751 PMC-309, A HIGHLY SELECTIVE ANTI-VISTA ANTIBODY REVERSES IMMUNOSUPPRESSIVE TME TO IMMUNE-SUPPORTIVE TME

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Background The tumor microenvironment (TME) consists of blood & lymphatic vessels, stromal cells, and immune cells such as lymphocytes, macrophages, and APC cells. V-domain immunoglobulin suppressor of T cell activation (VISTA) is highly expressed in myeloid-derived cells and its blockade enhances antitumor immunity in multiple tumor models. Therefore, anti-VISTA agents may provide additional cancer immunotherapy and may work synergistically with PD1/PDL1 targeting drugs.

Methods Target cell analysis: human peripheral blood mononuclear cells (PBMC) containing lymphocyte and myeloid lineage cells were used for target cell analysis with flow cytometry.

T cell activity (ex vivo): human PBMC was employed for the evaluation of T cell activity (IRB #1041107-201703-BR-002-02) and CD3+ T cells and CD14+ monocytes were isolated from human PBMC and co-cultured in a 2.5 mg/ml anti-CD3 antibody-coated plate for 6 days in the presence of PMC-309 or other drugs. Culture media were harvested and evaluated the secreted levels of IFN-γ by ELISA.

MDSC suppression activity (ex vivo): MDSCs cells (5x10^4 cells) were cultured with CD3+ T cells (2x10^5 cells) in the presence of anti-CD3/28 bead with 10, 30, 100 μg/ml of PMC-309, or 100 μg/ml of anti-PD1, anti-PDL1, and anti-CTLA4 and for 3 days. IFN-g production was measured by ELISA.

In vivo study: MC38 bearing human VISTA knock-in (KI) mice were employed for the assessment of anti-tumor activity of PMC-309.

The tumor infiltrated immune cells: Immune cells in the TME were evaluated by immunohistochemistry (IHC) or flow cytometry (FACS) analysis.

Results PMC-309 binding to VISTA expressing cells is highly selective and the selectivity is maintained even in the low pH conditions that mimic TME. PMC-309 enhances the secretion of IFN-gamma, TNF-alpha, and IL-2 in T cell and monocyte co-culture settings. In addition, PMC-309 promoted monocyte differentiation into M1 macrophage that stimulates proinflammatory cytokine secretion of T cells. For the in vivo study, PMC-309 was intravenously administrated in VISTA-KI mice. The tumor growth rate was suppressed accompanied by a synergistic effect with an anti-PD1 antibody. The anti-tumor activity was associated with enhanced T cell activation, increased secretion of pro-inflammatory cytokines, and increased penetration of cytotoxic T cells, but lowing immune-suppressive MDSC cells into TME as demonstrated with IHC analysis.

Conclusions PMC-309 increased the number of T cell infiltration while a decrease of MDSCs in the TME. PMC-309 in combination with chemotherapy or other IO drugs could address highly medical unmet needs from patients with drug resistance to currently available IO treatment options.

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