TUMOR MUTATIONAL BURDEN CORRECTED FOR HUMAN LEUKOCYTE ANTIGEN SOMATIC DEFECTS PREDICTS RESPONSE TO CHECKPOINT BLOCKADE IN ADVANCED NON-SMALL CELL LUNG CANCER

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Background Tumor mutational burden (TMB) has been proposed as a biomarker for predicting response to immune checkpoint blockade (ICB) therapies in patients with non-small cell lung cancer (NSCLC). However, a subset of patients with high TMB tumors do not have a long-term response to ICB. Several studies have hypothesized that somatic events in the antigen processing machinery may contribute to ICB resistance. In this study, we determined that TMB adjusted for the number of neoantigens lost due to human leukocyte antigen (HLA) somatic defects better predicted response to ICB.

Methods Using the real-world Tempus Database, we selected a cohort of 378 de-identified NSCLC patient records with DNA data and recorded outcomes following ICB. Loss of heterozygosity in HLA-I genes (HLA-LOH) were identified in this cohort. TMB was adjusted to match the proportion of neoantigens estimated to escape HLA presentation due to loss of specific HLA alleles. Cox proportional hazards models were fitted to determine the relationship between HLA-adjusted TMB and time to progression (TTP), with hazard ratios (HRs) and confidence intervals (CIs) reported. In addition, immune inflammation signatures were calculated for 249 patients for whom paired RNA data were available.

Results HLA-LOH was observed in 27% of late-stage NSCLC tumors. Notably, the presence of HLA-LOH was significantly associated with shorter TTP in TMB-high (>10mut/Mb) tumors versus TMB-high, HLA-stable tumors (HR [CI]=2.99 [1.39–6.40]). This association was not observed in tumors with low levels of TMB (HR [CI]=0.75 [0.46–1.20]). In addition, HLA-adjusted TMB improved the estimated risk ratio in comparison to unadjusted TMB. Binarization of HLA-adjusted TMB further stratified TMB-low and TMB-high groups (TMB-low HR[CI]=1.67[1.09–2.56]; HLA-adjusted TMB-low HR[CI]=2.08[1.19–3.08]). Immune-inflamed environment was also associated with longer TTP in the HLA-adjusted TMB-low group (HR[CI]=0.58 [0.36–0.92]), indicating that HLA-adjusted TMB can be used in conjunction with immune phenotypes to predict outcomes to ICB.

Conclusions In this study, we observed that high TMB, HLA-stable patients had a longer TTP in NSCLC. Furthermore, we discovered that HLA-adjusted TMB outperformed unadjusted TMB in predicting ICB response, and that an inflamed immune phenotype was associated with longer TTP within HLA-adjusted TMB subgroups. Our findings suggest that HLA-adjusted TMB can be used alone as a DNA-based biomarker or in combination with immune signatures to better predict ICB response in NSCLC patients.