MYTX-011: A pH-dependent anti-cMET ADC with increased payload delivery in vivo and potent activity against cMET-expressing tumors of various epithelial origins

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BACKGROUND

- cMET is an oncogenic receptor tyrosine kinase overexpressed in multiple types of solid tumors, including non-small cell lung cancer (NSCLC), gastric cancer, head & neck squamous cell carcinoma (HNSCC), and others.
- Antibody-drug conjugates targeting cMET (anti-cMET-ADCs) have been developed to treat patients with cMET+ cancers but have shown clinical activity largely in a subset of NSCLC patients whose tumors express high cMET levels.[1]
- MYTX-011 is an investigational, pH-sensitive, vcMMAE-based ADC, designed to potentially benefit not only patients whose tumors express high levels of cMET, but also a broader set of patients with low to moderate levels of cMET.
  - MYTX-011 is engineered to rapidly dissociate from cMET at the acidic pH of the endolysomal compartment (pH5.4) while retaining high affinity at neutral pH[2]
- We previously demonstrated that MYTX-011 exhibits markedly superior efficacy in NSCLC xenografts with moderate cMET expression as compared to either the Parent ADC, or benchmark ADCs representing clinical-stage anti-cMET ADCs with vcMMAE and maytansinoid payloads.[2,3]
- Here we show by pharmacodynamic studies that MYTX-011 exerts enhanced efficacy by delivering increased levels of payload to cMET+ tumors compared to the Parent ADC.
- We further demonstrate that MYTX-011 is efficacious against cMET+ xenograft models derived from gastric (non-MET amplified), esophageal, and HNSCC cancer types.
- Together, these findings highlight the potential of MYTX-011 as a therapeutic candidate for treating a broader range of cMET-expressing malignancies.

METHODS

- cMET surface expression levels were quantified by flow cytometry using Quantibrite™ beads. mAb uptake was assessed by treating cells with pHrodo-conjugated Fab-mAb complexes and fluorescence intensity was measured after a 24 h-treatment.
- Cytotoxicity assays in 62 cancer cell lines were performed using CellTiter-Glo assay. IC_{50} values (50% maximal inhibitory concentration) were determined from 9-point dose response curves, following 96-hr incubation.
- MMAE levels in xenograft tumors were measured by an LC/MS assay. Phospho-Histone H3 (pHH3) quantitation in NCI-H1975 xenografts was conducted using an IHC research assay.
- For cell line derived xenograft (CDX) studies, cancer cells were implanted in the flanks of nude (SNU-16 and NUGC-4), SCID (NCI-H1975), NOD/SCID (KYSE-150, FaDu) or NCG (Detroit 562) mice. Animals were randomized into treatment groups (n=8/group) once tumors volumes reached 100-150 mm^3. ADCs were administered intravenously as a single or repeat dose as indicated in the legends.
- cMET expression in tumors was assessed by immunohistochemistry (IHC) (SP44/Ventana IVD kit). cMET positivity was qualitatively assessed as low, moderate or high based on intensity of staining (1+, 2+ or 3+, respectively). Of note, while the IHC assay used for this preclinical work is similar to the assay currently in use clinically (NCT05652868), the thresholds and their descriptors are different.

MYTX-011 shows superior uptake and cytotoxicity over Parent ADC across a panel of cMET-expressing cell lines

- MYTX-011 drives increased internalization and cytotoxicity in tumor cells expressing a range of moderate cMET levels compared to a matched Parent non-pH sensitive ADC.

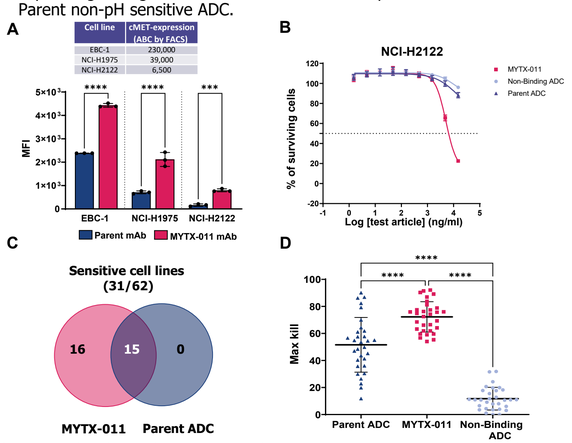

Figure 1: (A) Differential accumulation of MYTX-011 mAb over Parent mAb in cell lines expressing various levels cMET. (B) Representative cell cytotoxicity assay in NCI-H2122 cell line with MYTX-011 and Parent ADC (C) ADC cytotoxicity in 62 cancer cell lines. (D) Max cell kill of ADCs in MYTX-011 sensitive lines. One-way ANOVA: ***<0.001; ****<0.0001.

