Background Single-targeting immunotherapeutic agents for the tumor-associated antigens HER3 and MUC1 have shown limited efficacy in the clinic.\cite{1-4} Notably, as MUC1 can undergo auto-proteolysis, the efficacy of drugs targeting the MUC1-N region is very limited.\cite{2} We hypothesized that targeting HER3 and the juxtamembrane domain of MUC1 with a bispecific antibody may result in improved anti-tumor efficacy. We generated antibodies for both HER3 and MUC1 in RenLite® fully human antibody mice, which contain a common light chain to facilitate bispecific antibody assembly. One parental antibody targeting the juxtamembrane region of MUC1 and two HER3 antibodies were selected for further assembly into DM002 bispecific antibodies (BsAbs) using knobs-into-holes technology.

Methods Affinity of DM002 BsAbs to human and cynomolgus monkey antigens was measured using surface plasmon resonance (SPR) and flow cytometry. Endocytosis of BsAbs with or without MMAE conjugation was assessed using Incucyte imaging. In vivo efficacy of DM002 in multiple cell line-derived and patient-derived xenografts was subsequently evaluated.

Results DM002 is cross-reactive to human and cynomolgus monkey targets with an affinity ($K_D$) of approximately $10^{-8}$ M. The endocytosis activity of DM002 BsAbs was stronger than parental antibodies and benchmarks in the NUGC-4 cell line, suggesting synergy between the two targets. DM002 demonstrated robust in vivo efficacy in cell line-derived and patient-derived xenografts (PDX) with varying levels of HER3 and MUC1 expression. In PDX models, DM002 candidates outperformed benchmarks.

Conclusions We generated novel bispecific antibodies targeting HER3 and the juxtamembrane domain of MUC1 and demonstrate their ability to function as effective antibody-drug conjugates with MMAE payloads in vivo, with other payloads under investigation. Thus, DM002 is a promising novel therapeutic with potential to treat cancers co-expressing HER3 and MUC-1.

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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