N-Myristoyltransferase (NMT) inhibitors are completely novel payloads for Antibody Drug Conjugates that deliver extensive tumor regression at well tolerated doses

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Introduction

N-myristoylation is the N-terminal modification of proteins with myristic acid, a 14-carbon fatty acid. Catalysed by two enzymes, N-myristoyltransferase (NMT1, NMT2), this modification can be co- or post-translational [1]. NMT inhibitors (NMTi) have been shown to inhibit viability and growth of cancers [2]. Here, we have developed novel highly potent and selective NMTi which are cytotoxic in multiple cell lines and exhibit tumour regression in *in vivo* models. To explore targeted delivery of NMTi, we tethered a selective NMTi to trastuzumab (HER2+ mAb) , Sacituzamab (Trop2+ mAb) and Ifinatamab (B7-H3+ mAb) to produce antibody drug conjugates (ADC) each of which display excellent *in vivo* efficacy in solid cancer xenograft models at well tolerated doses.

Cytotoxic effects of NMTi in cancer cell lines

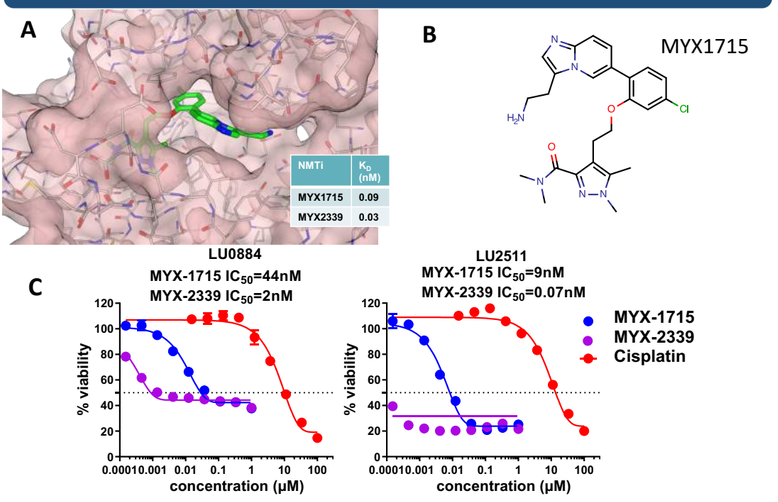


Figure 1: Structure (A) and dissociation constant (K_D) of NMTi (B) Structure of MYX1715. (C) IC_{50} of MYX1715 and MYX2339 in NSCLC PDXs