MYTX-011 shows increased *in vivo* tumor delivery of MMAE as compared to the Parent ADC

- MYTX-011 demonstrated markedly improved efficacy compared to Parent ADC in moderate cMET-expressing NCI-H1975 xenografts.
- Pharmacodynamic studies in NCI-H1975 xenografts showed that MYTX-011 treatment resulted in increased levels of MMAE and pHH3 (IHC marker of M phase arrest) in tumors as compared to Parent ADC.

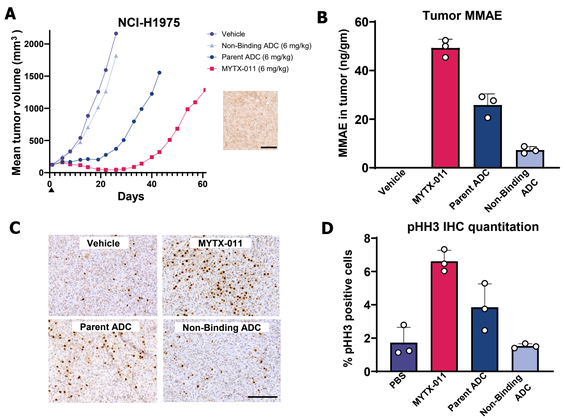

Figure 2: (A) Efficacy of single dose MYTX-011 and Parent ADC in NCI-H1975 xenografts. Inset shows cMET levels (IHC). Scale Bar = 200 µm. (B) MMAE levels in NCI-H1975 tumors (48hr) after with single dose of 3 mg/kg ADCs (C) IHC detection of pHH3 (brown staining) in NCI-H1975 xenografts. (D) Quantitation of pHH3 positive cells (48hr).

MYTX-011 is active across a range of NSCLC xenografts with various levels of cMET expression, histotypes, and mutation profiles

CDX/PDX Model and histotypes		*EGFR* status	*MET* status	Xenograft cMET IHC grading	cMET expression	Response to MYTX-011
EBC-1	SqCC	WT	*MET* amplified	3+	High	CR at 0.5 mg/kg
NCI-H1373	*KRAS* mutant, LuAd	WT	WT	2+	Moderate	PR at 2 mg/kg
NCI-H1975	LuAd	L858R/T790M mutant	WT	2+	Moderate	PR at 6 mg/kg
NCI-H2122	*KRAS* mutant, LuAd	WT	WT	1+	Low	SD at 6 mg/kg
CTG-3414	LuAd	T790M, E746_A750del	*MET* amplified	5% tumor cells as 3+, rest is 0	High	SD at 6 mg/kg
CTG-1353	SqCC	WT	WT	2+	Moderate	SD at 6 mg/kg
CTG-2669	LuAd	WT	T301A, D1028N	2+	Moderate	CR at 6 mg/kg
CTG-2533	LuAd	WT	WT	2+	Moderate	SD at 6 mg/kg
CTG-2082	SqCC	WT	WT	0	Negative	NR at 6 mg/kg

WT: Wild type; SqCC: Lung Squamous Cell Carcinoma; LuAd: Lung adenocarcinoma; CR: Complete Response; PR: Partial response; SD: Stable disease; NR: No response. Responses were after single dose treatment. All models were insensitive to non-targeting control.

Table 1: Gene mutation status, histology, cMET expression and MYTX-011 activity in CDX/Patient derived xenograft (PDX) models. [2,3]

MYTX-011 is active in cMET-expressing gastric, esophageal and HNSCC cancer cell lines *in vitro*

- Activity of MYTX-011 beyond NSCLC was explored *in vitro* by measuring MYTX-011 activity in cancer cell lines.

