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HBM7008, A FIRST-IN-CLASS BISPECIFIC ANTIBODY TARGETING BOTH B7-H4 AND 4-1BB, EXHIBITS ROBUST ANTI-TUMOR IMMUNITY AND LOW TOXICITY THROUGH B7-H4-DIRECTED 4-1BB ACTIVATION

Bing Huang*, Fangfang Du, Xiaocheng Lv, Jianxun Zhao, Fei Chen, Zailian Lu, Yang Zhang, Victor Chen, Xin Gan, Jiujiao Zhao, Yun He, Xiaodong Wu, Yiping Rong. *Harbour BiMed Co., Ltd, Shanghai, China*

Background 4-1BB is an immune costimulatory receptor. Anti-4-1BB agonistic monoclonal antibodies have high potential of therapeutic efficacy in cancers. However, 4-1BB agonistic antibody urelumab shows dose-limiting hepatotoxicity in clinical trials. B7-H4 is a member of the B7 superfamily. It shows limited expression in most normal tissues but high expression on the surface of tumor cells in breast, ovarian, and endometrial cancers. B7-H4 also inhibits the proliferation and activation of T cells. Blockade of B7-H4 demonstrates some efficacy in mouse models. To overcome the hepatotoxicity of systemically active 4-1BB agonist and to improve the anti-tumor activity of B7-H4 antagonist, HBM7008, a B7-H4x4-1BB bispecific antibody specifically activated in tumor microenvironment, has been developed.

Methods B7-H4 expression of multiple tumor tissues was evaluated by immunohistochemistry staining. Anti-B7-H4 fully human IgG antibodies and anti-4-1BB fully human heavy chain only antibodies (HCAb) were generated from H2L2 and HCAb Harbour Mice[®], respectively. HBM7008 was developed from Harbour BioMed HCAb based bispecific immune cell engager (HBICE[®]) platform. It is composed of anti-B7-H4 IgG1 monoclonal antibody and anti-4-1BB HCAb variable domain fused at the C-terminus of heavy chain constant region with LALA (L234A and L235A) mutations. Its proposed mechanism of action and nonclinical pharmacology were characterized by a series of *in vitro* and *in vivo* assays.

Results B7-H4 showed high prevalence of expression on breast, ovarian, cervical, endometrial cancers, and squamous non-small-cell lung carcinoma. HBM7008 can bind to B7-H4 and 4-1BB simultaneously. HBM7008 robustly induced T cell activation *in vitro* in a B7-H4-dependent manner with activity comparable to that of urelumab. HBM7008 demonstrated potent antitumor activity with complete response and resistance to tumor rechallenge in a mouse model. It also increased proliferation of tumor infiltrating lymphocyte (TIL) cytotoxic CD8+ T and effector memory CD8+ T cells. HBM7008 is a first-in-class bispecific T cell engager targeting both B7-H4 and 4-1BB and enhances T cell function by dual mechanisms: (1) blockade of the B7-H4 mediated T cell inhibition and (2) activation of 4-1BB+ T cells only in a B7-H4 cross-linking dependent manner. In a good laboratory practice-compliant non-human primate 4-week repeat dose toxicity study, HBM7008 was well tolerated up to 100 mg/kg with no discernable drug-related toxicity.

Conclusions HBM7008 demonstrated comparable biological activity to urelumab and improved safety profile characterized by *in vitro* functional assays, *in vivo* antitumor efficacy model, and TIL analysis. These preclinical data support the clinical investigation of HBM7008 for the treatment of cancers.

Ethics Approval The cancer tissue microarray was purchased from Fanpu Biotech, Inc. The company ensured ethical approval from the patients, and patient consent for publication. The anti-tumor efficacy and pharmacodynamics studies in mice were approved by the internal ethics board of the respective contract research organization (CRO). The good laboratory

practice-compliant toxicity studies in non-human primate were approved by Ethics Board of an appropriate contract research organizations (CROs).

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