Preclinical evaluation of fully human bispecific antibody-drug candidates targeting HER3 and the juxtamembrane region of MUC1

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INTRODUCTION

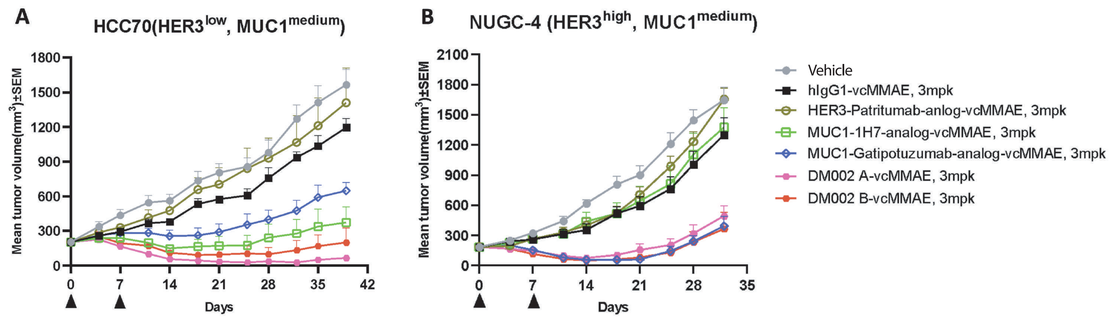
Despite MUC1 being a well-known tumor associated antigen (TAA), earlier anti-MUC1 agents have shown limited efficacy in the clinic [2-4]. Notably, one complicating factor was that the soluble N-terminal autoproteolytic product of MUC1 could neutralize many of these earlier anti-MUC1 antibodies. HER3 ADCs have shown encouraging early clinical efficacy in multiple tumors recently (for example, see ref 1). However, majority of patients still did not respond. Therefore, improved therapies targeting these TAAs are needed for unmet medical needs.

HER3 and MUC1 are co-expressed in a number of cancers. 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. Further, we aim to target the juxtamembrane domain of MUC1 (MUC-1C) to avoid the interference of soluble MUC1. We generated antibodies against both HER3 and MUC-1C in RenLite® common light chain fully human antibody transgenic mice. Two monoclonal antibodies (mAbs) targeting HER3 and one mAb targeting MUC-1C were selected and used to construct two bispecific antibodies (bsAbs, DM002 bsAbs) and the corresponding bsADCs.

In the present abstract, we show that DM002 bsAbs bound to human and cynomolgus monkey antigens with higher capacity and internalized with higher rates than its parental mAbs, suggesting synergy between the two arms. In vivo, DM002 bsADCs, 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. The bsADC DM002-vcMMAE also showed more potent in vivo efficacy than its parental mAb ADCs, consistent with their in vitro internalization activities.

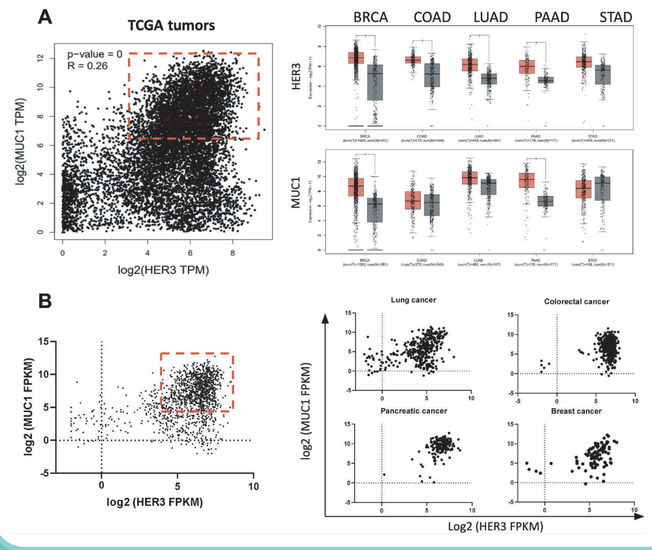
DM002-BLD1102 further demonstrated strong anti-tumor activity in DM002-vcMMAE-resistant PDX models, suggesting the superiority of this new DNA topoisomerase I inhibitor linker/payload over the classical vcMMAE linker/payload. In summary, DM002 bsADCs, in particular DM002-BLD1102, which targets HER3xMUC1, demonstrated enhanced in vitro internalization activity and superior in vivo anti-tumor activities in a number of HER3 and MUC1 double positive PDX models, making them promising preclinical candidates for treating HER3 and MUC-1 positive tumors.

