1150 DM005, AN EGFR × MET BISPECIFIC ANTIBODY-DRUG CONJUGATE, SHOWED ROBUST ANTI-TUMOR ACTIVITY IN PDX MODELS

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Background Bispecific antibodies (BsAb) that target dual tumor-associated antigens can invoke synergistic effects between two signaling pathways, increase target tissue specificity, and reduce systemic toxicity. Combining antibody-mediated specific targeting with potent killing from a cytotoxic payload, antibody-drug conjugates (ADC), especially bispecific ADCs (BsADC), have become powerful therapeutic strategies. EGFR and MET are oncogenic proteins that are co-expressed in a wide range of tumors. Moreover, MET amplification is largely associated with drug resistance to EGFR tyrosine kinase inhibitors (EGFR-TKI) in non-small cell lung cancer (NSCLC) patients.

Methods Biocytogen developed a fully human EGFR × MET BsADC using our proprietary common light chain RenLite® mouse platform and knobs-into-holes technology, evaluated internalization by flow cytometry and IncuCyte, and binding affinity potential by flow cytometry. *In vivo* drug efficacies were screened in severely combined immunodeficient B-NDG mice inoculated with NCI-H1975 and NCI-H292 cell-derived xenografts, as well as patient-derived NSCLC and pancreatic ductal adenocarcinoma (PDAC) xenograft models.

Results The BsAb showed enhanced internalization and binding affinity compared to parental monoclonal and monovalent antibodies in the EGFR/MET co-expressing NCI-H1975 cell lines. After conjugating the BsAb with monomethyl auristatin E (MMAE) via a protease-cleavable linker, the resulting BsADC, DM005, exhibited a remarkable and dose-dependent anti-tumor efficacy in NCI-H1975 and NCI-H292 cell line-derived xenograft models. Moreover, in multiple patient-derived xenografts of NSCLC and pancreatic ductal adenocarcinoma (PDAC), which co-express EGFR and MET, DM005 demonstrated superior and durable efficacy that outperformed benchmark antibodies at a lower dose (3 mg/kg).

Conclusions Collectively, these results suggest that DM005 can be an effective treatment option for EGFR and MET co-expressing tumors and overcome MET-driven EGFR-TKI resistance to improve patient outcomes.

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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