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Preclinical efficacy of DM002, a bispecific HER3×MUC1-C antibody-drug conjugate with DNA topoisomerase I inhibitor, in solid tumor models

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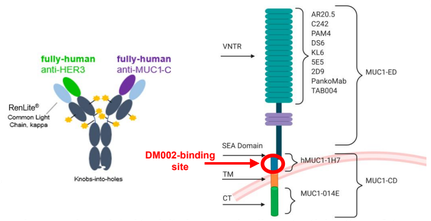
ABSTRACT

HER3 and MUC1 are co-expressed in a number of cancers, including lung, breast, colorectal, pancreatic, ovarian, gastric, endometrial and urothelial carcinoma[1]. We hypothesized that targeting HER3 and MUC1 simultaneously with bispecific antibody drug conjugates (bsADCs) may potentially allow enhanced potency, reduced resistance, and improved safety in clinical setting. Here we generated fully human antibodies against both HER3 and MUC1-C targeting the juxtamembrane domain of MUC1 (MUC1-C) to avoid the interference of MUC1-N[2], in RenLite® common light chain platform.



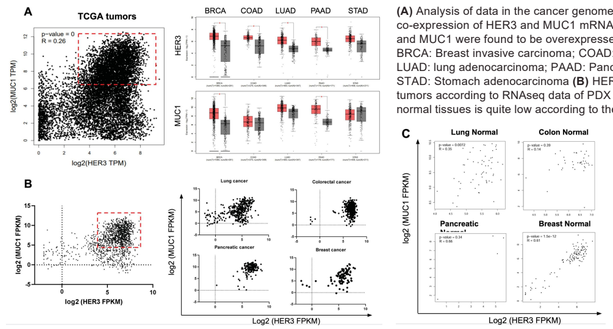
MUC1-C and HER3 block multiple major pathways in cancer cell proliferation, immune escape and invasion, which could result in 1) better efficacy than single target treatment, 2) reduced drug resistance of HER3 block. HER3-MUC1-C synergistic binding induced endocytosis will diminish HER3 broad expression related toxicity in normal cells, potential better safety than sole HER3 treatment. RenLite design of DM002 also ensure efficient production and quality control during scale up.

We show that DM002 bsAb can bind to tumor cells with different expression of HER3 & MUC1 and be internalized with higher rates than its parental mAbs, suggesting synergy between the two arms. In vivo, DM002 bsADC, both as vcMMAE conjugates and as novel DNA topoisomerase I inhibitor linker/payload conjugates (BLD1102) potently inhibited growth of HER3 and MUC1 double positive PDX tumors and showed more potent in vivo efficacy than mono-Ab ADCs, consistent with their in vitro internalization findings.

The potential indications of DM002 under research are focusing on lung cancer, breast cancer, CRC, pancreatic cancer, ovarian cancer and gastric cancer.

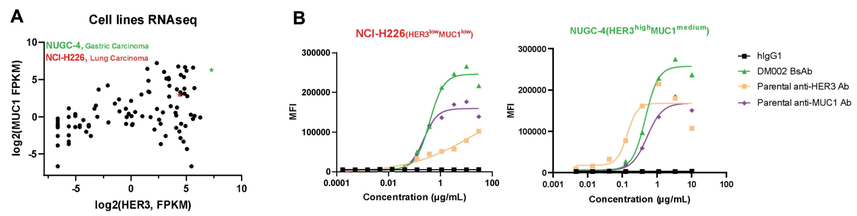
[1]Reference: Tang Z, Kang B, Li C, Chen T, Zhang Z. GEPIA2: an enhanced web server for large-scale expression profiling and interactive analysis. Nucleic Acids Res. 2019 Jul 2;47(W1):W556-W560. doi: 10.1093/nar/gkz430.
[2]Reference: Bose, M.; Mukherjee, P. Potential of Anti-MUC1 Antibodies as a Targeted Therapy for Gastrointestinal Cancers. *Vaccines* **2020**, *8*, 659. https://doi.org/10.3390/vaccines8040659

