Background EGFR is a promising therapeutic target expressed on multiple tumor cell types. While single-targeting antibodies and ADCs have been explored, limitations encountered with current therapies, such as drug resistance and lack of cytotoxicity, indicate a need for alternative treatments. As EGFR and the tumor-associated antigen TROP2 are co-expressed in multiple types of solid tumors, we hypothesize that developing a bispecific ADC with this target combination could provide therapeutic benefit for a wide range of tumors. Thus, we generated DM001, a TROP2/EGFR bispecific antibody conjugated with monomethyl auristatin E (MMAE) via a protease-cleavable linker.

Methods Binding assessments of DM001 were performed using surface plasmon resonance (SPR). Internalization was assessed through IncuCyte, by briefly observing the internalized area via a fluorescence microscope. Flow cytometry binding assays were subsequently performed to determine selectivity of DM001 for cells expressing various levels of TROP2 and EGFR. Cytotoxicity, bystander killing, and cell cycle assays were performed using and flow cytometry, respectively, to assess DM001 potency in vitro. In vivo studies were subsequently performed, including pharmacokinetic assays to determine stability, and tumor efficacy studies to evaluate efficacy of DM001 in preventing growth of human cancer cell line-derived and patient-derived xenografts.

Results In vitro, DM001 demonstrated high affinity and cytotoxicity in multiple cell lines expressing TROP2 and EGFR, with preferential binding to cells expressing both antigens: In vivo, DM001 exhibited potent, dose-dependent efficacy in multiple cell line and patient-derived xenografts when compared to benchmarks. Notably, DM001 efficacy was superior to parental ADCs in patient-derived lung and pancreatic xenograft models.

Conclusions DM001 is a novel, first-in-class bispecific ADC targeting EGFR and TROP2 that demonstrates in vivo efficacy against a variety of cell and patient-derived tumors.

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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