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A HUMAN BISPECIFIC ANTIBODY TARGETING LAG-3 AND PD-1 (INCA32459) POTENTLY ACTIVATES EXHAUSTED T CELLS

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Background Exhausted T cells are characterized by the expression of negative immune regulatory receptors, including programmed death protein-1 (PD-1) and lymphocyte-activation gene 3 (LAG-3), which inhibit the proliferation and function of T cells and limit antitumor immunity. We describe the generation and characterization of INCA32459, a human IgG1 Fc-silenced bispecific antibody that simultaneously binds to PD-1 and LAG-3 and reverts their inhibitory function.

Methods INCA32459 was generated using the Merus common light chain Biclomics[®] platform. LAG-3 and PD-1 Fab panels were generated through immunization of Merus MeMo[®] mice, and large panels of Biclomics[®] libraries were screened before optimizing lead candidate molecules.

Results INCA32459 binds with high affinity to both human ($K_D=0.39$ nM) and cynomolgus monkey ($K_D=0.44$ nM) PD-1, and human ($K_D=1.15$ nM) and cynomolgus monkey ($K_D=0.20$ nM) LAG-3, as measured by surface plasmon resonance. The monovalent PD-1 arm of INCA32459 blocks PD-1 with similar potency as a bivalent PD-1 antibody (nivolumab analog) in a PD-1/PD-L1 reporter assay. In a loss-of-function reporter assay where luciferase expression increases upon blockade of both LAG-3 and PD-1, INCA32459 significantly induced luciferase expression to a greater extent than either PD-1 (nivolumab analog) or LAG-3 (relatlimab analog) single agent antibody controls, and greater than PD-1 (nivolumab) and LAG-3 (relatlimab) analog antibodies combined. In 2 human primary immune cell assays, a T-cell exhaustion model using chronically SEB-stimulated peripheral blood mononuclear cells (PBMCs), and an antigen recall assay using CEFT MHCII peptide pool-stimulated PBMCs, INCA32459 treatment resulted in higher interleukin-2 and interferon- γ induction, respectively, compared with PD-1 (nivolumab analog) and LAG-3 (relatlimab analog) antibodies combined. In a human MDA-MB-231 breast tumor model in CD34⁺ humanized NSG mice, INCA32459 treatment decreased tumor growth compared with a combination of PD-1 (pembrolizumab) and LAG-3 (relatlimab analog) antibodies. Pharmacodynamic analysis in mice demonstrated a dose-dependent increase in receptor occupancy at 1 and 10 mg/kg. Pharmacokinetic characterization of INCA32459 in cynomolgus monkeys after a single IV infusion at 3 and 30 mg/kg demonstrated an average clearance, steady-state volume of distribution, and mean residence time of 0.515 mL/h/kg, 74.1 mL/kg, and 144 h, respectively.

Conclusions We have developed INCA32459, a potent dual inhibitor of PD-1 and LAG-3 in preclinical models, which induces activation of exhausted T cells to a greater extent than a combination of bivalent monospecific antibodies targeting PD-1 (nivolumab analog) and LAG-3 (relatlimab analog). These data support the clinical evaluation of INCA32459, and a phase 1 study in cancer patients is underway.

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