Mersana THERAPEUTICS

Learnings from Translational and Clinical Development of Dolaflexin and Dolasynthen ADCs

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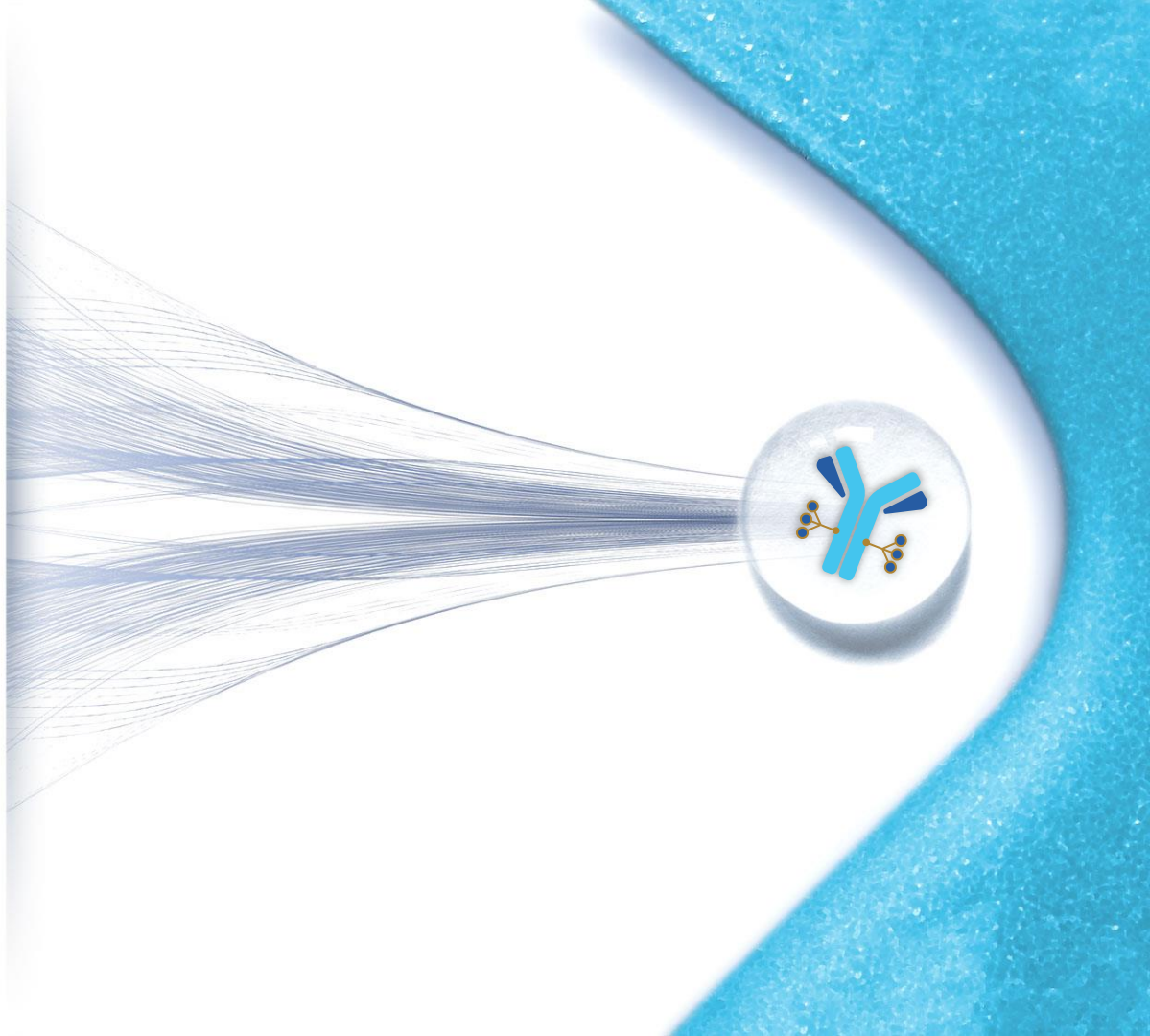
World ADC San Diego 2024



Similarities and Differences of XMT-1536 & XMT-1592

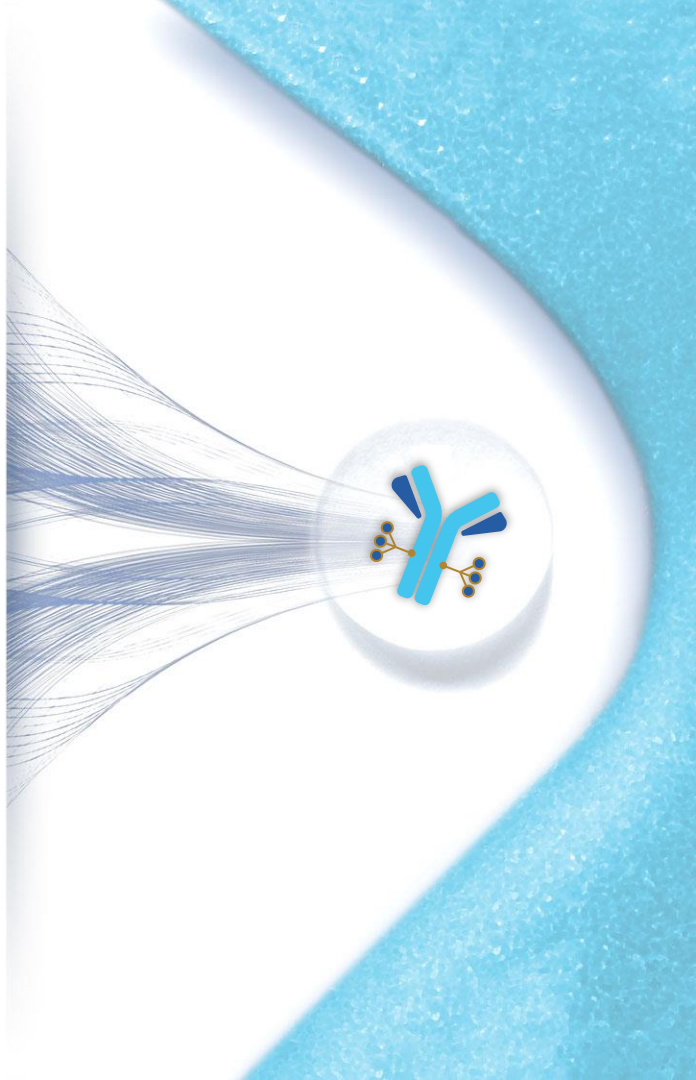
Dolaflexin (biodegradable polymer-based ADC platform)

Dolasynthen (Next-generation fully synthetic, homogeneous ADC platform)

	XMT-1536 (UpRi)	XMT-1592
Platform	Dolaflexin	Dolasynthen
mAb	Identical NaPi2b targeting mAb	
Payload	AF-HPA payload with controlled bystander effect; highly potent anti-tubulin inhibitor selectively toxic to rapidly dividing cells and designed to avoid dose-limiting neuropathy or neutropenia	
Bioconjugation Method	Stochastic (random)	Site-specific
Bioconjugation Chemistry	Maleimide conjugation to native cysteine	Glycoconnect™ Click chemistry
DAR	Heterogeneous DAR ~10	Homogeneous DAR 6

ADC, antibody-drug conjugate; AF-HPA, Auristatin F hydroxypropyl amide; DAR, drug-to-antibody ratio

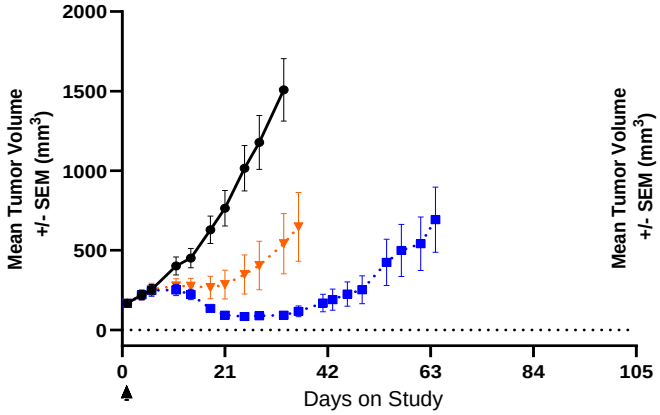
Non-Clinical Comparisons



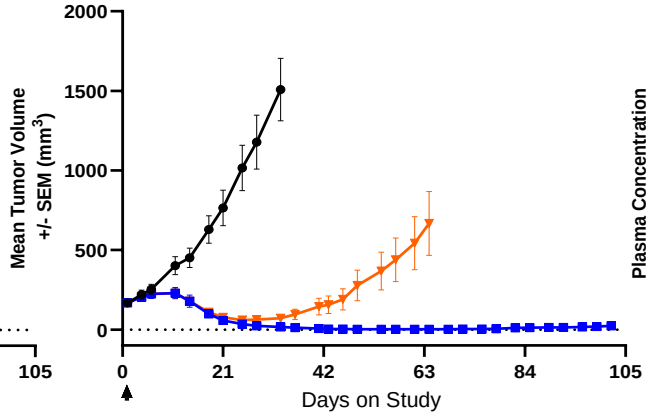
Head-to-Head Non-Clinical Efficacy and Mouse PK Reveals Potential Advantages for Dolasynthen vs. Dolaflexin

