Exhausted T cells express high levels of several immune checkpoint proteins, including the programmed death-1 (PD-1) receptor. Preclinical and clinical data support the role of the PD-1/PD-L1 axis in promoting tumor evasion by curtailing immune responses. We present the preclinical characterization of GLS-010 (AB122), a novel fully human PD-1 monoclonal antibody currently in Phase 1 clinical trials.

**Methods**

The affinity of GLS-010 (AB122) for human and cynomolgus monkey PD-1, its specificity for PD-1, and its ability to block the PD-1 interaction with PD-L1 and PD-L2 were measured by ELISA, flow cytometry and receptor-activated reporter gene assays. Functional assessment of GLS-010 (AB122) on T cell responses (IFN-γ, IL-2, and proliferation) was performed using mixed lymphocyte reaction (MLR) and co-stimulation with cytomegalovirus (CMV) pp65 peptide. The antitumor efficacy of GLS-010 (AB122) was evaluated using a mouse MC-38 tumor model grown in syngeneic human PD-1 knockout mice. For PK analysis, GLS-010 (AB122) was dosed in a single intraperitoneal injection to male and female cynomolgus monkeys at doses of 2, 18 and 110 mg/kg.

**Results and Conclusion**

GLS-010 (AB122) is a fully human IgG4 monoclonal antibody that binds to human PD-1 (IC50 = 216 nM, ELISA, T-cell blocking, CD28 cytoplasm), cyno PD-1 (EC50 = 150 mM, ELISA), but not rat or mouse PD-1. Lack of GLS-010 (AB122) binding to other related members of the CD28 family, such as ICOS, CD28 and CTLA-4, confirms the specificity of the interaction. Functional studies showed that binding of GLS-010 (AB122) to cell-expressed PD-1 inhibits the interaction between both PD-L1 and PD-L2 with an EC50 of 580 nM and 870 nM, respectively (by flow cytometry) and 2.2 nM and 5.8 nM, respectively (in reporter gene assays). Using polyethylene oxide-derived dendritic cells, we observed a dose-dependent enhancement of IFN-γ production and proliferation by CD4 T cells, saturating at concentrations below 0.1 nM. Similar results were obtained in an antigen-specific T cell recall response assay using CMV-infected donors. GLS-010 (AB122) was very effective at blocking MC-38 tumor growth in PD-1 knockout mice. PK analysis following a single i.v. dose of GLS-010 (AB122) administered to male and female cynomolgus monkeys was dose-proportional and the ratio of clearance was dose-independent.

GLS-010 (AB122) is a novel and selective antagonist of PD-1 antibody that potently blocks the interaction of human PD-1 with both PD-L1 and PD-L2. This blockade translates into potent enhancement of T cell activation in a variety of cell culture studies, which combined with its in vivo profile in mouse and monkey supports its ongoing clinical development in oncology.

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**References**

1. Arcus Biosciences Inc., Hayward, CA, USA. 2. WuXi AppTec, Shanghai, China. 3. Harbin Gloria Pharmaceuticals, Beijing, China.