*DM005, an EGFR x MET bispecific antibody-drug conjugate with a novel DNA topoisomerase I inhibitor payload, showed robust anti-tumor activity in preclinical models

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INTRODUCTION

Bispecific antibodies (bsAbs) that target dual tumor associated antigens may provide enhanced anti-tumor activity and increased targeting specificity and reduced on target, off tumor toxicity. EGFR and MET are oncogenic proteins that are co-expressed in a wide range of tumors, such as non-small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma (HNSCC). Moreover, MET pathway is one of the key factors that leads to resistance to EGFR tyrosine kinase inhibitors (EGFR-TKIs) in NSCLC patients. Amivantamab, an EGFRxMET bsAb, has been approved for NSCLC with EGFR ex20ins[1].

We hypothesized that an EGFRxMET bsADC could also work effectively in NSCLC. To achieve this, we generated a fully human anti-EGFR x MET bsAb (DM005 bsAb) using our proprietary, common light chain RenLite® mouse platform. DM005 bsAb showed enhanced cell binding and internalization in a cell line. As a proof of concept, we conjugated the DM005 bsAb to vcMMAE with a drug-to-antibody ratio (DAR) of 4 (DM005-vcMMAE). DM005-vcMMAE demonstrated stronger anti-tumor activity against patient-derived xenograft (PDX) models as opposed to the parental, monoclonal ADCs.

DM005 is the DM005 bsAb conjugated to BLD1102, a novel, proprietary linker/payload system composed of a DNA topoisomerase I inhibitor payload (BCPT02) and a very hydrophilic, protease-cleavable linker, with a DAR of 4. DM005 showed excellent internalization activity in vitro and demonstrated potent efficacy in multiple CDX and PDX models, including NSCLC models with both wild type EGFR and EGFR and MET TKI-resistant mutations. DM005 is currently under a preclinical development.

1.Park K, Haura EB, Leighl NB, et al. Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. *J Clin Oncol.* 2021;39(30):3391-3402. doi:10.1200/JCO.21.00662

Figure 1. EGFR and MET are co-expressed in a wide range of solid tumors

A. Co-expression of EGFR and MET mRNAs was detected by analysis of data from The Cancer Genome Atlas (TCGA) database. Both EGFR and MET were found to be expressed in multiple tumors, in particular LUAD (lung adenocarcinoma), LUSC (lung squamous cell carcinoma), HNSC (head and neck squamous cell carcinoma), PAAD (pancreatic adenocarcinoma), COAD (colorectal adenocarcinoma) and STAD (gastric adenocarcinoma).

B. RNA-seq data from PDX samples (n=2485) showing co-expression of EGFR and MET.

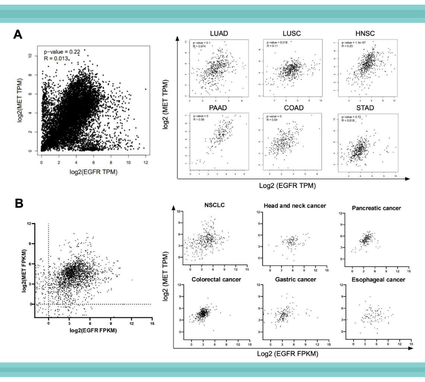
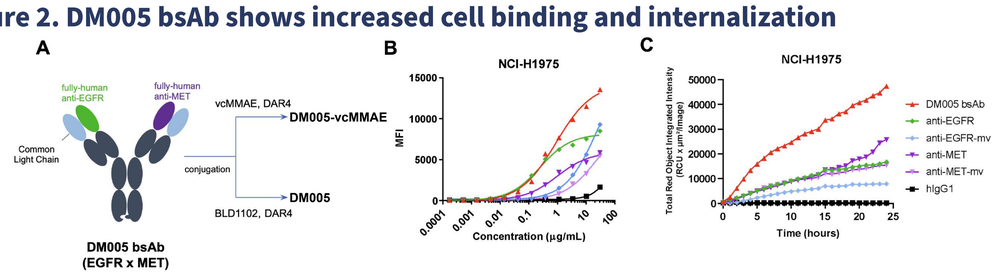


Figure 2. DM005 bsAb shows increased cell binding and internalization



A. DM005 bsAb (EGFRxMET) structure. The parental anti-EGFR and anti-MET antibodies sharing the common light chain were generated in the RenLite® mice. They were assembled into anti-EGFRxMET bsAb **(DM005 bsAb)** and gave rise to DM005-vcMMAE and DM005 after conjugation.

