

TUMOR MICROENVIRONMENT BASED ON PD-L1 AND CD8 T-CELL INFILTRATION CORRELATED WITH THE RESPONSE OF MSS MCRC PATIENTS TREATED VACTOSERTIB IN COMBINATION WITH PEMBROLIZUMAB

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Background The expression of PD-L1 and tumor-infiltrating CD8 T cells were reported to have a decisive effect on the immunotherapy response (PMID: 26819449). Microsatellite stable (MSS) metastatic colorectal cancer (mCRC) shows a limited clinical benefit to immunotherapy alone known to be having an ‘immune-cold’ microenvironment. To understand the basis of the clinical responses to anti-PD-1 and TGF- β inhibitor combination therapy in MSS mCRC, we conducted a comprehensive analysis of survival outcome, whole transcriptome sequencing (WTS) data, and multiplex immunohistochemistry (mIHC) data from a combination treatment of vactosertib and pembrolizumab.

Methods Clinical outcomes were evaluated by RECIST v1.1 and iRECIST. Tumor tissue biopsy samples for WTS and mIHC were obtained in screening and cycle 2 post-treatment time point. CD274(PD-L1) and CD8A expression cut-off were calculated as a median value in the merged data set of TCGA Pan-cancer and MP-VAC-204 study. Having over median value defined as a high group and under median value as a low group. Tumor immune status by a combination of gene expression (high or low) was classified into four subtypes (1: CD274 high, CD8A high; 2: CD274 low, CD8A low; 3: CD274 high, CD8A low; 4: CD274 low, CD8A high). Tumor tissue slides stained with PD-L1, CD8, and granzyme B (GZB) in tumor nest and stroma.

Results Among 43 patients whose WTS data are available, thus included in the analysis, 9 patients were responders (7 PRs and 2 iPRs). Subtype 2 showed a major proportion in the MP-VAC-204 CRC patients (1: 14%, 2: 58%, 3: 12%, 4: 16%). Responders were observed in subtype 2 and 4 (24% and 14%, RECIST). The CD8A expression and median overall survival (mOS) showed a significantly positive correlation (**P=0.0028) and there was no significance in the correlation of CD274 and mOS. mOS was significantly longer in high expression of CD8A patients (*P=0.0083, Not reached vs 9.9 months, hazard ratio 8.812 [95% CI 3.19–24.31]). After the combination treatment, CD8 and GZB positive T cells were increased significantly in both tumor nest and stroma.

Conclusions Our study suggests a high level of CD8 T cells, even in the case of low PD-L1 expression, is significantly correlated with the improved clinical outcomes in MSS mCRC patients treated with vactosertib and pembrolizumab. The increases in CD8 T cells both in tumor nest and stroma after the combined inhibition of PD-1 and TGF- β pathway may contribute to the survival benefit. Further clinical investigations are warranted. (Clinical trial information: NCT03724851)

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