Antitumour efficacy of NMTi - ADCs

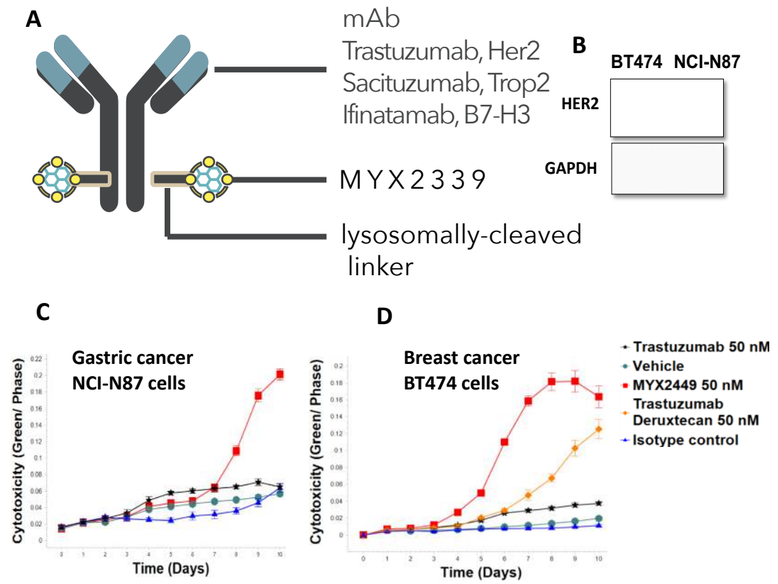
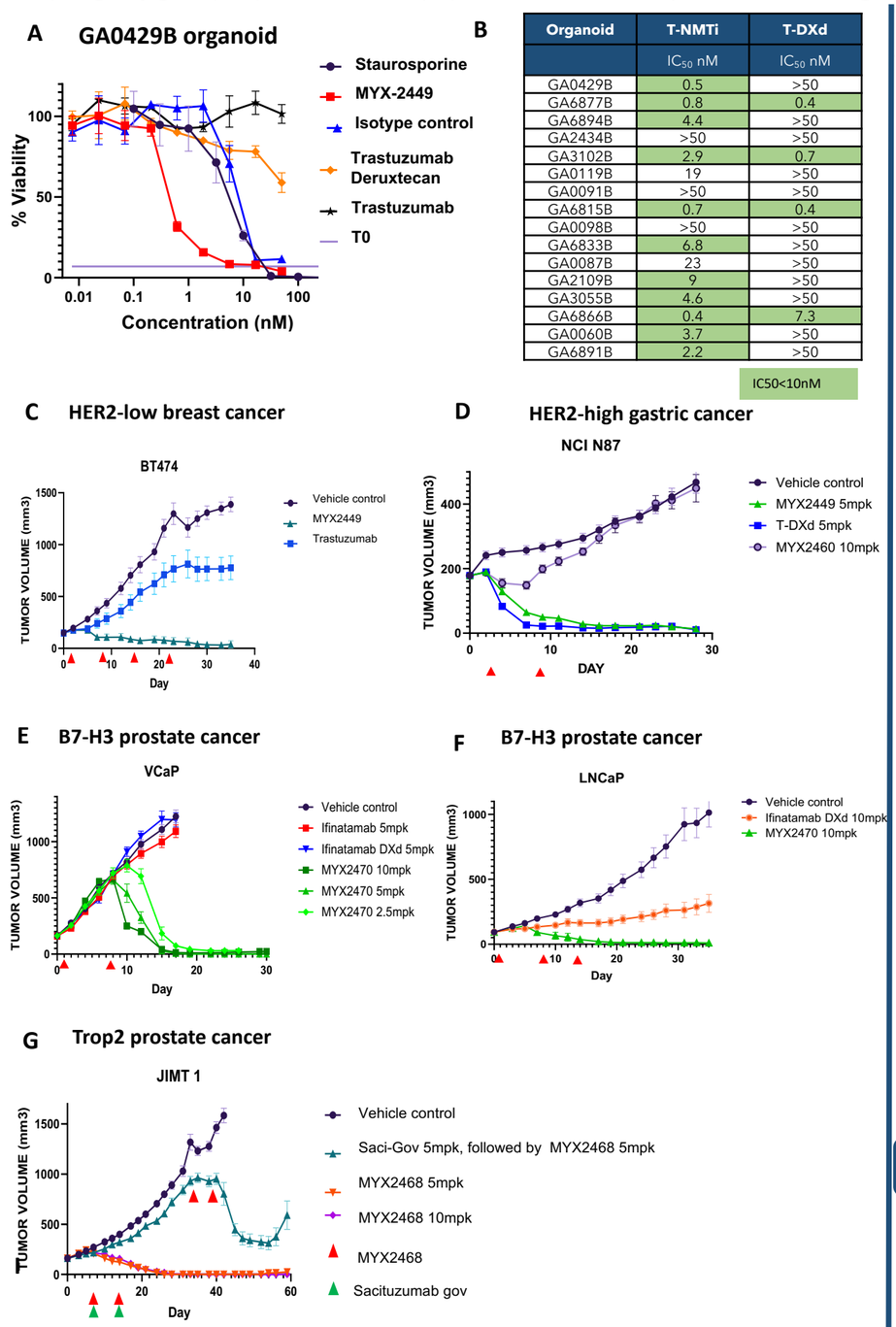


Figure 2: Cartoon of NMTi- ADCs, Her2-NMTi (MYX2449), Trop2-NMTi (MYX2468) and B7-H3-NMTi (MYX2470) (A). Expression of HER2 in breast (BT474) and gastric (NCI-N87) cancer cell lines (B). Anti tumor effects of MYX2449 in gastric (C) and breast cancer(D) cell lines

References
1. Wright MH, Heal WP, Mann DJ, Tate EW. Protein myristoylation in health and disease. J Chem Biol 2010 Mar;3(1):19-35.
2. Beauchamp E., Yap M.C., Iyer A. et al. Targeting N-myristoylation for therapy of B-cell lymphomas. Nat Commun 2020; 11(1): 5348