B-C. DM005 bsAb showed increased cell binding (B) and internalization (C) activities as opposed to the parental monoclonal antibodies (mAbs) and monovalent (mv) antibodies in the NCI-H1975 cell line co-expressing both EGFR and MET.

Figure 3. DM005-vcMMAE bsADC demonstrates superior anti-tumor activity *in vivo* as opposed to parental mAb ADCs or their combination

DM005-vcMMAE showed greater inhibition of tumor growth in the NCI-H1975 model than either the parental mAb ADCs or their combination. B-NDG is a severely immune deficient mouse strain.

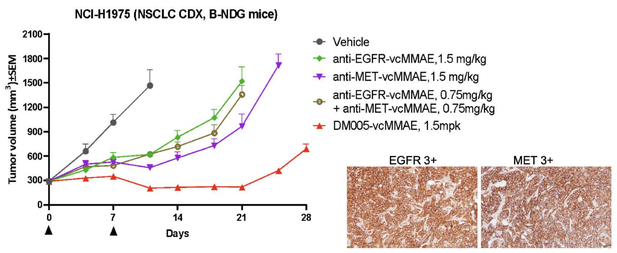
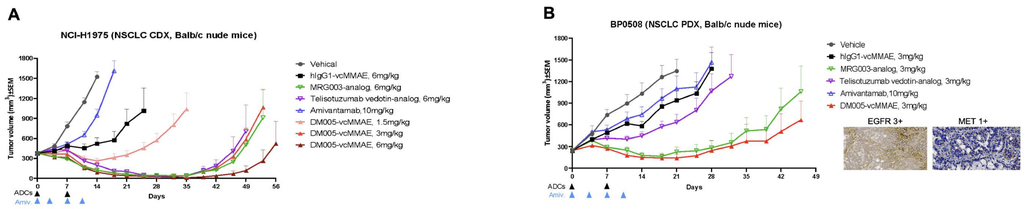


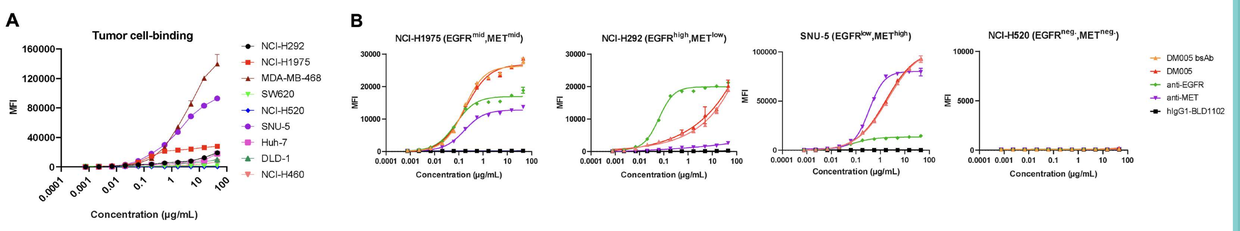
Figure 4. DM005-vcMMAE demonstrated superior anti-tumor activity in both CDX and PDX models



Efficacy of DM005-vcMMAE in NSCLC models in nude mice. DM005-vcMMAE also showed dose-dependent anti-tumor activity in NCI-H1975 **(A).** DM005-vcMMAE showed superior anti-tumor efficacy in both CDX (A) and PDX **(B)** models. outperforming benchmark ADCs.

DM005: EGFR x MET bsAb conjugated to a novel DNA topoisomerase I inhibitor payload

Figure 5. DM005 binds as well as DM005 bsAb to a variety of cell lines expressing different levels of EGFR and MET



A. DM005 bsAb bound to a variety of cancer cell lines with varying degree of EGFR and MET expression levels.

B. DM005 bsAb and DM005 bound equally well to tumor cell lines with varying degree of EGFR and MET expression levels, suggesting BLD1102 conjugation did not interfere with binding.

Figure 6. DM005 internalizes as well as DM005 bsAb in two tumor cell lines

DM005 internalized as fast as DM005 bsAb, suggesting that conjugation did not impact endocytosis capability. Both showed improved internalization kinetics compared with the parental mAbs in the NCI-H1975 (A) and NCI-H292 (B) cell lines as measured by Incucyte.

