20 DEVELOPMENT OF VISTA-CENTRIC TUMOR IMMUNOPHENOTYPING AS A NOVEL APPROACH FOR IDENTIFICATION OF POTENTIAL BIOMARKERS FOR ANTI-VISTA THERAPY

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Background V-domain immunoglobulin suppressor of T cell activation (VISTA) is a negative checkpoint regulator of immune cells. VISTA has been recognized as a potential mediator of resistance to anti-PD-1 and anti-CTLA-4 immunotherapies in cancer patients. Targeting the VISTA signaling pathway has been suggested as a promising approach for overcoming resistance to current immune checkpoint therapies. Herein, we report the design, development, and analytical algorithm for comprehensive VISTA-centric tumor immunophenotyping to explore potential tumor biomarkers for novel anti-VISTA therapeutic antibody CI-8993, currently under clinical development in Phase 1 trial.

Methods Formalin-fixed paraffin embedded (FFPE) tumor tissue sections from 10 cases of non-small cell lung carcinoma (NSCLC) were purchased from NovoVita Histopath Laboratory. Serial tumor tissue sections were double-immunostained with VISTA combined with CD8 (cytotoxic T cell marker), CD4 (T helper cell marker), CD11b (myeloid cell marker), CD68 (monocyte/macrophage marker), CD56 (NK cell marker), CD19 (B cell marker) or Programmed Death-Ligand 1 (PD-L1).

Results Immunohistochemical analysis revealed the presence of CD8+ cells (9/10 cases), CD4+ cells (3/10 cases), CD11b+ cells (10/10 cases), CD68+ cells (10/10 cases), CD56+ cells (4/10 cases) and CD19+ cells (8/10 cases) in lung tumors. Using double IHC staining, we found that VISTA was expressed in CD8+ cells (5/9 tumors), CD11b+ cells (5/10 tumors) and CD19+ cells (5/8 tumors), whereas VISTA was hardly detectable in CD4+, CD68+ or CD56+ cells. Expression of PD-L1 was detected in cancer cells in 6/10 tumors, whereas VISTA-pos cancer cells were revealed in 1/10 tumors. We developed an algorithm for evaluation of VISTA-centric tumor immunophenotyping and demonstrated that every tumor has a unique cell-type-specific pattern of VISTA expression which could serve as a potential biomarker.

Conclusions Our results demonstrate that comprehensive VISTA-centric immunophenotyping enables spatially resolved and cell-type-specific characterization of VISTA expression in solid tumors and can serve as applicable bioanalytical approach for identification of potential biomarkers to guide anti-VISTA therapeutic treatment decisions.

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