Discovery and preclinical development of a highly potent NaPi2b-targeted antibody-drug conjugate (ADC) with significant activity in patient-derived non-small cell lung cancer (NSCLC) xenograft models

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Summary

XMT-1536 is a novel, highly potent anti-NaPi2b ADC comprised of an average of 15 auristatin molecules conjugated to XMT-1535, a novel humanized anti-NaPi2b antibody, via the Dolaflexin ADC platform. The auristatin payload is enzymatically cleaved upon ADC trafficking to the endosome/lysosome compartment, releasing a cytotoxic auristatin derivative that is capable of bystander effect killing.

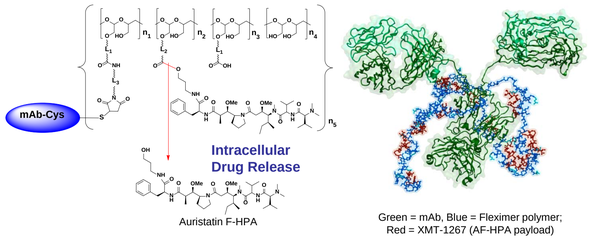
In cell binding assays, XMT-1535 antibody binds to non-mucinous ovarian cancer (OC) cells with low nanomolar affinity, which is unaffected by conjugation of the Dolaflexin drug conjugate. XMT-1536 is 1-2 logs more potent than a non-binding Dolaflexin ADC control, consistent with target-dependent cytotoxic effect.

In vivo XMT-1536 induced partial tumor regressions in the OVCAR3 OC model after a single dose of 3 mg/kg (0.21 mg/kg payload equivalent dose), and complete tumor regressions after a single dose of 5 mg/kg (0.36 mg/kg payload dose) or 3 weekly doses of 3 mg/kg. XMT-1536 was also tested in a patient-derived models of NSCLC, where it led to significant tumor growth delay and regressions.

XMT-1535 is cross-reactive with cynomolgous monkey NaPi2b, allowing an informative evaluation of whether XMT-1536 retains good tolerability in non-human primate. XMT-1536 was administered to cynomolgous monkeys in an exploratory single dose study up to 5 mg/kg ADC (4294 µg/m2 auristatin payload equivalents), with no observed target-mediated toxicity and limited adverse findings. Of note, there was no evidence of bone marrow toxicity, which has been observed generally for cleavable auristatin ADCs, and specifically for a recently published auristatin-based NaPi2b ADC (Lin et al., Clinical Cancer Research, 2015).

Based on these data XMT-1536 is advancing to early clinical development for the treatment of NaPi2b-expressing tumors.

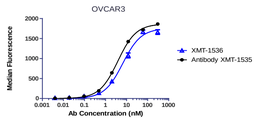
Dolaflexin ADC Structure and Drug Release



Green = mAb, Blue = Fleximer polymer;
Red = XMT-1267 (AF-HPA payload)

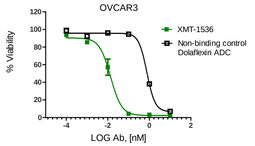
Dolaflexin ADC (XMT-1536) is highly active in vitro

Dolaflexin conjugation does not adversely affect ADC target binding



	Antibody XMT-1535	XMT-1536
Kd	3.8	6.6

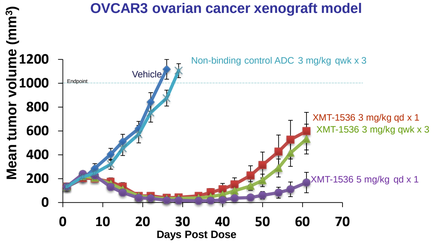
CellTiter-Glo® Luminescent Cell Viability Assay, 144 h



Tumor cells	Receptor number/cell (NaPi2b-PE)	XMT-1536	Non-binding control Dolaflexin ADC
OVCAR-3	32,000	0.01	1.13
IGROV1	35,000	0.38	37.3
HCC-4006	52,000	0.35	5.29

XMT-1536 Induces Tumor Regressions In Vivo and is Active in Patient Derived NSCLC Xenograft Models

OVCAR3 ovarian cancer xenograft model



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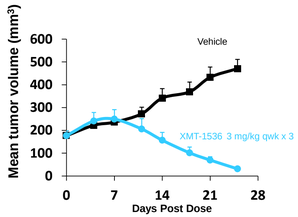

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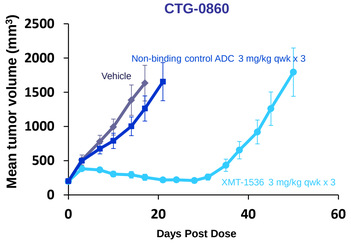

