PRECLINICAL CHARACTERIZATION OF OR502, AN ANTI-LILRB2 ANTIBODY THAT RESCUES INNATE AND ADAPTIVE IMMUNE RESPONSES FROM LILRB2 MEDIATED IMMUNE SUPPRESSION

Meghan Zuck*, Myriam Bouchlaka, Huyen Dinh, Kevin Green, Meilyn Sylvestre, Francisco Zapata, Ramya Chandrasekaran, Gajendra Naika, Lauren Loh, Ray Fox, Darbie Whitman, Tom Graddis, Kamal Puri, Peter Probst. OncoResponse, Seattle, WA, United States

Background The inhibitory receptor leukocyte immunoglobulin-like receptor subfamily B member 2 (LILRB2, ILT4) is expressed on immunosuppressive myeloid cells and expression correlates with poor survival in multiple cancers and contributes to anti-PD1 resistance. Interaction of LILRB2 with HLA class I ligands (e.g., HLA-G, HLA-A, etc.) mediates immune suppression by myeloid cells and promotes tumor immune evasion in the tumor microenvironment (TME). Blocking this interaction may enhance efficacy of T cell checkpoint inhibitors. Antibodies targeting LILRB2 are currently being evaluated in clinical trials for the treatment of cancer.

Methods Anti-LILRB2 antibodies were cloned from B cells derived from rabbits immunized with human LILRB2 recombinant protein. Clones were humanized after selection based on activity in a panel of functional and phenotypic assays using primary human macrophages and T cells. Humanized variants were screened for their ability to rescue T cell activity (proliferation and IFN-γ) from M2c macrophage-mediated suppression and enhance LPS-induced IFN-γ production by PBMCs. The top variants were also evaluated for cytokine release in whole blood. The pharmacokinetic profiles of lead LILRB2 antibodies were determined in humanized FcRn mice.

Results We have identified a panel of humanized anti-LILRB2 antibodies that specifically bind to human LILRB2-expressing cell lines and human myeloid cells without detectable binding to other LILRA or LILRB family members. These antibodies block LILRB2 interaction with HLA-G expressed on tumor cells. The lead antibody, OR502, enhanced LPS-induced IFN-γ production by PBMCs, and relieved M2c macrophage-mediated suppression of proliferation and IFN-γ secretion by anti-CD3-activated human CD8+ T cells in coculture assays. 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. OR502-treatment did not trigger inflammatory cytokine release or activation of neutrophils in human whole blood. The pharmacokinetics of OR502 in humanized FcRn mice demonstrated a half-life of 6-10 days.

Conclusions We have identified a novel humanized anti-LILRB2 antibody, OR502, that restores innate and adaptive immune responses by modulating immunosuppressive myeloid cells. These data provide a strong rationale for further development of OR502 for cancer treatment.