OVCAR-3 model

Matched payload dose, 0.05 mg/kg

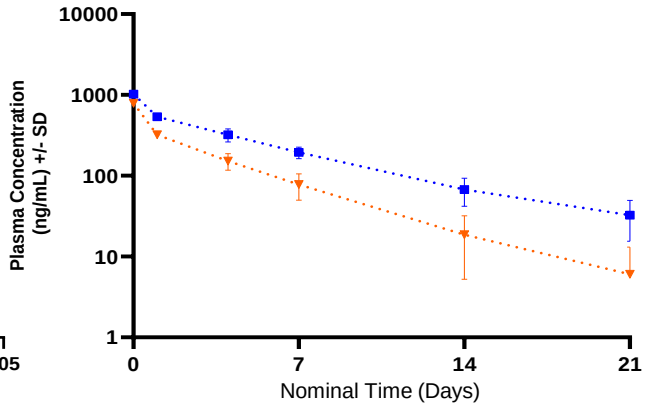


Matched payload dose, 0.1 mg/kg



Conjugated Drug in Plasma

0.05 mg/kg Payload Dose



- Vehicle
- 1.05 / 0.05 mg/kg
- 2.11 / 0.1 mg/kg — XMT-1536, Dolaflexin
- 1.37 / 0.05 mg/kg
- 2.73 / 0.1 mg/kg — XMT-1592, Dolasynthen

Doses shown as antibody / payload

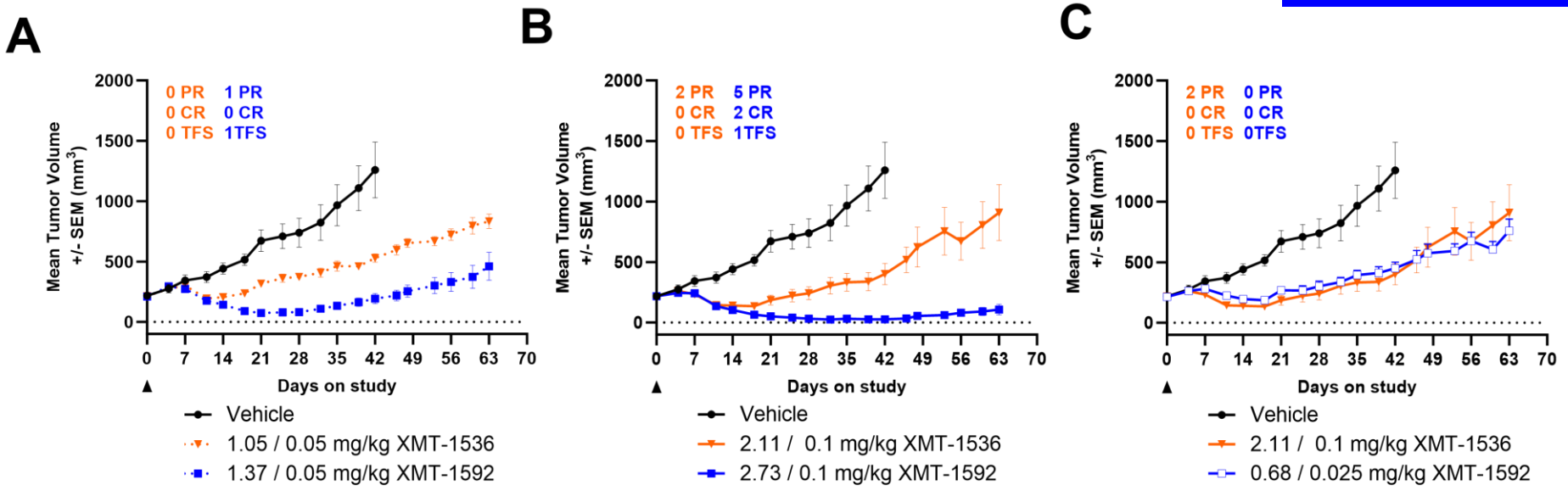
Clearance (mL/day/kg)	Half-life (Day)	AUC (Day*ng/mL)
12	5	4,150
27	3.1	1,880

Non-clinical Advantage of Dolasynthen Extends Across Models

CTG-0852 lung cancer PDX model

XMT-1536, Dolaflexin

XMT-1592, Dolasynthen



NSCLC PDX Mice (n=8/group) were given a single IV injection of XMT-1592 or XMT-1536 at **(A)** 0.05 mg/kg or **(B)** 0.1 mg/kg matched payload doses and tumor growth was monitored over time. **C.** A single IV injection of XMT-1592 at 0.025 mg/kg by payload results in comparable efficacy as 0.1 mg/kg XMT-1536 by payload, a 4-fold higher payload dose.

NSCLC: Non-Small Cell Lung Cancer. PDX: Patient-Derived Xenograft. PR: Partial responders, CR: complete responders, TFS: tumor-free survivors. Doses shown as antibody / payload.

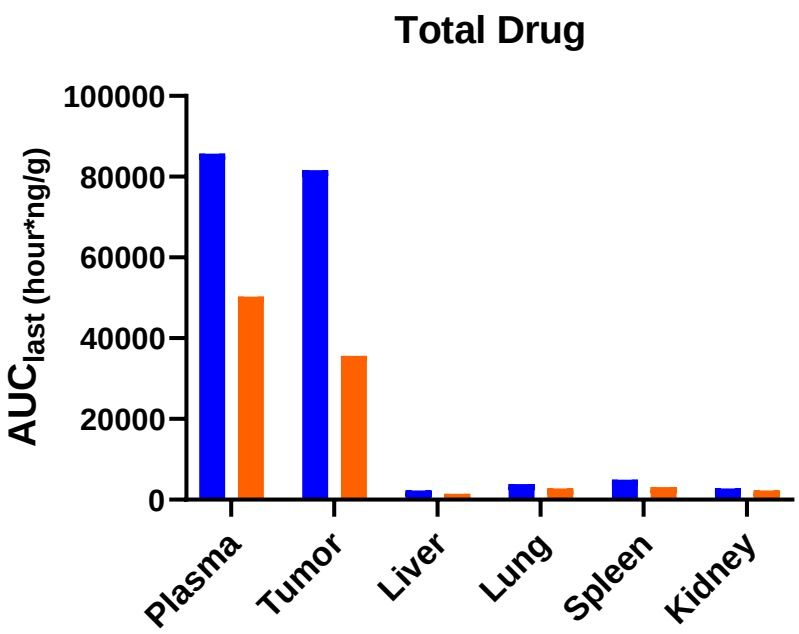
XMT-1592 (Dolasynthen) has Improved Biodistribution to Tumor

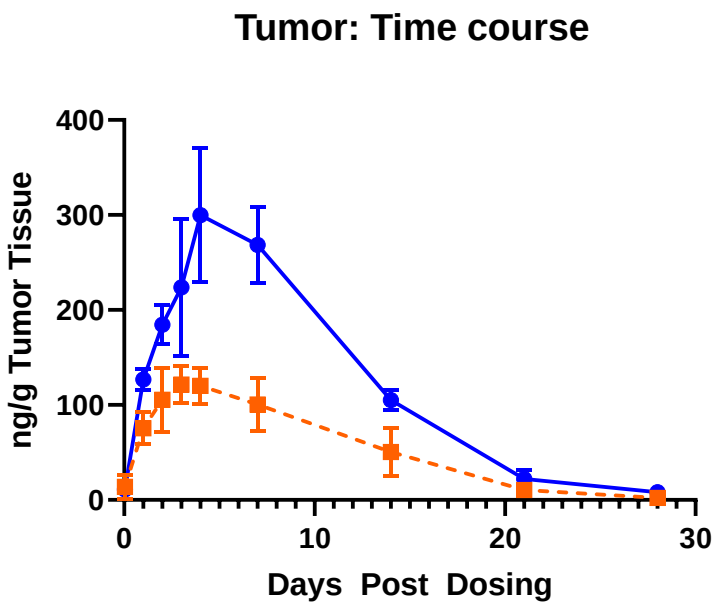
XMT-1536, Dolaflexin
XMT-1592, Dolasynthen