Organoid	T-NMTi	T-DXd
	IC_{50} nM	IC_{50} nM
GA0429B	0.5	>50
GA6877B	0.8	0.4
GA6894B	4.4	>50
GA2434B	>50	>50
GA3102B	2.9	0.7
GA0119B	19	>50
GA0091B	>50	>50
GA6815B	0.7	0.4
GA0098B	>50	>50
GA6833B	6.8	>50
GA0087B	23	>50
GA2109B	9	>50
GA3055B	4.6	>50
GA6866B	0.4	7.3
GA0060B	3.7	>50
GA6891B	2.2	>50

IC50<10nM

Figure 3: Antitumour effects of MYX2449 in gastric cancer (GC) PDX organoids (A,B). Antitumour effects of MYX2449 in HER2 breast cancer (C) and HER2 gastric cancer (D), MYX2470 in B7-H3 prostate cancers (E,F) and MYX2468 in Trop2 breast cancer (G) xenograft models.

MYX2449 exhibits good bystander effect in cell lines

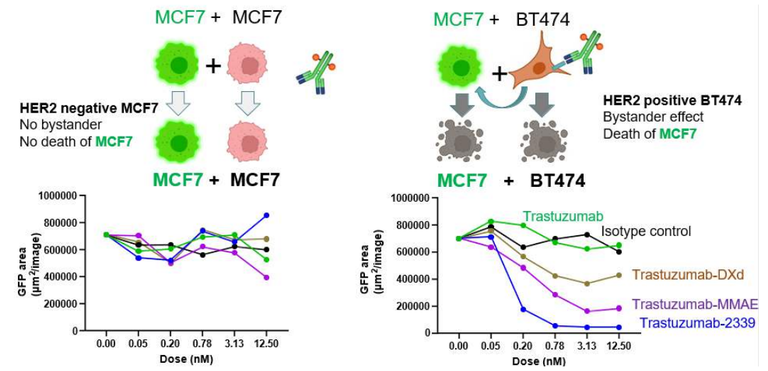


Figure 4: Bystander effect of MYX2449.

In vivo tolerability of MYX2449

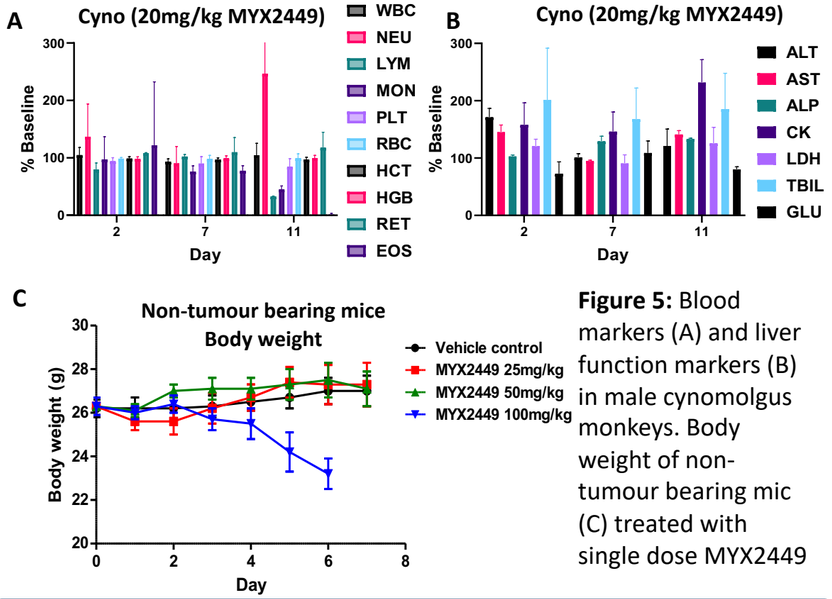


Figure 5: Blood markers (A) and liver function markers (B) in male cynomolgus monkeys. Body weight of non-tumour bearing mic (C) treated with single dose MYX2449

Conclusion

NMTi-ADCs MYX2449 (Her2), MYX2468 (Trop2) and MYX2470 (B7-H3) each demonstrate extensive tumor regression in a range of solid cancer models at well tolerated doses with superior or equal efficacy to comparator Topo1-ADCs. MYX2449 was shown to be well tolerated in mice (50mpk) and Cyno (20mpk). MYX2468 and MYX2470 are currently in Cyno repeat dose tox studies. NMTi has the potential to deliver a completely novel and highly differentiated class of ADC payload.

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