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DEVELOPMENT OF OR2805, AN ANTI-CD163 ANTIBODY DERIVED FROM AN ELITE RESPONDER TO CHECKPOINT INHIBITOR THERAPY THAT RELIEVES IMMUNOSUPPRESSION CAUSED BY M2C MACROPHAGES

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Background OR2805 antibody was discovered using B cells derived from an elite responder to checkpoint inhibitor (CPI) therapy. It is a fully human IgG1 antibody that binds to CD163, an immune-suppressive receptor highly expressed on tumor associated macrophages (TAMs). High numbers of CD163-expressing TAMs generally predict an unfavorable prognosis in solid tumors. These CD163-expressing TAMs contribute to an immune-suppressive tumor microenvironment and inhibit an anti-tumor T-cell response by engaging immune checkpoints and secreting immune-suppressive cytokines. Relieving the immune suppression of CD163-expressing TAMs to improve anti-tumor T-cell responses is a rational therapeutic strategy as monotherapy and in combination with CPI therapy. **Methods** Cocultures of immunosuppressive primary human polarized M2c macrophages with autologous CD8+ T cells or phytohemagglutinin (PHA)-T cell blasts (exhausted T cells) were used to interrogate OR2805-dependent immunomodulatory responses as single agent and in combination with pembrolizumab, an anti-PD1 antibody. The anti-tumor activity of OR2805 was evaluated in humanized mouse models. Safety and pharmacokinetics (PK) profile of OR2805 was evaluated in cynomolgus monkeys and human whole blood for cytokine release assessment.

Results In coculture assays, OR2805-treatment relieved the suppressive effect of M2c macrophages as demonstrated by increased T-cell proliferation and the release of IFN- γ and perforin. OR2805 restored the IFN- γ production of exhausted T cells and showed a synergistic effect on cocultures treated in combination with pembrolizumab. OR2805-treatment demonstrated significant anti-tumor activity in lung cancer xenograft models in humanized NSG-SGM3 mice. In cynomolgus monkeys, OR2805 demonstrated a typical IgG1 PK profile and good serum exposure. Furthermore, OR2805 did not trigger the release of IL-1 β , IL-2, IL-4, IL-6, IL-10, IFN- γ , or TNF- α cytokines in whole blood from either healthy donors or NSCLC patients.

Conclusions OR2805 reduced M2c-mediated immunosuppression and enhanced T cell effector functions. OR2805-treatment resulted in significant anti-tumor activity in lung cancer xenograft models in humanized mice. The pharmacology, PK, and toxicokinetic data support further development of OR2805 as an anti-cancer therapy, both as a monotherapy and in combination with CPI therapy.

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