Equal Payload Dose, 0.05 mg/kg

Study Design

- OVCAR3 tumor-bearing mouse
- Single-dose administration at 0.05 mg/kg payload
- 4-week time course of tissue collection
- Mass spec analysis
- N=4 per timepoint per group

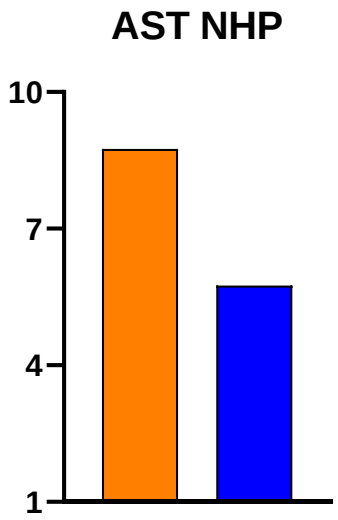


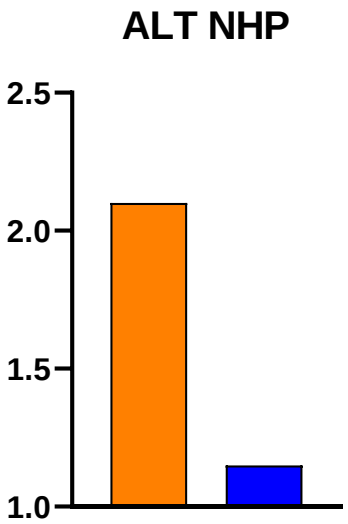


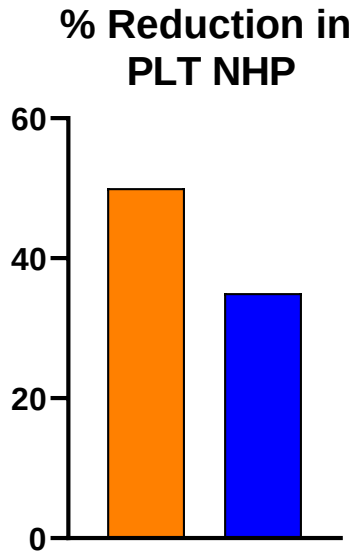
XMT-1592 (Dolasynthen) Demonstrated Improvements in Preclinical Safety Studies

XMT-1536, Dolaflexin
XMT-1592, Dolasynthen

Y-axis values are fold-change vs. baseline in same animal



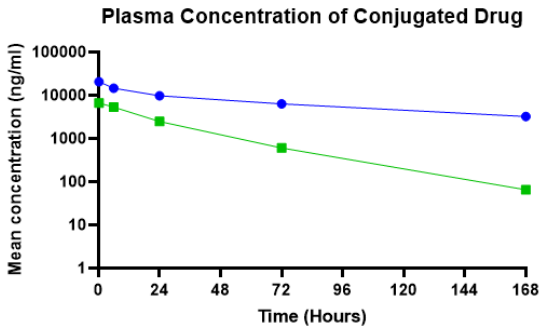




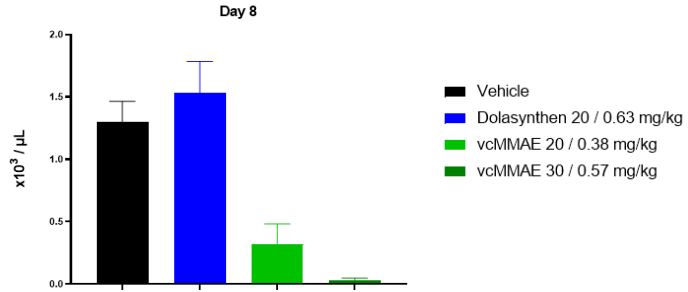
Day 8 at Equal Payload (NHP 0.06 mg/kg); AST: aspartate aminotransferase; ALT: alanine aminotransferase; PLT: Platelets

Dolasynthen Outperforms vcMMAE ADC Platform in Multiple Preclinical Models and Across mAbs

Increased Exposure Independent of Target

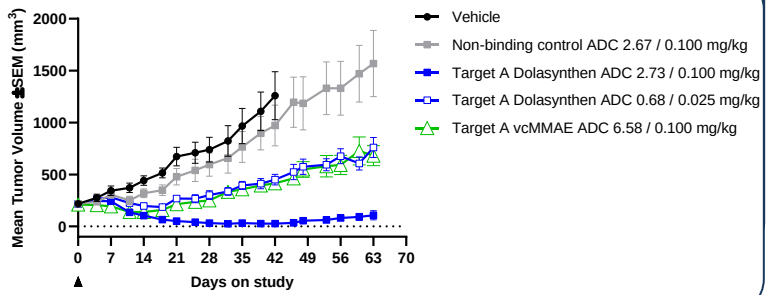


Unlike vcMMAE, No Impact on Neutrophils

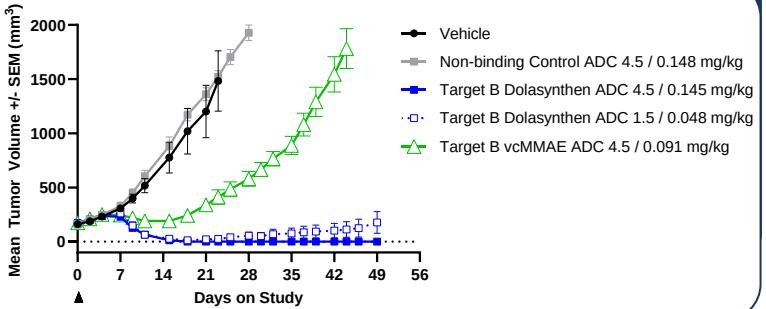


Dolasynthen ADC
vcMMAE ADC

Better Efficacy Against Target A

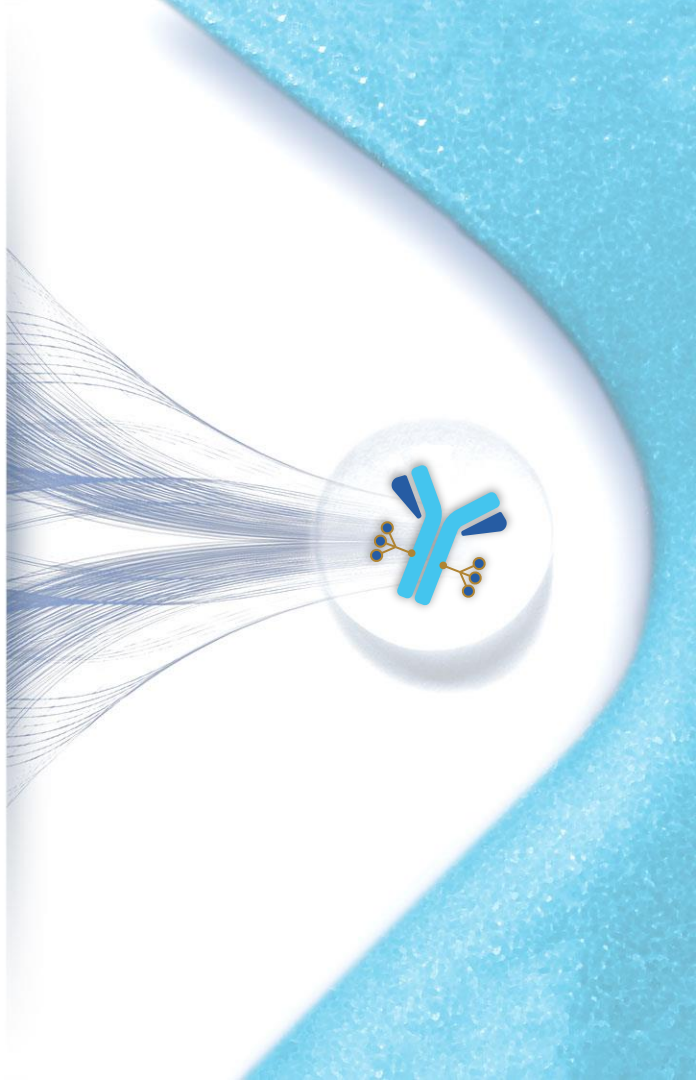


Better Efficacy Against Target B



▲ Time of single administration
Dosing above represented as antibody dose (mg/kg) / payload dose (mg/kg)

Clinical Comparisons



Dolaflexin (XMT-1536)

UPLIFT (ENGOT-ov67/GOG-3048): Clinical Study Design

Patient Population

- HGSOC[a] progressing after standard treatments; measurable disease per RECIST v1.1; ECOG PS 0 or 1; enrolling regardless of NaPi2b expression

Key Inclusion Criteria

- Platinum-resistant[b] ovarian cancer
- 1–4 prior lines of therapy
- Grade ≤2 peripheral neuropathy
- Available archived or fresh tissue for retrospective NaPi2b evaluation

Key Exclusion Criteria

- 1–2 prior lines AND bevacizumab-naive
- Primary platinum-refractory disease

UpRi 36 mg/m^2 up to max 80 mg; IV Q4W

(36 mg/m^2 ~ 1 mg/kg)

Primary Endpoint

- Confirmed INV-assessed ORR in NaPi2b-positive (TPS ≥75)

Secondary Endpoints

- Confirmed INV-assessed ORR in overall population
- Confirmed ORR by BICR in the NaPi2b positive and in the ITT population
- INV-assessed DOR in the NaPi2b positive population
- Safety

[a] HGSOC including fallopian tube and primary peritoneal cancer. [b] Platinum-resistant is defined as disease that has progressed within 6 months of last dose of platinum.

DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HGSOC, high-grade serous ovarian cancer; IV, intravenous; NaPi2b, sodium-dependent phosphate transport protein 2B; ORR, overall response rate; q4w, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; UpRi, upifitamab rilsodotin; TPS, Tumor Proportion Score

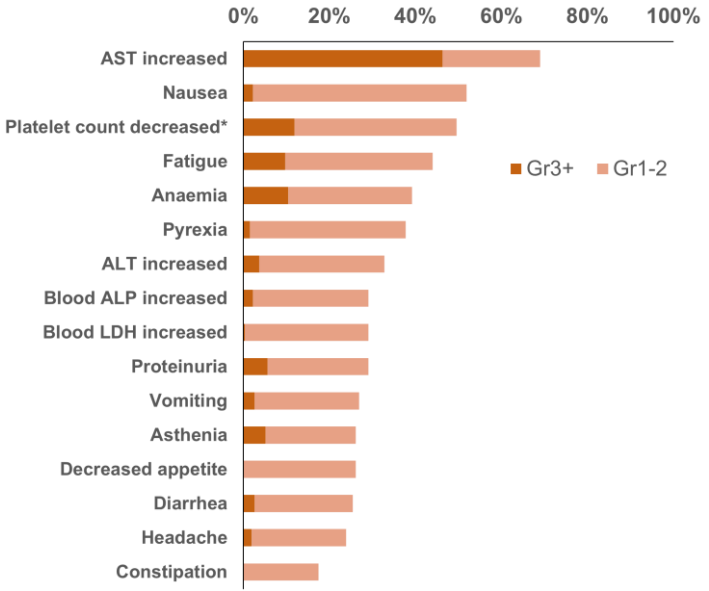
Dolaflexin (XMT-1536) Clinical Data Overview

	NaPi2b-Positive Population (TPS ≥75)	ITT Population
N	141	268
ORR[a], n (%);	22 (15.6%)	35 (13.1%)
Two-sided 95% CI	10.0%, 22.7%	9.3%, 17.7%
CR, n (%)	2 (1.4%)	3 (1.1%)
PR, n (%)	20 (14.2%)	32 (11.9%)
DCR[b]	93 (66.0%)	157 (58.6%)
Median DOR, Months	7.4	7.4
Two-sided 95% CI	4.2,NR	3.6, 10.4

Data cut: May 31, 2023

Safety & Tolerability

Treatment Related Adverse Events (TRAEs) observed in ≥15% of patients (N=268)



* Includes thrombocytopenia

[a]ORR is determined by investigator radiologic review and defined as the proportion of patients who achieve a confirmed CR or PR per RECIST v1.1.The exact two-sided 95% CI is calculated based on binomial distribution using the Clopper-Pearson method; [b]DCR is defined as the proportion of patients who achieve a confirmed CR, PR, or SD. NR, not reached.
ALT, alanine transaminase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; Gr, grade; LDH, lactate dehydrogenase; NaPi2b+, NaPi2b positive

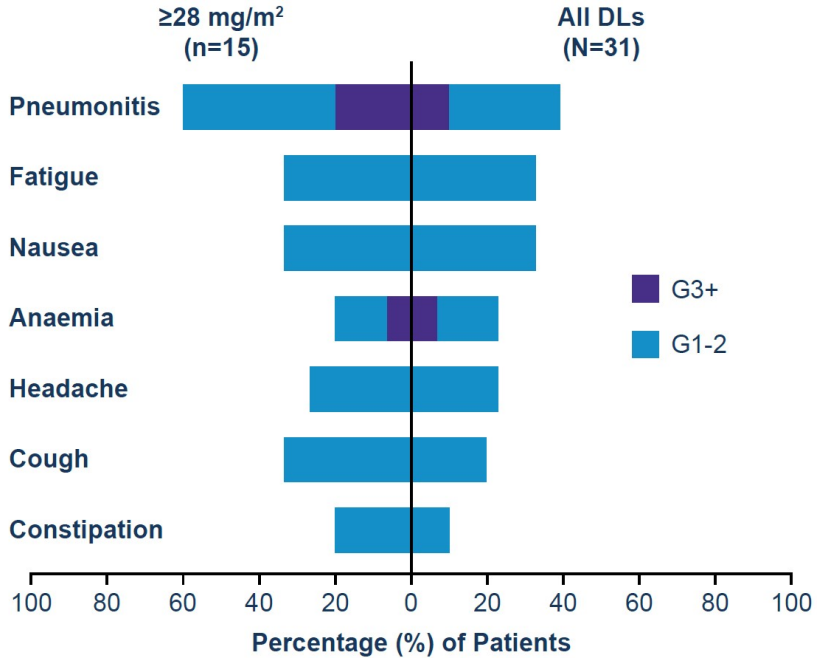
Dolasynthen XMT-1592 Dose Escalation Clinical Data Overview

	Ovarian Cancer ≥28 mg/m^2
Patients, N	13[e]
ORR, n (%)	4 (31%)
SD, n (%)	7 (54%)
DCR, n (%)	11 (85%)
Median DOR, months	7.9

Data cut: November 1, 2022

Safety & Tolerability

Safety TRAEs in ≥15% of patients dosed with XMT-1592.



e Evaluable patients; excludes one patient at 56 mg/m^2 who was non-evaluable by RECIST due to withdrawal of consent before first scan.
DCR, disease control rate; DOR, duration of response; ORR, objective response rate; SD, stable disease

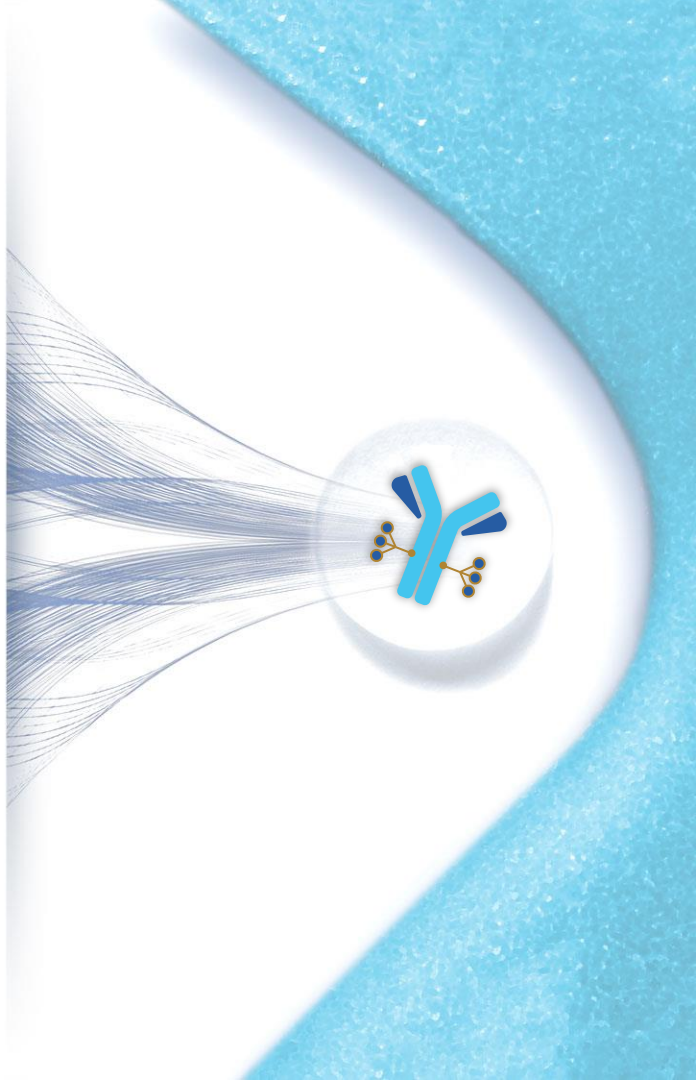
Clinical Comparisons - Dolaflexin (XMT-1536) vs Dolasynthen (XMT-1592)