DM002 A/B-vcMMAE demonstrated robust anti-tumor activity in two CDX models



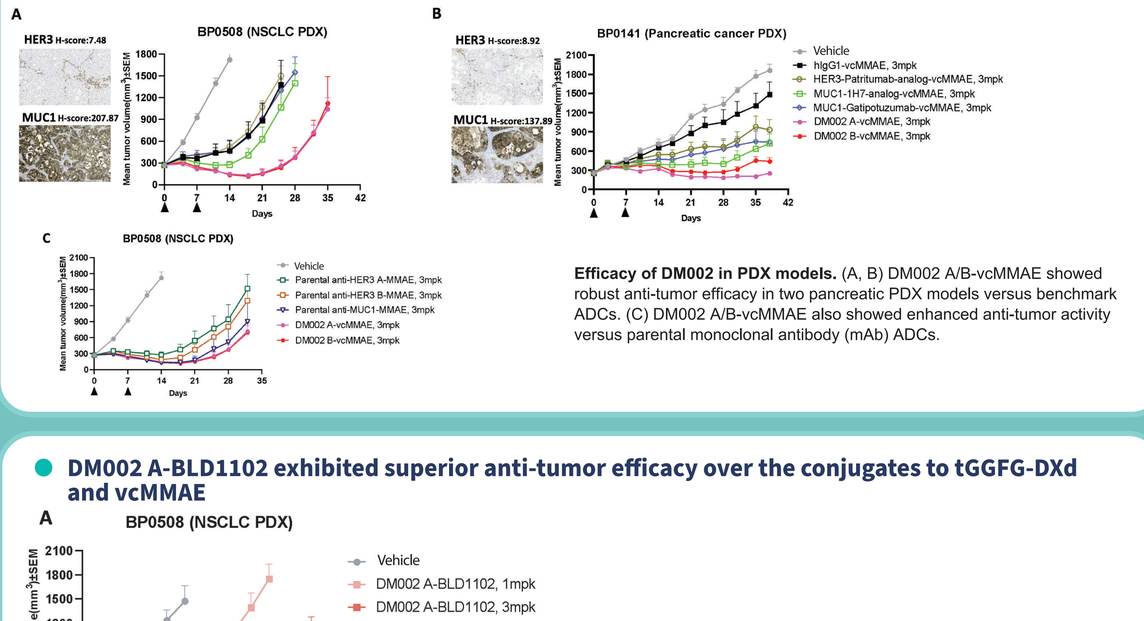
(A, B) Efficacy of DM002 A/B-vcMMAE *in vivo*. DM002 A/B-vcMMAE demonstrated robust anti-tumor activity in cell line-derived xenografts (CDX) with different levels of HER3 expression. The DM002 A/B-vcMMAE ADC showed stronger efficacy in HCC70 CDX than all of the benchmark ADCs.

HER3 and MUC1 are co-expressed in multiple solid tumors



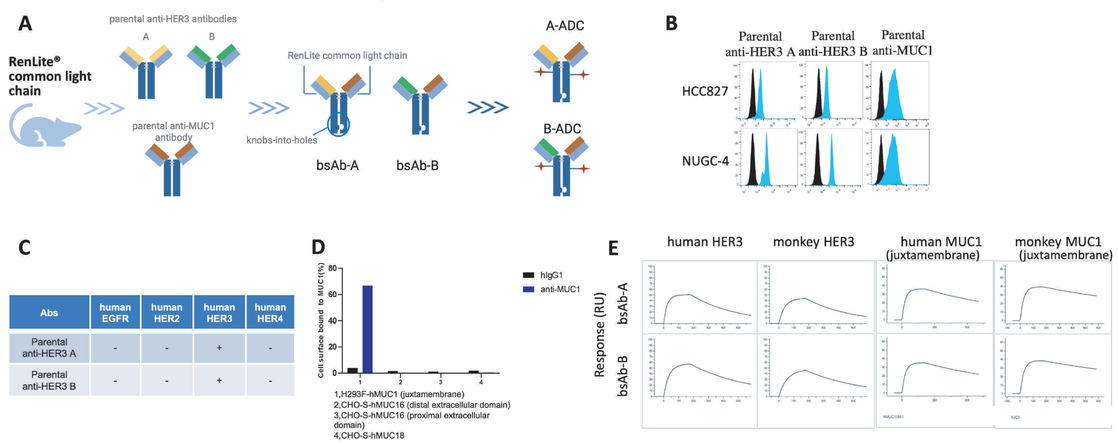
(A) Analysis of data in the cancer genome atlas (TCGA) database revealed co-expression of HER3 and MUC1 mRNAs (left panel). In the GEPIA2 database [5], both HER3 and MUC1 were found to be overexpressed in multiple tumors, especially in LUAD (lung adenocarcinoma), BRCA (breast invasive carcinoma), and PAAD (pancreatic adenocarcinoma) (right panel). (B) HER3 and MUC1 are co-expressed in multiple tumors according to RNAseq data of PDX samples (n=1462).

