ANTI-VISTA ANTIBODY HMBD-002 REPROGRAMS TUMOUR ASSOCIATED MACROPHAGES AND PROMOTES CYTOTOXIC T CELL RESPONSE


Background VISTA is an emerging, predominantly myeloid, immune checkpoint, and its blockade has shown benefit in multiple preclinical models of cancer as both a monotherapy and in combination with other immune checkpoint inhibitors (ICI) such as anti-PD1 and anti-CTLA-4. In some murine models of cancers, such as non-small cell lung cancer, clear-cell renal cell carcinoma and colorectal carcinoma, VISTA is expressed on both T cells and macrophages. Understanding the cell subset specific immunomodulatory functions of VISTA is important to inform patient selection, develop effective combination strategies, and identify biomarkers of response to anti-VISTA therapy.

Methods The murine colon cancer model, CT26, exhibits robust infiltrations of multiple immune cells into tumors, and has been reported to respond to VISTA blockade. This allows simultaneous investigation of VISTA-mediated immune modulation in multiple cell subsets. Here, HMBD-002, an IgG4 anti-VISTA antibody which does not deplete VISTA-expressing cells, was used to assess the functional role of VISTA blockade in the absence of Fc-mediated effects. CT26 tumor-bearing mice were treated with HMBD-002 and/or anti-PD1. Tumors were harvested and profiled via multicolor flow cytometry to determine underlying changes in the polarization and functional status of immune infiltrates associated with anti-tumor responses.

Results In CT26 tumors, VISTA expression was highest on macrophages followed by MDSCs, DCs and T cells. VISTA blockade polarized macrophages to an activated pro-inflammatory anti-tumor phenotype with significant increases in TNFα and MHCII expressing macrophage subsets. VISTA blockade also resulted in significant increases in tumor antigen gp70-specific CD8 T cells. A concurrent increase in CD8 T cell activation was seen with an upregulation of several cytotoxicity associated markers, including Granzyme B. However, no change in T cell exhaustion levels was observed. The combination of VISTA blockade with anti-PD1 treatment led to further increases in tumor antigen-specific CD8 T cells, significant decreases in T cell exhaustion levels and enhanced anti-tumor efficacy when compared to monotherapy anti-VISTA or anti-PD1 arms.

Conclusions Reprograming of the tumor microenvironment by blockade of VISTA is associated with polarization of macrophages to an inflammatory phenotype and increases in both tumor antigen-specific CD8 T cells and their cytotoxic activity. Further, combining anti-VISTA with other immune checkpoint inhibitors that can reprogram exhausted T cells has the potential for synergistic activity.

Ethics Approval The study was approved by the Institutional Animal Care and Use Committee, approval number 2021/SHS/1660