Treatment-Related AEs		Dolaflexin XMT-1536 (n=268)[d] 36mg/m² N (%)		Dolasynthen XMT-1592 (n=31) All Dose Levels N (%)	
		All grades	≥Grade 3	All grades	≥Grade 3
Presumed off-target platform toxicities	AST Elevation N (%)	185 (69.0%)	124 (46.3%)	3 (9.7%)	0
	Platelet Count Decrease / Thrombocytopenia N (%)	133 (49.6%)	32 (11.9%)	0	0
	Nausea N (%)	139 (51.9%)	6 (2.2%)	10 (32.3%)	0
	Fatigue N (%)	118 (44.0%)	26 (9.7%)	10 (32.3%)	0
Presumed on-target toxicity	Pneumonitis N (%)	26 (9.7%)	2 (<1%)	12 (38.7%)	3 (9.7%)

XMT-1592 had reduced incidence of off-target/platform toxicities compared to XMT-1536; however, the incidence of pneumonitis, considered on-target due to NaPi2b expression on Type II pneumocytes, was increased with XMT-1592.

[d] Data cut: May 31, 2023 (UPLIFT: Phase 2 trial). Based on two independent studies; select AEs.

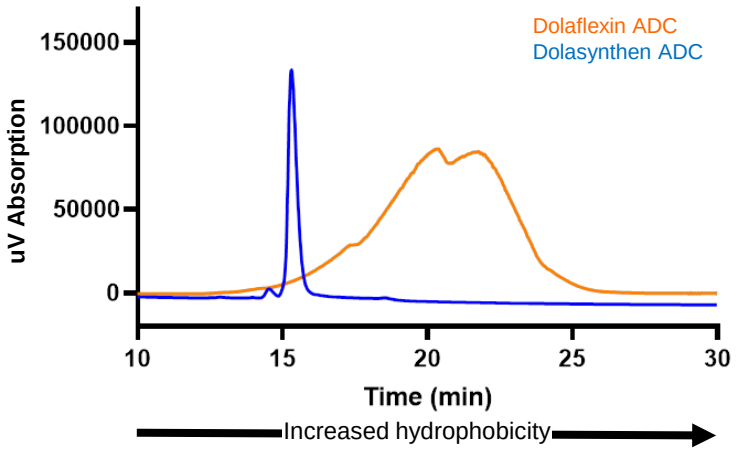
Learnings and Interpretations



The Heterogeneity of Dolaflexin Likely Impacts its Performance Relative to Dolasynthen

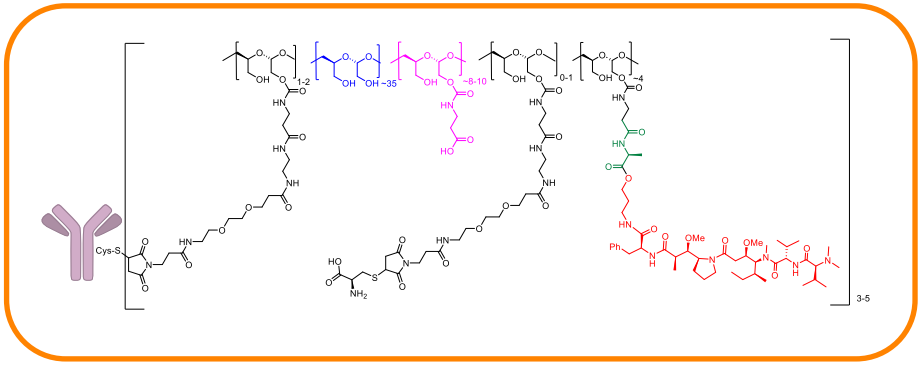
Heterogeneous Population vs. Homogeneous Outperformer

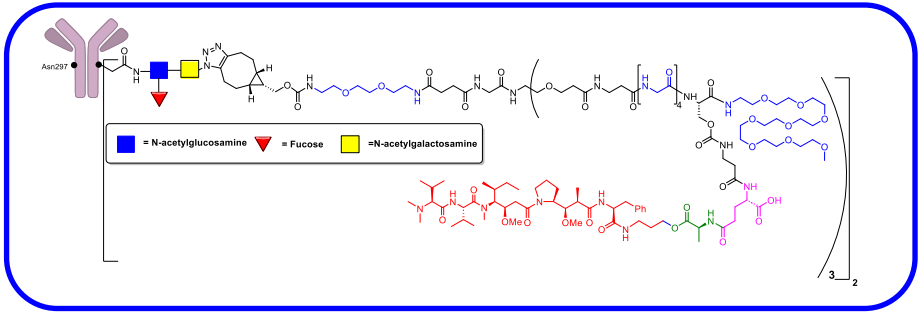
Population Distribution*



Dolasynthen platform enables the creation of single-species outperformers

* As measured by hydrophobic interaction chromatography, 280 nanometers

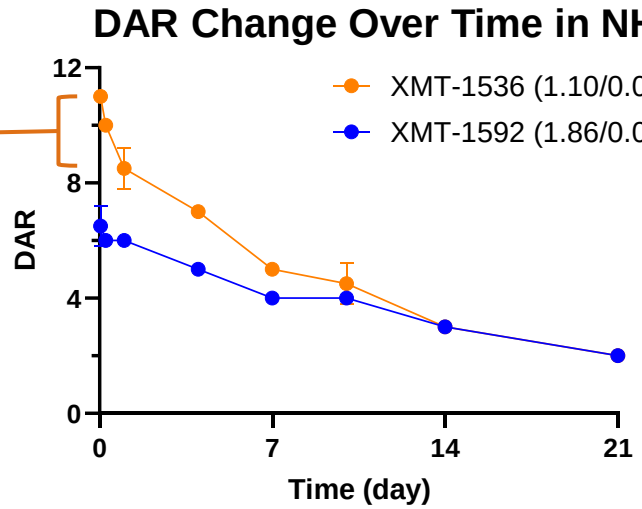


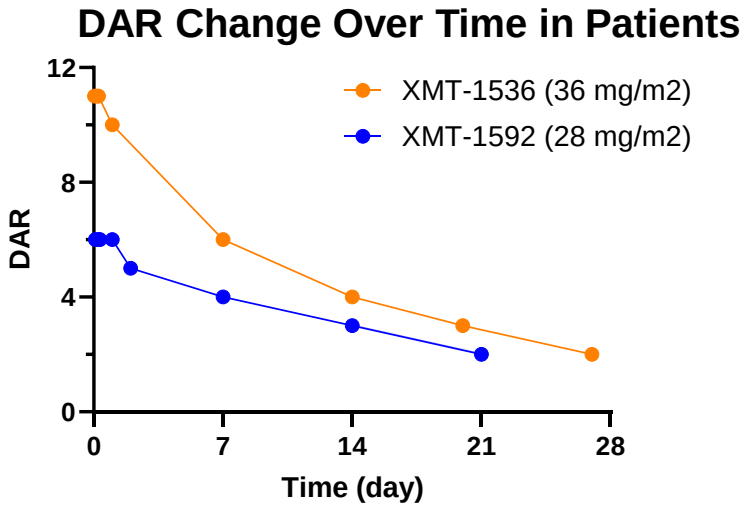


XMT-1592 (Dolasynthen) has a More Stable DAR Profile that Likely Contributes to Reduced Platform Toxicities