DM002 A/B-vcMMAE bsADCs exhibited potent anti-tumor activity in HER3-low PDX models



Efficacy of DM002 in PDX models. (A, B) DM002 A/B-vcMMAE showed robust anti-tumor efficacy in two pancreatic PDX models versus benchmark ADCs. (C) DM002 A/B-vcMMAE also showed enhanced anti-tumor activity versus parental monoclonal antibody (mAb) ADCs.

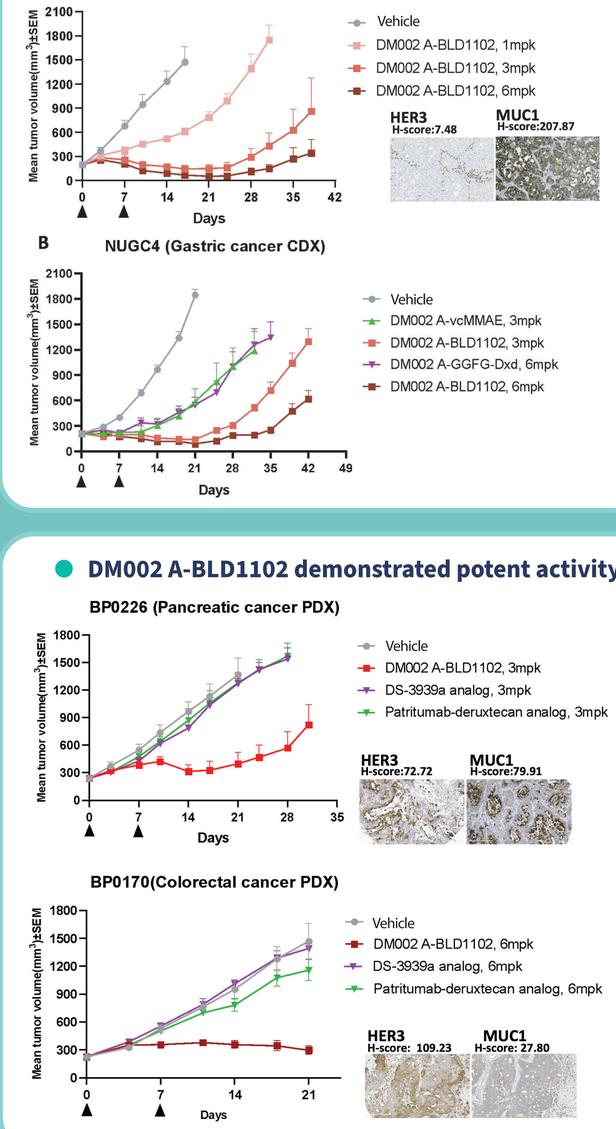
Characterization of DM002 parental antibodies



Abs	human EGFR	human HER2	human HER3	human HER4
Parental anti-HER3 A	-	-	+	-
Parental anti-HER3 B	-	-	+	-

(A) Arms of two parental anti-HER3 antibodies and one parental anti-MUC1 antibody generated based on our RenLite® common light chain antibody platform were assembled into two DM002 bsAbs and used for conjugation. (B) Parental antibodies bind to two tumor cell lines. (C) Parental anti-HER3 antibodies A and B do not bind to other EGFR family members as assessed by SPR. (D) Binding assessments (flow cytometry) indicate that the parental anti-MUC1 targets the juxtamembrane domain of MUC1, avoiding antibody neutralization induced by shedding of MUC1-N. Anti-MUC1 did not bind other MUC family proteins. (E) The affinities (K_{Ds}) of DM002 BsAb to both HER3 and the juxtamembrane domain of MUC1 (human and cynomolgus monkey) are approximately 10^{-8} M as measured by SPR.

DM002 A-BLD1102 exhibited superior anti-tumor efficacy over the conjugates to tGGFG-DXd and vcMMAE



DM002 A-BLD1102 is the bsADC where DM002 bsAb-A is conjugated to BLD1102, a novel, proprietary linker/payload composed of DNA topoisomerase I inhibitor payload and a very hydrophilic protease-cleavable linker with a drug-to-antibody ratio (DAR) of 8.

