6 IMMUNE CORRELATES OF CLINICAL BENEFIT IN PATIENTS WITH HPV-ASSOCIATED MALIGNANCIES TREATED WITH BINTRAFUSP ALFA

Yo-Ting Tsai*, Renee Donahue, Nicole Toney, Julius Strauss, James Gulley, Jeffrey Schlom.
NIH, Bethesda, MD, USA

Background The safety and efficacy of bintrafusp alfa, a first-in-class bifunctional fusion protein targeting TGFβ and PD-L1 pathways, have been demonstrated in patients with HPV-related cancers in an open-label, multicenter phase 1 trial (NCT02517398), and an open-label, single-center phase 2 trial (NCT03427411). The current study aimed to identify immune related biomarkers prior to and following 1 cycle of bintrafusp alfa that associate with clinical benefit.

Methods Immune parameters were compared in patients (n=65) deriving clinical benefit from bintrafusp alfa (defined as BOR of stable disease (SD) or better, which included SD, mixed, partial, and complete responses) versus patients with a BOR of progressive disease (PD). Peripheral blood was obtained from patients before and after 1 cycle of therapy, and evaluated for complete blood counts, plasma cytokines/soluble factors, 158 immune subsets, and T cells specific for HPV-16 E6 and E7.

Results Prior to therapy, patients who developed a BOR of SD or better had lower counts of neutrophils, monocytes, and platelets, lower levels of TGF-β1 and sCD73, and higher levels of sCD27:sCD40L than patients with a BOR of PD. Lower baseline frequencies of MDSCs, monocytes, naïve CD4+ and CD8+ T cells, and CD8+ T cells that express CD73, an immune checkpoint associated with adenosine metabolism, were detected in patients with a BOR of SD or better than those with PD. Following 1 cycle of treatment, lymphocyte counts were reduced, while neutrophil counts and the NLR were increased, in patients with PD compared to those with a BOR of SD or better. IL-8, a cytokine involved in tumor progression and associated with reduced clinical benefit to immune checkpoint inhibitors, was increased in patients with PD compared to those with a BOR of SD or better, while conventional dendritic cells and CD8+ T cells expressing the proliferative marker ki67 were increased in patients with a BOR of SD or better compared to those with PD. Greater increases in the frequency and magnitude of HPV-16 specific CD8+ T-cells were also detected in individuals with a BOR of SD or better compared to PD.

Conclusions Immune profiling identified specific measures prior to therapy, as well as changes induced early after therapy (preceding restaging), that may serve as predictive biomarkers to identify patients with HPV-related cancers most likely to benefit from bintrafusp alfa. These findings also provide the rationale to combine bintrafusp alfa with other therapies including HPV-targeted therapeutic vaccines and agents that block IL-8 signaling.

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Ethics Approval The study protocol was approved by ethics committees at all participating institutions, and each patient provided written informed consent before study enrollment.

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