XMT-1536, Dolaflexin
XMT-1592, Dolasynthen

Sub-populations that may disproportionately contribute to toxicity over efficacy

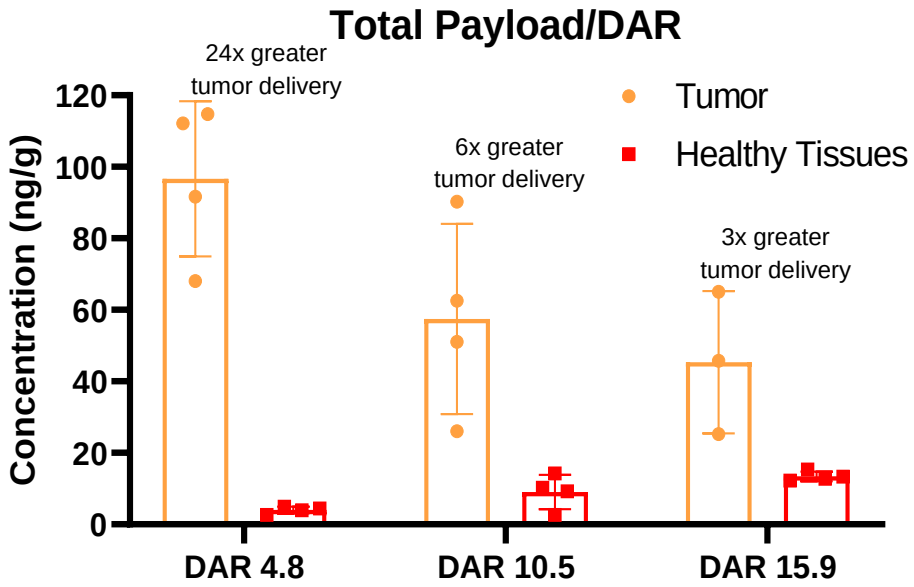




- **Rapid decrease of XMT-1536 average DAR is likely not due to payload deconjugation (free payload levels remain low; data not shown).**
- **It is hypothesized that the high DAR species within XMT-1536 are cleared more rapidly, leading to a reduction in DAR over time.**

DAR = [Concentration (Conjugated payload)/MW(payload)]/[Concentration (Total Ab)/MW(mAb)]

High-DAR Dolaflexin Sub-Populations are Less Effective at Delivering Payload to Target



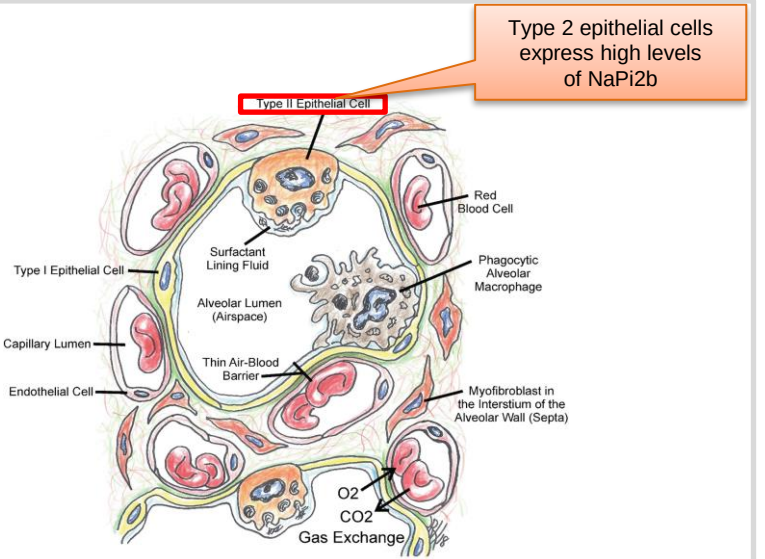
- JIMT-1 tumor-bearing mice were dosed with 3 mg/kg of HER2-targeting Dolaflexin ADC that had been fractionated into subpopulations of different DAR
- Tissues were sampled after 168hrs
- High DAR fractions demonstrated inferior tumor delivery which also correlated with reduced efficacy and increased toxicity characteristics compared to low DAR fractions

NaPi2b is Expressed at High Levels in Type II Pneumocytes

NaPi2b Highly Expressed in Normal Lung and Ovarian Cancer Tissues[1]

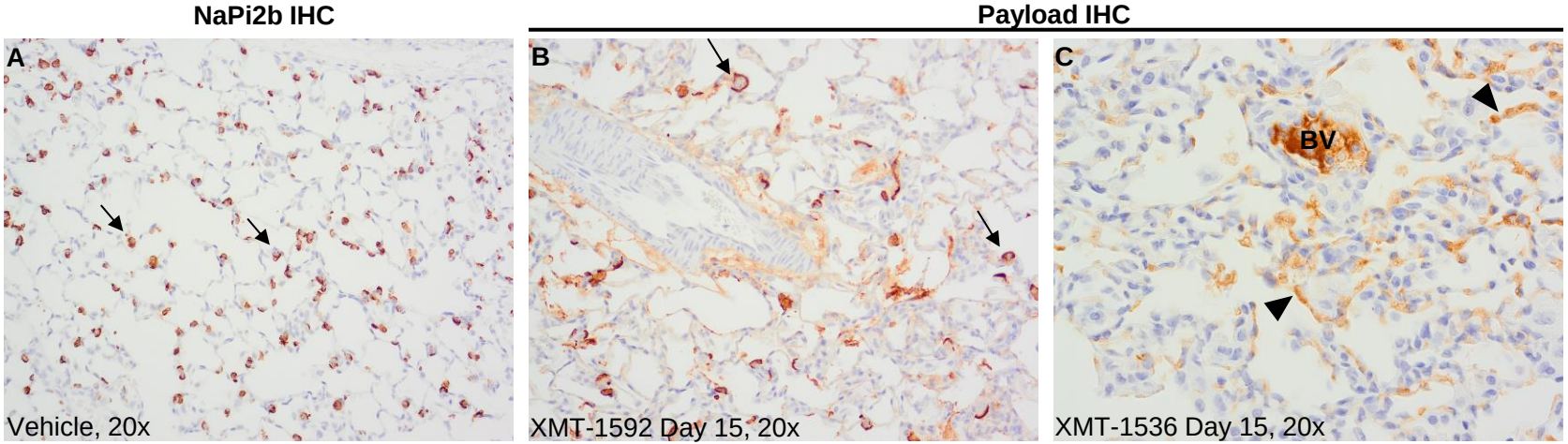
Type of Tissue	IHC Score[a]			
	0	1	2	3
Normal breast (n=4)	0	0	1	3
Breast cancer (n=10)	8	2	0	0
Normal lung (n=9)	0	0	1	8
Lung cancer (n=11)	5	5	0	1
Normal uterus (n=3)	0	0	1	2
Normal oviduct (n=2)	0	0	0	2
Normal ovary (n=5)	5	0	0	0
Ovarian cancer (n=10)	0	1	1	8

Table 1: Semi-Quantitative Scoring of IHC Staining for NaPi2b (MX35) in a Panel of Normal and Cancer Tissues



[a]IHC labeling intensity: 1+ = weak; 2+ = moderate; 3+ = strong.

The Dolasynthen Platform Increased Delivery of the Payload to Target-Expressing Cells Despite Lower Payload Dose



(A) NaPi2b has high expression in Type II pneumocytes (arrows), as illustrated by NaPi2b immunohistochemistry (IHC) in vehicle-treated rat lung

(B) Using an anti-payload antibody, staining of drug in the lungs of animals administered 9 / 0.29 mg/kg (mAb / payload dose) of XMT-1592 revealed a pattern of expression consistent with co-localization of drug in cells expressing the NaPi2b target (Type II pneumocytes, arrows)

(C) Payload IHC in the lungs of rats administered 9 / 0.52 mg/kg (mAb / payload dose) of XMT-1536 revealed less staining in Type II pneumocytes, consistent with less lung-specific pathology. For XMT-1536, payload was primarily within blood vessels (BV) including capillaries (arrowheads)

