146 HLA-B44 MOTIF NEOEPITOPE IS ASSOCIATED WITH AN ANTI-TUMOR IMMUNE MICROENVIRONMENT AND PREDICTS RESPONSE TO IMMUNE CHECKPOINT BLOCKADE IN NON-SMALL CELL LUNG CANCER

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Background Tumor neoantigens need to be presented in a HLA class I-restricted manner in order for effective CD8 T cell-mediated antitumor response to immune checkpoint blockade (ICB). B44 is the most common HLA-B supertype and has distinct peptide antigenic specificity, termed the peptide-binding motif. We and others have shown that HLA-B44 supertype is associated with survival in melanoma and lung cancer patients treated with ICB. Herein, we hypothesize that HLA-B44, together with its specific motif neoepitopes, generates anti-tumor immune microenvironment, leading to a favorable outcome upon ICB in non-small cell lung cancer (NSCLC).

Methods Lung cancer datasets were obtained from TCGA and CPTAC. WES, RNA sequencing and Mass Spectrometry were used for HLA-B44 denotation, B44 motif neoantigen identification, RNA and protein expression analysis. B44 motif neoepitope required a radical glutamic acid (E) substitution in the anchor position as we previously demonstrated. Patient cohorts for ICB response were selected from trials of single-agent anti-PD-1 treatment from UCLA, MSKCC, DF and SKCCC.

Results Among NSCLC patients with HLA-B44 allele(s), a pooled analysis of lung adenocarcinoma (LUAD) and lung squamous carcinoma (LUSC) demonstrated elevated gene expression of *PD-L1*, *CTLA-4*, *LAG-3*, *CXCL9*, *CXCL10*, *CXCL13*, *CD8A* and cytolytic gene signature (*GZMA* and *PRF1*) in patients with B44 motif neoepitopes compared to those without motif neoepitopes. Analysis of immune cell component revealed increased infiltration of Th1, Th2 and CD8 T cells in LUAD and cDCs, macrophages and monocytes in LUSC with motif neoepitopes. We also found enhanced tumor antigen-processing and -presenting via pathway analysis in motif patients in LUSC. Although B44 motif count correlates with high tumor mutational burden (TMB), a general linear model suggested an independent role of B44 motif neoepitope in anti-tumor immune microenvironment. Additionally, patients with motif and high TMB had the highest level of above-tested gene expression and immune cell infiltration. We also found that B44 motif neoepitopes were less expected in tumors at protein level based on otherwise linear association of number of non-radical E substitutions with number of total non-synonymous mutations at protein level, indicating possible immunoediting of B44 motif neoepitopes. Lastly, we showed that combining B44 motif with either TMB or PD-L1 improves prediction of progression-free survival upon ICB in NSCLC patients.

Conclusions HLA-B44 motif neoepitopes are associated with anti-tumor immune microenvironment and can potentially serve as an additional biomarker in NSCLC patients receiving ICB.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0146