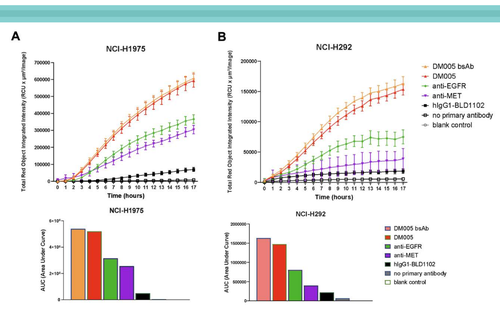
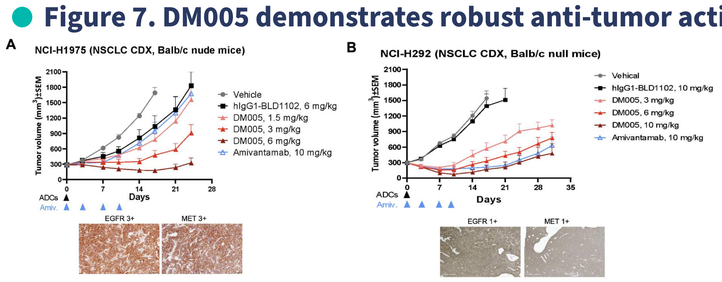
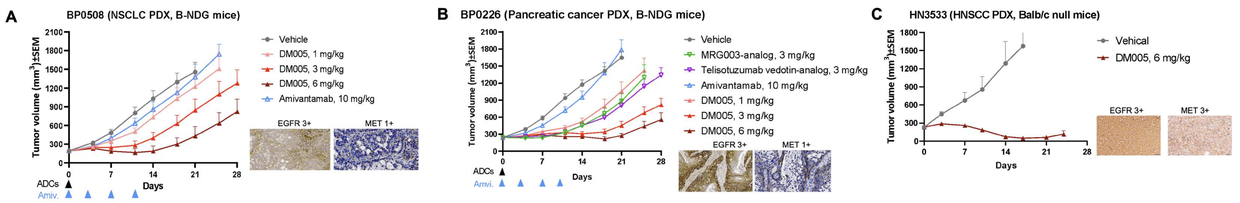


Figure 7. DM005 demonstrates robust anti-tumor activity in CDX models of NSCLC



Efficacy of DM005 in NSCLC CDX models. DM005 showed robust and dose-dependent anti-tumor activity in NCI-H1975 (A) and NCI-H292 (B) CDX models.

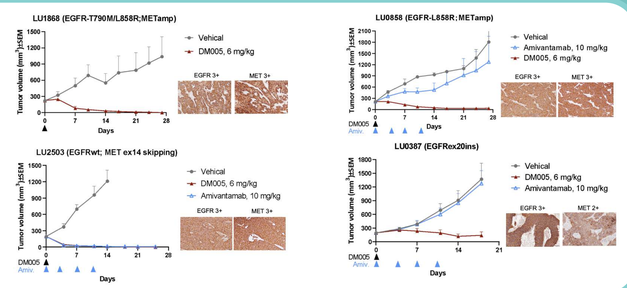
Figure 8. DM005 demonstrates strong anti-tumor activity in PDX models of NSCLC, HNSCC and pancreatic cancer



Efficacy of DM005 in PDX models. DM005 demonstrated potent and dose-dependent anti-tumor activity in the BP0508 (A) and BP0226 (B) PDX models. DM005 has also shown strong activity in HN3533 (C), a PDX model of HNSCC. DM005 showed superior efficacy to benchmark ADCs in pancreatic PDX (BP0226).

Figure 9. DM005 is effective in clinically relevant PDX models of NSCLC, irrespective of EGFR and MET molecular profiles

Efficacy of DM005 in PDX models carrying various EGFR mutations and MET mutation.



SUMMARY

- DM005 is a novel bsADC that targets EGFR and MET with a novel DNA topoisomerase I inhibitor payload. EGFR and MET are co-expressed in a broad spectrum of tumor types, including EGFRwt and EGFRmut NSCLC, making them excellent targets for bsADC.
- The unconjugated DM005 bsAb showed enhanced tumor cell binding and internalization activity in EGFR/MET co-expressing tumor cells.
- EGFRxMET bsADCs (DM005 and its prototype DM005-vcMMAE) showed potent and stronger anti-tumor activity in multiple CDX and PDX models than their parental mAb ADCs and benchmark ADCs.
- DM005 inhibited both EGFRwt and EGFRmut NSCLC PDX models.
- Preclinical development of DM005 is ongoing.

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