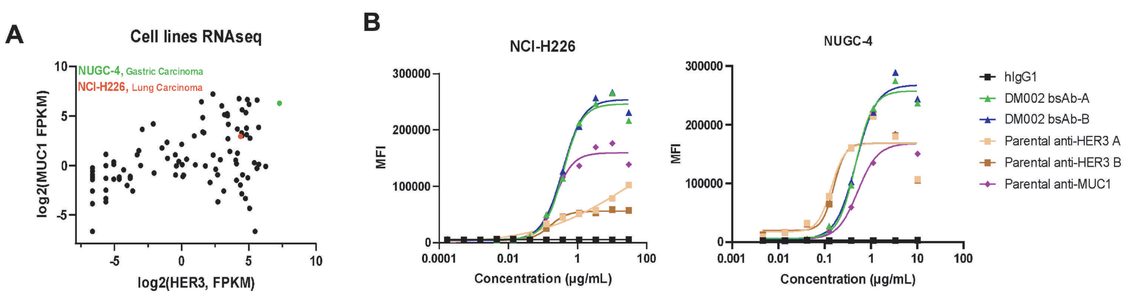
(A) DM002 A-BLD1102 demonstrated dose-dependent antitumor activity in an NSCLC PDX model.
(B) DM002 A-BLD1102 showed greater efficacy than the conjugate to GGFG-DXd (DAR8) and vcMMAE (DAR4) at doses of 6 mg/kg and 3 mg/kg, respectively.

DM002 A-BLD1102 demonstrated potent activity in BP0226 and BP0170 PDX models

Superior anti-tumor activity of DM002 A-BLD1102 in benchmark ADC-resistant BP0226 and BP0170 PDX models.

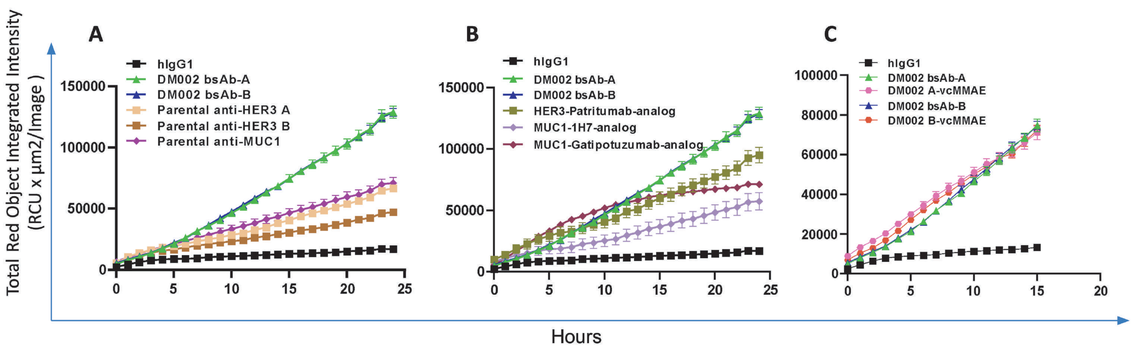
DS-3939a is a MUC1 PankoMab-GEX (gatipotuzumab) ADC, conjugated to GGFG-Dxd with DAR 8. Patritumab-deruxtecan (HER3-Dxd, DAR 8) and DS-3939a are in clinical development by Daiichi Sankyo.

DM002 bsAbs demonstrated increased cell binding avidity



(A) RNA sequencing analysis (in house) of tumor cell lines to assess HER3 and MUC1 co-expression. (B) DM002 bsAbs showed stronger binding capacity than their parental antibodies in the NCI-H226 and NUGC-4 cell lines.

DM002 bsAbs showed enhanced internalization in NUGC4 tumor cells



DM002 bsAbs showed increased endocytosis activity over parental mAbs (A) and benchmark mAbs (B) in the NUGC4 cell line (Incucyte). (C) Conjugation to vcMMAE did not affect DM002 internalization. The conjugates of DM002 BsAb-A/B with vcMMAE were named DM002 A-vcMMAE and DM002 B-vcMMAE, respectively.

SUMMARY

- HER3 and MUC1 are co-expressed in a variety of solid tumors, including those with the high mortalities, making them excellent bsAb targets.
- DM002 bsAb is a novel fully human bispecific antibody targeting HER3xMUC1, generated by the RenLite® common light chain antibody platform, cross-reactive with human and monkey HER3 and the MUC1 juxtamembrane domain.
- DM002 bsAb demonstrated higher endocytosis activity compared with its parental antibodies and HER3 and MUC-1 benchmark antibodies.
- DM002 bsADCs displayed potent inhibition of tumor growth of HER3 and MUC1 double positive CDX and PDX tumor
- BLD1102 is our novel DNA topoisomerase I inhibitor-based linker payload system.
- DM002-BLD1102 bsADC potently inhibited growth of PDX models that were resistant to benchmark ADCs.
- DM002 is a first in class (FIC) bsADC with promising potential targeting a variety of HER3 and MUC-1-positive cancers.

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