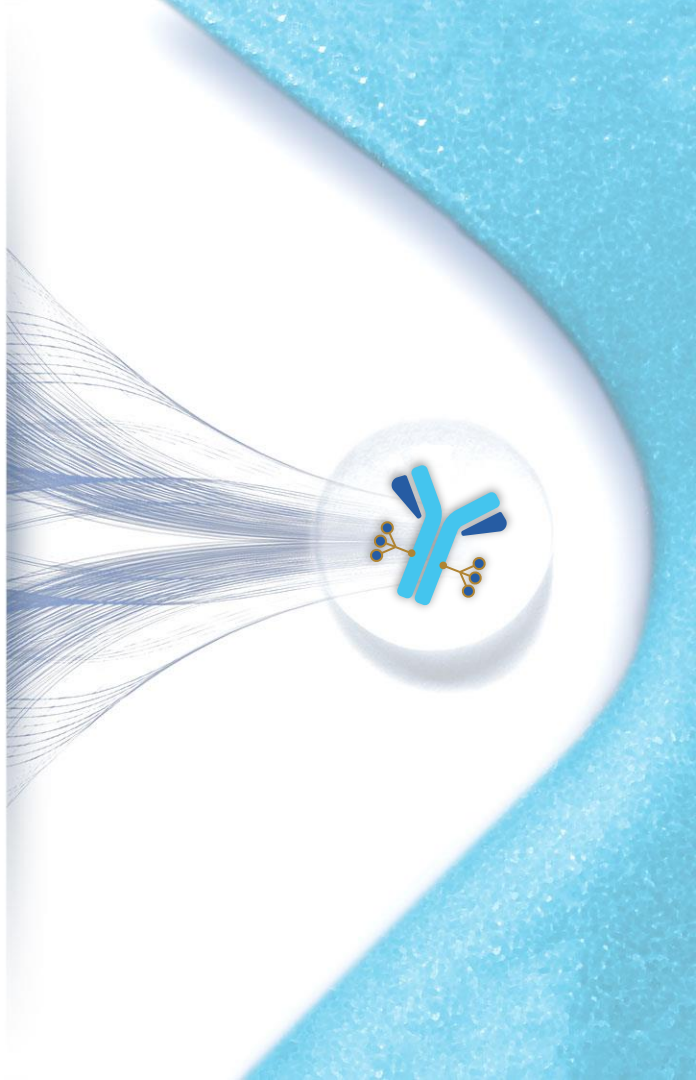
XMT-1660

Platform: Dolasynthen

Target: B7-H4

DAR: 6

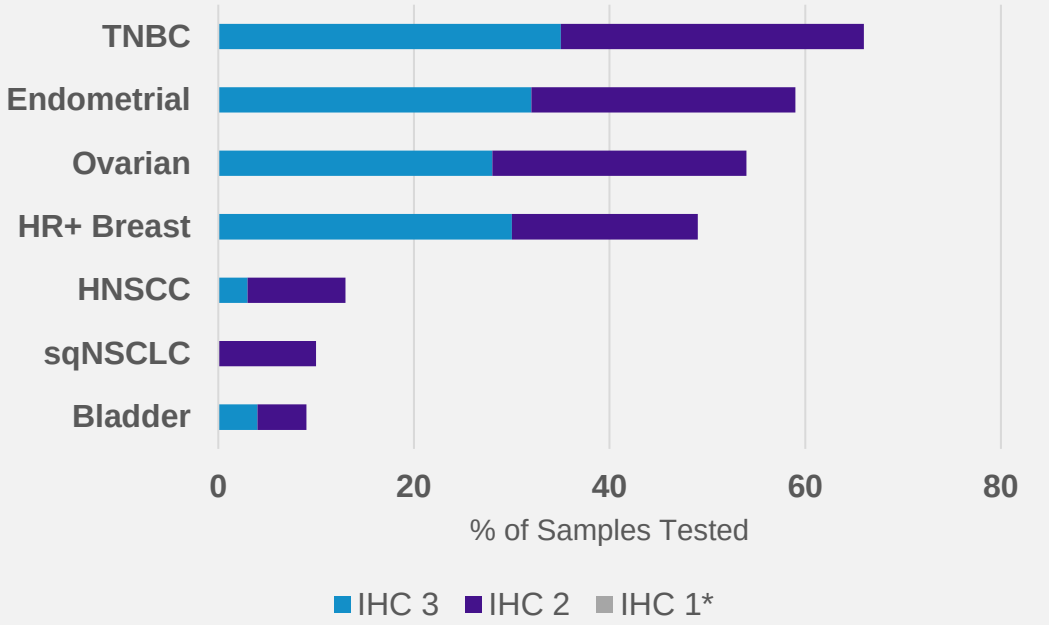
Initial Cancers of Interest Include: Triple negative breast, HR+ breast, endometrial and ovarian cancers



ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio; HR+, hormone-receptor-positive

B7-H4: Highly Expressed in a Range of Solid Tumors with Limited Expression in Healthy Tissue

Reported prevalence of B7-H4 expression across tumor types, measured by IHC[5]



*IHC 1 cut-off = H-score ≥50

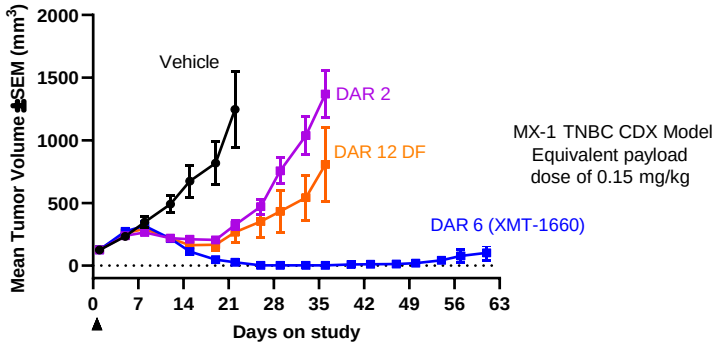
- B7-H4 is a member of the CD28/B7 family of cell surface proteins that promotes tumorigenesis by suppressing anti-tumor immunity and serves as a negative prognostic indicator for multiple tumor types[3]
- Limited expression in normal human tissue but highly expressed on multiple tumor types with high unmet need, including breast, ovarian and endometrial cancers[1,2,3,5]
- PD-L1 expression has been reported as inversely related to B7-H4 expression, suggesting potential utility in cold tumors[4]

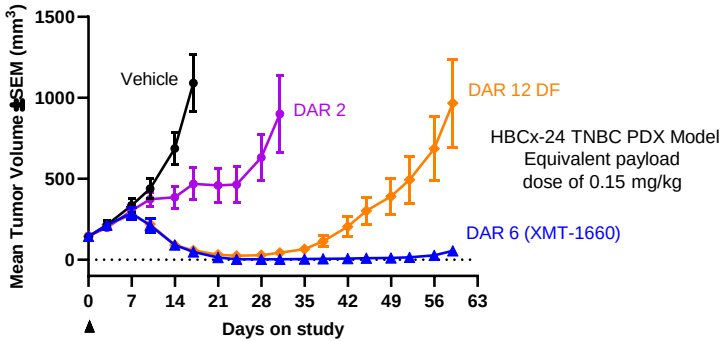
1. Rahbar et al. 2015. *Cancer Immunology Research*
2. Leong et al. 2015. *Molecular Pharmaceutics*
3. MacGregor et al. 2017. *Clinical Cancer Research*
4. Altan et al. 2018. *NPJ Breast Cancer*
5. Sachdev et al. *ASCO 2019*

HNSCC, head and neck squamous cell carcinoma; HR+, hormone receptor positive; IHC, immunohistochemistry; sqNSCLC, squamous non–small-cell lung cancer; TNBC, triple negative breast cancer

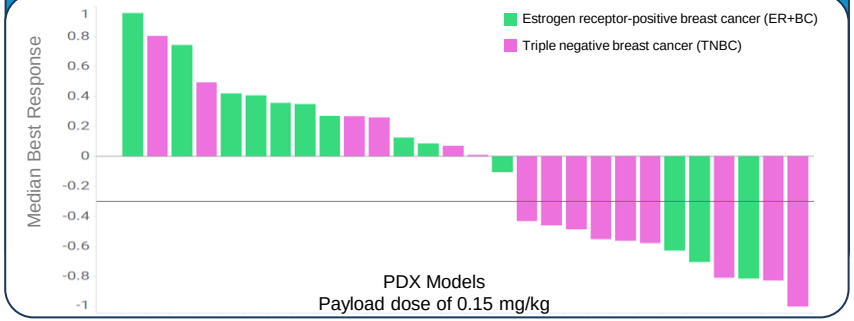
Encouraging XMT-1660 Preclinical Activity Observed

DAR 6 Outperforms Lower and Higher DARs[1,2]

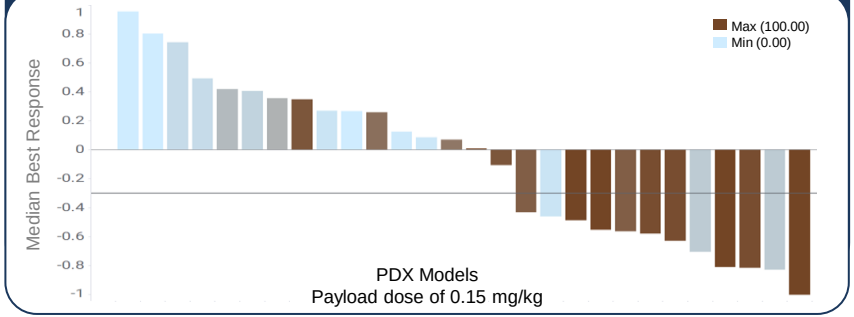




Activity in Both TNBC and ER+BC[2]



Activity Correlates with B7-H4 Expression[2, 3]



