Letter to the Editor

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. Tawee 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),

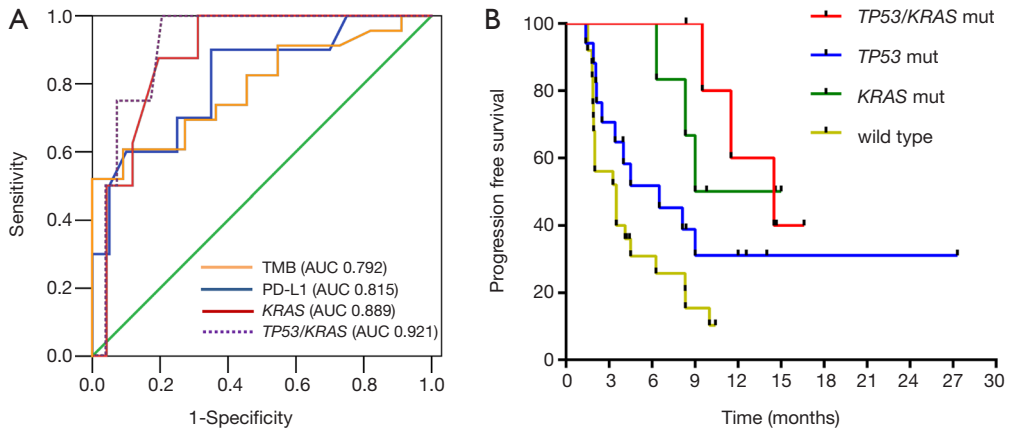

Figure 1 Co-occurring *TP53/KRAS* mutations manifested the optimal predictive value for PD-1 blockade in non-small cell lung cancer. (A) Receiver operating characteristic curves of different factors (TMB, PD-L1, *KRAS*, and *TP53/KRAS*) to predict progression free disease (PFS) of patients in Memorial Sloan Kettering Cancer Center (MSKCC) cohort; (B) Kaplan-Meier survival curves estimates of PFS based on *TP53* and *KRAS* mutation status in the patients from MSKCC and Guangdong Lung Cancer Institute (GLCI) cohorts treated with PD-1 inhibitors. TMB, tumor mutation burden; AUC, area under roc curve; mut, mutation.

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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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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