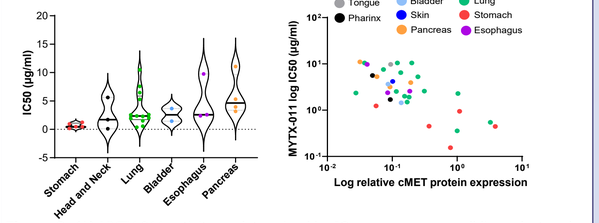

Figure 3: (A) MYTX-011 activity as determined by IC_{50} across cancer cell lines clustered according to their tissue of origin (B) MYTX-011 cytotoxicity and relative cMET protein expression (FACS).

MYTX-011 is active in moderate cMET-expressing, Detroit 562 HNSCC xenograft

- MYTX-011 was highly active in moderate (2+) cMET-expressing Detroit 562 HNSCC xenografts, whereas it showed limited activity in low (1+) cMET-expressing HNSCC FaDu xenografts.

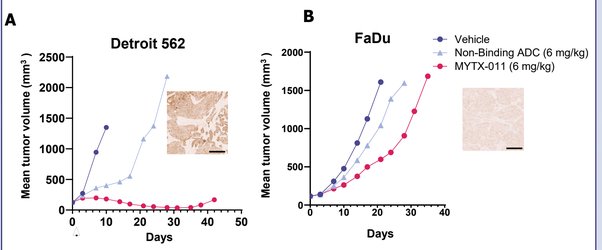

Figure 4: (A) Efficacy of single dose MYTX-011 in Detroit 562 xenografts. (B) Efficacy of repeat dose (Q2Wx2) MYTX-011 in low cMET-expressing FaDu xenografts. Insets show cMET expression in representative tumors by IHC. Scale Bar = 200 µm.

MYTX-011 is active in moderate cMET-expressing, esophageal cancer CDX model KYSE-150

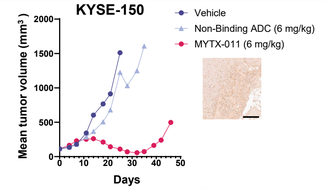

Figure 5: Efficacy of repeat dose (Q2Wx2) MYTX-011 in KYSE-150 xenograft. Inset shows cMET expression by IHC in representative tumor. Scale Bar = 200 µm.

MYTX-011 is active in cMET-expressing gastric cancer CDX models

- MYTX-011 is active in moderate cMET-expressing SNU-16 and high cMET-expressing NUGC-4 xenografts.

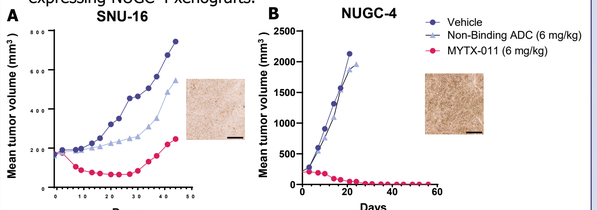

Figure 6: Efficacy of single dose MYTX-011 in (A) SNU-16 and (B) NUGC-4 gastric cancer xenografts. Insets show cMET expression by IHC in representative tumors. Scale Bar = 200 µm.

CONCLUSIONS

- The pH-engineered antibody component of MYTX-011 demonstrates markedly increased uptake in cancer cells expressing high, moderate or low cMET levels compared to its matched Parent antibody.
- MYTX-011 exhibits broader and more potent cMET-dependent cytotoxicity, compared to the Parent ADC, in cancer cell lines of various epithelial origins.
- MYTX-011 delivers increased levels of MMAE to moderate cMET-expressing NCI-H1975 xenografts as compared to the Parent ADC.
- MYTX-011 is active across a range of NSCLC PDX and CDX models with various levels of cMET expression levels, histotypes, and mutations.
- MYTX-011 is active in moderate cMET-expressing HNSCC and esophageal cancer xenografts. MYTX-011 shows activity in both high and moderate cMET-expressing gastric cancer xenografts.
- Together, these findings highlight the potential of MYTX-011 as a therapeutic candidate for treating a broad number of cMET-positive epithelial cancers.
- MYTX-011 is currently in Phase I multicenter dose escalation and dose expansion study (NCT05652868)[4]

REFERENCES

1. Camidge DR, Morgensztern D, Heist RS, et al. *Clin Cancer Res.* 2021;27(21):5781.
2. Gera N, Fitzgerald K, Ramesh V, et al. *Cancer Res.* 2023;83 (7_Supplement): 5000.
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4. Spira AI, Johnson ML, Blumenschein GR, et al. *JCO.* 2023;41 (16_supplement):TPS9147.

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