▲ Time of administration

1. Lines indicate approximately equivalent dose by payload; Non-binding control antibody-drug conjugates and unconjugated B7-H4 antibodies were all inactive; Certain data omitted for clarity
2. Toader et al. Molecular Cancer Therapeutics. 2023
3. Expression measured by tumor proportion score

CDX, cell line-derived xenograft; DAR, drug-to-antibody ratio; DF, Dolaflexin; mg/kg, milligrams per kilogram; mm, millimeters; PDX, patient-derived xenograft; SEM, standard error of mean; TNBC, triple-negative breast cancer

XMT-1660 Phase 1 Dose Escalation Design

Dose Escalation (DES)
Primary Endpoints
MTD, safety and tolerability
Secondary Endpoints
ORR, DOR, DCR, PK, ADA

Indications Being Enrolled Include:

Triple-Negative Breast Cancer

HR+/HER2- Breast Cancer

Endometrial Cancer

Ovarian Cancer

Backfill Cohorts
Primary Endpoint
Safety and tolerability
Secondary Endpoints
ORR, DOR, DCR, PK, ADA

- In parallel with DES, backfill cohorts are enrolling additional participants at multiple dose levels from DES
- Each backfill cohort is enrolling up to 12 patients and may focus on tumor types of particular interest
- Data from both DES and backfill cohorts will be utilized to determine the RP2D

B7-H4 expression being assessed retrospectively based on fresh or archived tissue to inform biomarker strategy; investigating dose levels and schedules in parallel escalation and backfill cohorts to optimize profile for expansion

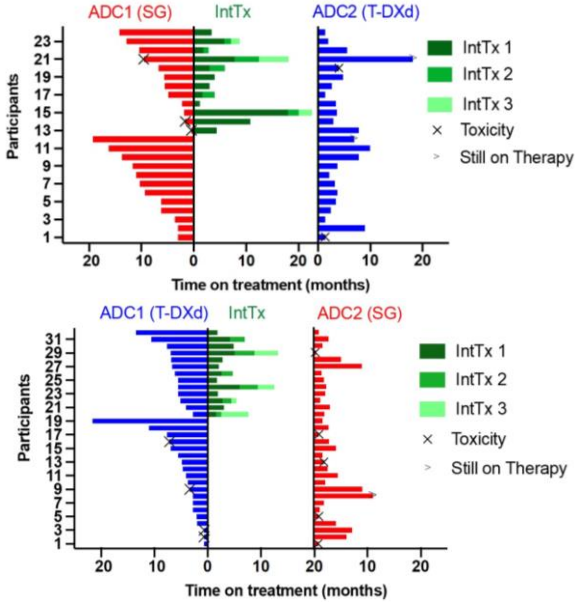
ADA, anti-drug antibody; DCR, disease control rate; DES, dose escalation; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR+, hormone-receptor-positive; MTD, maximum tolerated dose; ORR, objective response rate; PK, pharmacokinetics; RP2D, recommended Phase 2 dose

Emerging Understanding of ADC Resistance Highlights Need for New Payloads

Real World Data for Patients Receiving Two Topoisomerase ADC Treatment Lines

(HR+/HER2-Low)[1]

rwPFS



	ADC1 (SG)	ADC2 (T-DXd)
Median rwPFS from time of each ADC start, months	6.5	3.6

	ADC1 (T-DXd)	ADC2 (SG)
Median rwPFS from time of each ADC start, months	5.3	2.1

Real-world data suggest topoisomerase-1 payload resistance can greatly reduce clinical benefit

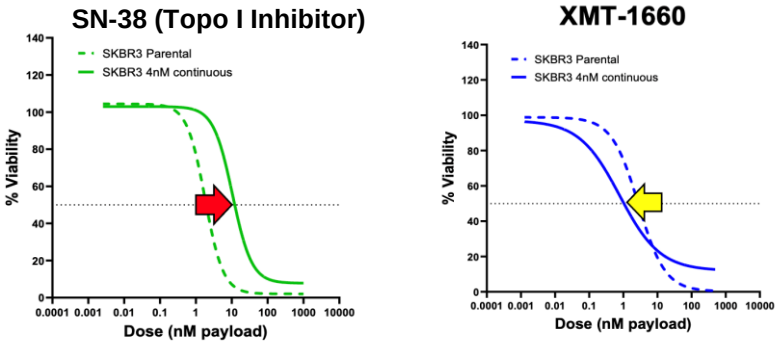
1. Huppert et al. ASCO 2024.

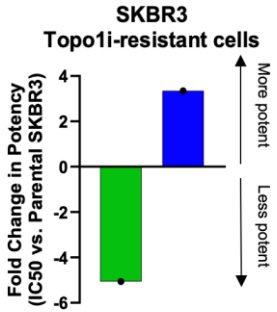
ADC, antibody-drug conjugate; ASCO, American Society of Clinical Oncology; HER2, human epidermal growth factor receptor 2; HR+, hormone-receptor-positive; IntTx, intervening chemotherapy; rwPFS, real-world progression-free survival; SG, sacituzumab govitecan (TRODELVY®); T-DXd, trastuzumab deruxtecan (ENHERTU®)

Prolonged In Vitro Exposure to Topo I Inhibitor Results in 5X Decrease in Sensitivity to SN38 but Increase in Sensitivity to AF-HPA / XMT-1660

Dashed line: Parental cell before prolonged SN38 Exposure

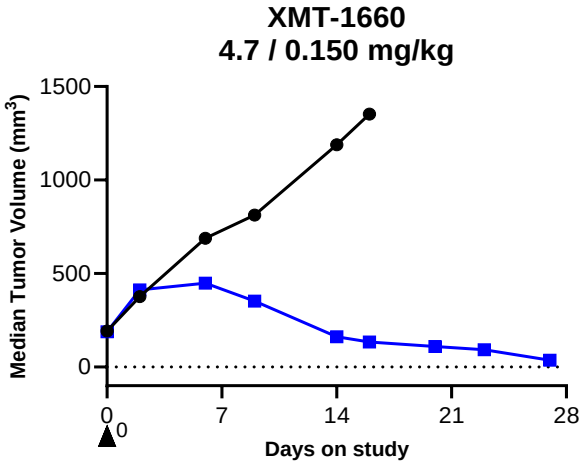
Solid Line: Topo I Emerging resistance line induced by prolonged SN38 exposure





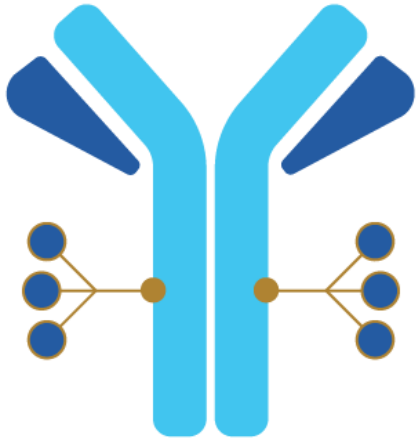
Similar Effects Seen in a Second Cell Line

In Vivo Efficacy of XMT-1660 Also Demonstrated In a Post-Topo I PDX Model



XMT-1660: A Differentiated B7-H4 ADC

- B7-H4 is a clinically validated target for a range of solid tumors
- *In vivo* data suggest robust activity with XMT-1660 in multiple cancers
- Dolasynthen platform provides XMT-1660 with the potential to overcome common dose-limiting ADC platform toxicities
- Fast Track Designation granted by the FDA in advanced/metastatic triple-negative breast cancer
- Phase 1 dose escalation and dose/schedule optimization continuing (NCT05377996)



Expected 2024 Milestones

Report initial Phase 1 dose escalation and backfill cohort data in second half of 2024

Initiate expansion in second half of 2024

ADC, antibody-drug conjugate; FDA, U.S. Food & Drug Administration

Advancing a Robust ADC Pipeline

Platform	ADC Program	Target	Indication(s)	Preclinical	P1 Dose Escalation	P1 Dose Expansion
Dolasynthen	**XMT-1660**	B7-H4	Multiple Solid Tumors			
Immunosynthen	**XMT-2056**	Novel HER2 Epitope	Multiple Solid Tumors			GSK*
	XMT-2068	Undisclosed	Undisclosed			
	XMT-2175	Undisclosed	Undisclosed			
	Collaborators					
Dolasynthen	J&J	Multiple	Undisclosed			
Immunosynthen	Merck KGaA Darmstadt, Germany	Multiple	Undisclosed			

* XMT-2056 is wholly owned by Mersana. GSK has an exclusive global license option to co-develop and commercialize the candidate

ADC, antibody-drug conjugate; HER2, human epidermal growth factor receptor 2

Mersana THERAPEUTICS

Thank You!