YH006, A FULLY HUMAN TREG-DEPLETING CTLA-4×OX40 BISPECIFIC ANTIBODY, DEMONSTRATES SUPERIOR PRECLINICAL EFFICACY AND FAVORABLE DEVELOPABILITY

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Background: Tumor-infiltrating regulatory T (Treg) cells aid the development and progression of tumors by inhibiting the antitumor immune response. This immunosuppressive effect often leads to resistance against current immunotherapies for certain cancers. Although the first generation Treg-depleting CTLA-4 antibody ipilimumab has shown clinical efficacy, its use, particularly in combination with PD-1 inhibitors, has been associated with severe immune-related adverse events. To address this difficulty, we set out to develop a next-generation Treg-depleting antibody with improved efficacy and safety. Since tumor-infiltrating Treg cells consistently exhibit higher expression levels of both CTLA-4 and OX40 compared to T cells in the periphery across multiple cancer types, we developed an Fc-enhanced CTLA-4×OX40 bispecific IgG1 antibody, YH006, designed to deplete tumor-infiltrating Treg cells with better specificity. YH006 was generated from the RenLite mouse, which contains a fully human common light chain to facilitate bispecific antibody assembly and the downstream CMC process.

Methods: The ability of YH006 to promote T-cell responses in vitro was measured by effector cytokine secretion from streptococcal enterotoxin b-stimulated human PBMCs, and ADCC activity in the context of effector NK-92 cells (with CD16A expression) and human Treg cells, measured by flow cytometry. The in vivo anti-tumor activity of YH006 was evaluated in B-hCTLA-4/hOX40 humanized mice with syngeneic tumors. Transaminase and serum cytokine levels were monitored to determine the preclinical safety of YH006 in vivo. The physicochemical properties of YH006 were assessed by HPLC and LC-MS.

Results: YH006 treatment and ADCC activity over ipilimumab in vitro. In vivo syngeneic tumor studies demonstrated a superior and dose-dependent anti-tumor activity of YH006 compared to both ipilimumab analog and its Fc-enhanced parental monoclonal antibodies at low doses. Tumor-infiltrating lymphocyte analysis revealed that YH006 treatment can better increase the intra-tumoral CD8/Treg ratio compared with ipilimumab analog. YH006 also showed dose-dependent efficacy in GL261 syngeneic model. Notably, YH006 synergized with PD-L1 antibodies in syngeneic MC38 and B16F10-OVA models. Importantly, YH006 treatment did not elevate liver enzymes or induce production of inflammatory cytokines. Ongoing CMC process development has a titer of 6.9 g/L at the 3L scale, and the purification yield is 80.7%, suggesting excellent quality without homodimers detected. YH006 has consistent quality from research cell bank (RCB) to passage 97.

Conclusions: YH006 demonstrated superior anti-tumor efficacy across several tumor models and excellent physicochemical properties, which make it a promising candidate for further development as a cancer treatment.

REFERENCES

Ethics Approval: All animal studies were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of Biocytogen Beijing Co., Ltd.

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