HER3 and MUC1 are co-expressed in many solid tumors

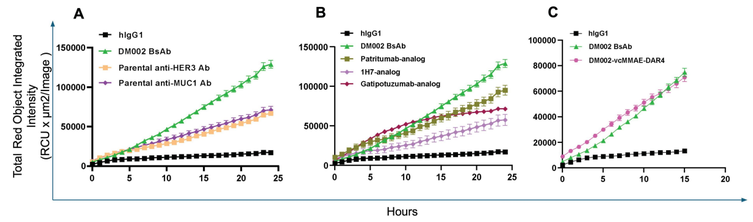


(A) Analysis of data in the cancer genome atlas (TCGA) database revealed co-expression of HER3 and MUC1 mRNAs. In the GEPIA2 database, both HER3 and MUC1 were found to be overexpressed in multiple tumors.
BRCA: Breast invasive carcinoma; COAD: Colon adenocarcinoma
LUAD: lung adenocarcinoma; PAAD: Pancreatic adenocarcinoma
STAD: Stomach adenocarcinoma **(B)** HER3 and MUC1 are co-expressed in multiple tumors according to RNAseq data of PDX samples (n=1462). **(C)** Co-expression in normal tissues is quite low according to the GEPIA2 database.

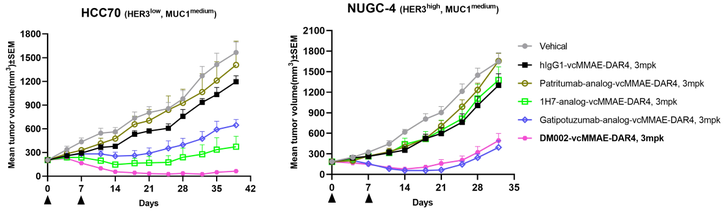
DM002 BsAb demonstrates increased cell binding avidity over their parental antibodies



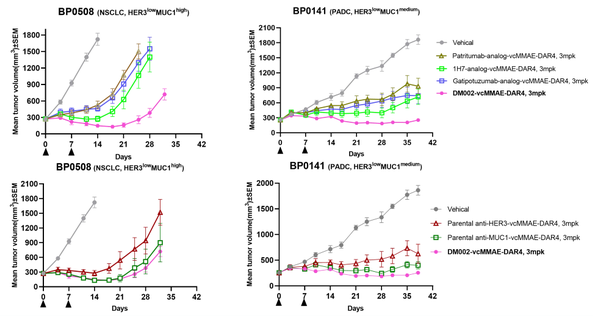
DM002 BsAb shows enhanced endocytosis in NUGC-4(HER3^{high}MUC1^{medium}) cell line and comparable endocytosis with DM002-vcMMAE-DAR4



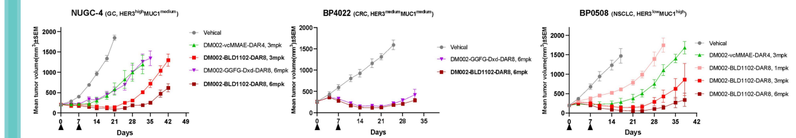
DM002-vcMMAE-DAR4 demonstrates stronger or comparable anti-tumor activities than mono-Ab ADCs in CDX models



DM002-vcMMAE-DAR4 exhibits better anti-tumor activity than benchmark and parental Ab-ADCs in PDX models



New linker-payload (BLD1102) exhibits superior anti-tumor efficacy over conjugate to GGFG-DXd and vcMMAE



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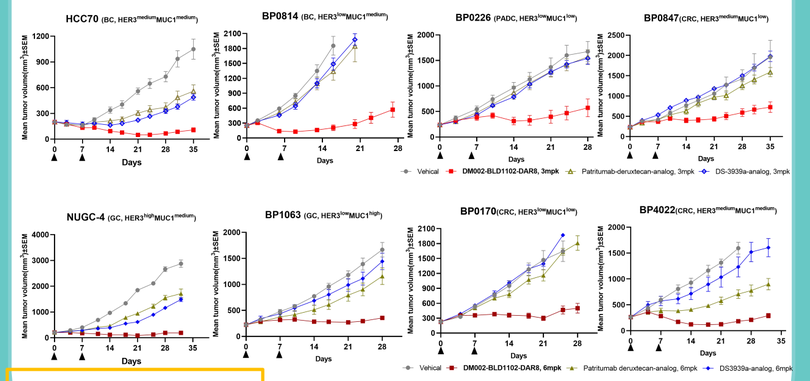
DM002-BLD1102 demonstrates stronger anti-tumor activities than mono-Ab ADCs



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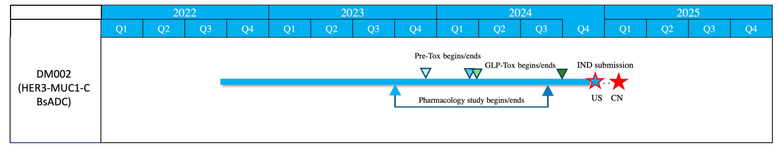
DM002 Development Timeline



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We are seeking global partners for licensing deals.

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