma, while KRAS/TP53 co-mutation is associated with inflammation and active immunoediting (11). In their report, 35 KRAS-mutant NSCLC patients, consisting of 6 (17%) KRAS/STK11 and 17 (49%) KRAS/TP53 co-mutations, and 12 (34%) KRAS single mutation, underwent anti-PD-1 therapy. KRAS/TP53 group displayed a favorable objective response rate (ORR: 59%), followed by KRAS-single group (ORR: 25%), while KRAS/STK11 group without any response (ORR: 0). Meanwhile, KRAS/TP53 group also showed a prolonged progression free survival (PFS) than the other two groups (median: 23 vs. 16 vs. 6 weeks; P=0.0003) (12). Coincidently, we have demonstrated those with co-occurring TP53/KRAS mutations showed extremely increased PD-L1 expression, high density of CD8+ lymphocytes, and high TMB.
Through the analysis of Memorial Sloan Kettering Cancer Center (MSKCC) cohort, we identified TP53 and KRAS co-mutation area under roc curve (AUC: 0.921; P<0.001) represented the optimal predictive factor of PFS of anti-PD-1 therapy in NSCLC, followed by KRAS mutation (AUC: 0.889), PD-L1-positive (PD-L1 ≥50%, AUC: 0.815), and high TMB (AUC: 0.792) (Figure 1A). Furthermore, through the analysis of total 54 patients from two cohorts [MSKCC and Guangdong Lung Cancer Institute (GLCI)], patients with TP53 and KRAS co-mutation showed the favorable clinical benefit than that of KRAS/TP53 single mutation and wild type patients (median: 14.5 vs. 12 vs. 6.5 vs. 3.5 months; P=0.0034; Figure 1B). These above results highlight the potential therapeutic vulnerabilities of the subgroup with TP53 and KRAS co-mutation. Nevertheless, there is still a long way to reach a precise immunotherapy. It is perhaps that we can combine two or more valuable and accessible biomarkers to reach an optimal prediction of immunotherapy in the future.

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Footnote

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References


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