OR641 IS A NOVEL DUAL ANTAGONIST ANTIBODY THAT TARGETS LILRB1 AND LILRB2 INHIBITORY RECEPTORS AND PROMOTES A TH1-LIKE IMMUNE RESPONSE

Meghan Zuck*, Kevin Green, Tatyana Pisarenko, Huynh Dinh, Myriam Bouchlaka, Francisco Zapata, Elsa L Hay, Gajendra Naika, Jacob Heit, Ray Fox, Darbie Whitman, Tom Graddis, Kamal D Puri, Peter Probst. OncResponse Inc., Seattle, WA, USA

Background The immune suppression of myeloid cells and lymphocytes within the tumor microenvironment (TME) limits efficacy of checkpoint inhibitors. LILRB1 (ILT2) and LILRB2 (ILT4) are inhibitory receptors on immune cells that interact with ligands including classical and nonclassical HLA Class I (e.g., HLA-A, HLA-G). LILRB1 and LILRB2 are expressed on myeloid cells, and LILRB1 is additionally expressed on subsets of B, NK, and T cells. Interaction of LILRB1 and LILRB2 receptors with their ligands promotes an immunosuppressive phenotype of myeloid cells, and inhibits T and NK cell cytotoxic activity required for tumor cell death. The LILRB1 receptor on macrophages contributes to ‘don’t eat me’ signals for cancer cells to evade phagocytosis by macrophages. Dual antagonism of LILRB1 and LILRB2 by a single antibody to restore both innate and adaptive immune responses is a promising strategy to enhance efficacy of checkpoint inhibitors. A dual LILRB1/2 antagonist antibody is currently being evaluated in clinical trials for cancer treatment. We have identified OR641 as a best-in-class dual antagonist antibody that demonstrates superior activity in relieving LILRB1- and LILRB2-mediated immune suppression and enhances both innate and adaptive anti-tumor immunity.

Methods OR641 is a humanized antibody derived from rabbit B cells immunized with LILRB2 protein. The antibody was evaluated for its activity in various biochemical and in vitro pharmacological assays using primary human macrophages, T cells and NK cells. The pharmacokinetic profile of OR641 was assessed in humanized FcRn mice.

Results OR641 binds specifically to human LILRB1 and LILRB2 proteins and blocks their interactions with HLA class I ligands. OR641 demonstrated superior activity to other antibodies in pharmacological assays modeling LILRB1 and LILRB2-mediated immunosuppression in the TME. OR641 promoted a Th1-like innate immune response by enhancing IFN-γ production and decreasing IL-10 secretion by PBMCs stimulated with TLR ligands. Treatment with OR641 restored the ability of peripheral blood T cells and exhausted T cells to secrete IFN-γ in the presence of suppressive macrophages. OR641 enhanced macrophage phagocytosis of HLA-G+ tumor cells, and rescued the cytotoxic activity of NK cells from LILRB1 mediated immune suppression. The half-life of OR641 in humanized FcRn mice was 10 days.

Conclusions OR641 is a unique dual anti-LILRB2/1 antagonist antibody that promotes a Th1-like immune response. OR641 modulates immunosuppressive myeloid cells through blockade of LILRB1 and LILRB2 and stimulates both innate and adaptive immune responses. These data provide a strong rationale for further development of OR641 as a treatment for solid tumor malignancies.

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Abstracts

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