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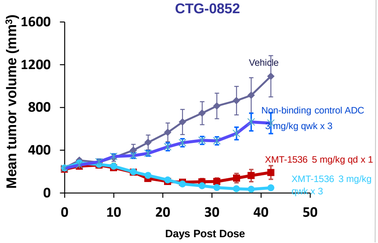
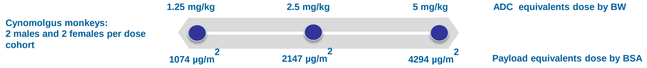


XMT-1536 is well-tolerated in non-human primates with good PK

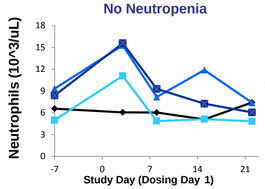
NHP study design



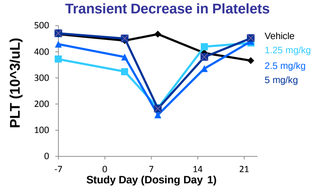
Single dose Day1, Terminal Necropsy Day 8, Recovery Necropsy Day 22

- **No test article-related clinical observations**
- **No test article-related body weight loss**

No Neutropenia



Transient Decrease in Platelets

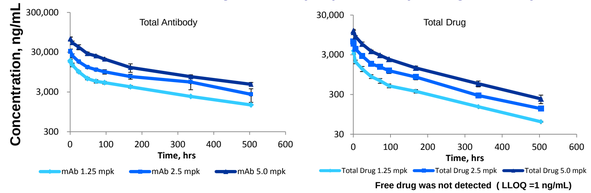


XMT-1536-related Pathology Findings Tend to be Minimal and Reversible

	Terminal Necropsy			Recovery Necropsy		
Organ	1.25 mg/kg	2.5 mg/kg	5 mg/kg	1.25 mg/kg	2.5 mg/kg	5 mg/kg
Bone Marrow	None	None	None	None	None	None
Liver*	None	None	Minimal hepatocyte apoptosis (1 female)	None	None	None
Testes	None	None	None	None	None	None
Lung	None	None	Minimal mixed inflammatory cell infiltrate (1 male)	None	None	Minimal mixed inflammatory cell infiltrate (1 male)
Urinary Bladder	None	None	Minimal mucosal apoptosis; occasional mitotic figures (1 male)	None	None	None
Stomach	Minimal mucosal neutrophil infiltrate (1 female)	None	Mild focal ulceration (1 male)	None	None	None
Cecum	None	Mild focal ulceration (1 female)	None	None	None	None

* Minimal Kupffer cell hypertrophy with occasional mitotic figures was seen in all XMT-1536 treated animals at terminal and recovery necropsies (non-adverse finding).

XMT-1536 demonstrates good stability in plasma in cynomolgus monkey



Free drug was not detected (LLOQ =1 ng/mL)

Plasma Exposure $AUC_{0\text{-}504}$, DN (µg*hrs/mL/mg/kg)		Plasma Half-life $T_{1/2}$, Dose Range Average (Days)		
Total Antibody	Total Drug	Total Antibody	Total Drug	Drug Release
1,407±99	157±13	8.8±0.7	5.2±0.2	11.6±0.9

Discussion and Conclusions

- XMT-1535 Dolaflexin conjugation (XMT-1536) does not adversely affect ADC target binding
- XMT-1536 is highly active in vitro
- XMT-1536 is highly active in vivo in OC xenograft model
- XMT-1536 is highly active in vivo in patient derived NSCLC xenograft models
- XMT-1535 is cross-reactive with cynomolgous monkey NaPi2b, allowing an informative evaluation of whether XMT-1536 retains good tolerability in non-human primates
- XMT-1536 demonstrates good stability of the drug conjugate in plasma and very low exposure to free drug
- XMT-1536 is well tolerated in cynomolgus monkeys when administered up to 5 mg/kg ADC (4294 µg/m^2 auristatin payload equivalents), with no observed target-mediated toxicity and limited adverse findings. There was no evidence of bone marrow toxicity.

Acknowledgements

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References

1. Lin K, Rubinfeld B, Zhang C, Firestein R, Harstad E, Roth L, Tsai SP, Schutten M, Xu K, Hristopoulos M, Polakis P. Preclinical Development of an Anti-NaPi2b (SLC34A2) Antibody-Drug Conjugate as a Therapeutic for Non-Small Cell Lung and Ovarian Cancers. Clin Cancer Res. 2015 21(22):5139-50.