494 OR502, A BEST-IN-CLASS ANTI-LILRB2 ANTIBODY THAT ENHANCES BOTH INNATE AND ADAPTIVE ANTI-TUMOR IMMUNE RESPONSES

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Background The inhibitory receptor leukocyte immunoglobulin-like receptor subfamily B member 2 (LILRB2, ILT4) is mostly expressed on immunosuppressive myeloid cells, and its expression correlates with poor survival in multiple cancers. OR502 is a humanized IgG1 antibody that blocks the interaction of LILRB2 with its ligands including HLA class I (e.g., HLA-G, HLA-A, B, etc.) to relieve LILRB2-mediated immune suppression by myeloid cells and diminish immune evasion in the tumor microenvironment. OR502 parental antibody demonstrated significant tumor growth inhibition and tumor regression in a humanized SK-MEL-5 tumor model. Antibodies targeting LILRB2 are currently being evaluated in clinical trials for the treatment of cancer as monotherapy and in combination with checkpoint inhibitors.

Methods OR502 functional activity was compared to other anti-LILRB2 antibodies for its ability to prevent the generation of new suppressive macrophages, to reprogram the suppressive function of existing macrophages, in M2c/$CD8^+$ T cell coculture assays, and to assess the modulation of LPS-induced IFN-γ and IL-10 production by human PBMCs.

Results OR502 binds specifically to human myeloid cells without binding to lymphocyte cell populations. OR502 antagonizes LILRB2 binding to its main ligand HLA-G expressed on cancer cells as well as to classical HLA class I molecules. Compared to other anti-LILRB2 antibodies, OR502 is superior in enhancing LPS-induced IFN-γ and reducing IL-10 production by PBMCs, preventing the generation of immune suppressive macrophages, relieving macrophage-mediated suppression of T cell proliferation, and enhancing IFN-γ and perforin secretion by $CD8^+$ T cells. Furthermore, OR502 restored the ability of exhausted T cells to secrete IFN-γ in the presence of M2c macrophages and significantly enhanced the activity of pembrolizumab in combination studies. These data demonstrate that OR502 has superior activity in relieving LILRB2-mediated immune suppression and enhancing both innate and adaptive anti-tumor immunity.

Conclusions OR502 is an anti-LILRB2 antibody with best-in-class activity to restore both innate and adaptive immune responses by modulating immunosuppressive phenotype of myeloid cells.

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