DM001, a Novel TROP2xEGFR Bispecific ADC, Demonstrates Potent Tumor Growth Inhibition in Preclinical Models and Favorable Safety Profile in Cynomolgus Monkey

Zhulin Li1, Chengzhang Shang1, Xuewa Guan1, Gao An1, Yuming Guo1, Chaoshu Guo1, W. Frank An1, Yi Yang1

1BIOCYTEN GENETIC PHARMACEUTICALS (BEIJING) CO., LTD., BEIJING, CHINA; 2DOMA BIOPHARMACEUTICAL (SUZHOU) CO., LTD., SUZHOU, JIANGSU, CHINA; 3EUROPE (BEIJING) BIOPHARMA CO., LTD., BEIJING, CHINA

INTRODUCTION
EGFR and TROP2 are validated therapeutic targets co-expressed on multiple tumor types. Single-targeting ADCs have shown clinical benefits; however, strategic dual-targeting strategies were observed due to their co-expression in normal tissues. This dual-targeting strategy may lead to lower resistance and potentially safer efficacies. Bispecific ADCs (bsADCs), by targeting EGFR and TROP2 simultaneously, potentially allow efficient efficacy, reduced resistance, and improved safety profiles.

We screened pools of anti-EGFR and anti-TROP2 monoclonal antibodies, and selected clones to construct a bispecific ADC targeting EGFR and TROP2 that provided optimized preclinical profile. In vivo, unconjugated DM001 (DM001 bsAb) demonstrated enhanced antitumor activity compared to its parental monovalent antibodies (monos). For proof of concept, the DM001-BS1202 was initially conjugated in nonclinical mouse xenografts (H22 tumor) via a proteo-alkylation-based linker (Rad50). The ADC, DM001-BS1202, demonstrated robust activity in nearly all PDX models, with the best activity in in vitro cytotoxicity assay, cell cycle analysis, and in vivo study. Further studies showed that DM001-BS1202 significantly outperformed the single-targeting ADC monovalent anti-TROP2 (vCMMAE conjugated ADC). DM001-BS1202 was effective in multiple tumor systems and significantly outperformed the single-targeting ADC in multiple PDX models. DM001 demonstrated superior, dose-dependent anti-tumor activity in CDX models.

Pharmacokinetics (PK) in N431 model and in vitro stability of DM001
DM001 showed potent anti-tumor activity in vitro in the H22 tumor xenograft model at day 8. DM001 demonstrated improved pharmacokinetics compared with its parental ADCs in vivo. In vivo, DM001 showed parent and tumor viability of ADC, including tumor less sensitive to vCMMAE-conjugated ADC. DM001 showed robust efficacy in a number of PDX models, including triple-negative breast cancer (TNBC), epidermal growth factor receptor (EGFR), small cell lung cancer (SCLC), colorectal cancer (CRC), gastric cancer (GC), and normal cell lines (SCLC) with and without EGFR mutations. In a dose range finding study, DM001 (DM001-BS1202) was well-tolerated in cynomolgus monkeys when dosed at 0.5 mg/kg intravenous (IV) at the start of each cycle (100 mg/kg at 28 days). Further toxicity study in planned.

DM001 tested with mAbs and bsAbs conjugated to mAbs. For a proof of concept, the TROP2xEGFR bsAb was initially conjugated to monomethyl auristatin E (MMAE) via a proteo-alkylation-based linker (Rad50). The ADC, DM001-BS1202, demonstrated robust activity in nearly all PDX models, with the best activity in in vitro cytotoxicity assay, cell cycle analysis, and in vivo study. Further studies showed that DM001-BS1202 significantly outperformed the single-targeting ADC monovalent anti-TROP2 (vCMMAE conjugated ADC). DM001-BS1202 was effective in multiple tumor systems and significantly outperformed the single-targeting ADC in multiple PDX models. DM001 demonstrated superior, dose-dependent anti-tumor activity in CDX models.

DM001 inhibited a variety of PDX models, including both EGRF-mutant and wild-type NSCLC PDX
DM001 inhibited the growth of multiple solid tumor PDX models.

DM001-BS1202: DM001 bsAb conjugated to a novel topoisomerase I inhibitor payload

DM001-BS1202 was conjugated to DAR4 payload and demonstrated robust activity in vitro and in vivo.

DM001 showed potent antitumor activity in multiple solid tumor PDX models.

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