The DolaLock-based ADC Platforms: Dolaflexin & Dolasynthen

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World ADC Summit
October 2019

Outline

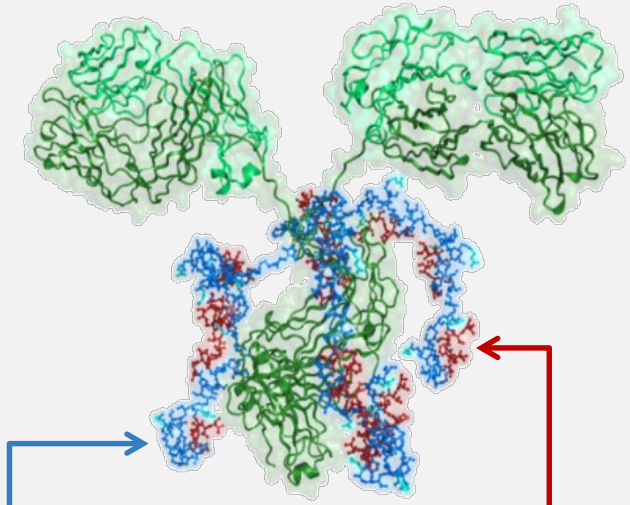
- Brief introduction to the Dolaflexin platform and the DolaLock payload
- Update on the clinical development of XMT-1536, a Dolaflexin ADC targeting NaPi2b
- Dolasynthen - a fully homogeneous ADC platform incorporating the DolaLock payload
- Immunosynthen – an immunostimulatory ADC platform

Dolaflexin and the DolaLock Payload

Mersana THERAPEUTICS

Novel Dolaflexin Platform Technology

Designed to Expand Therapeutic Index vs Other ADC Platforms

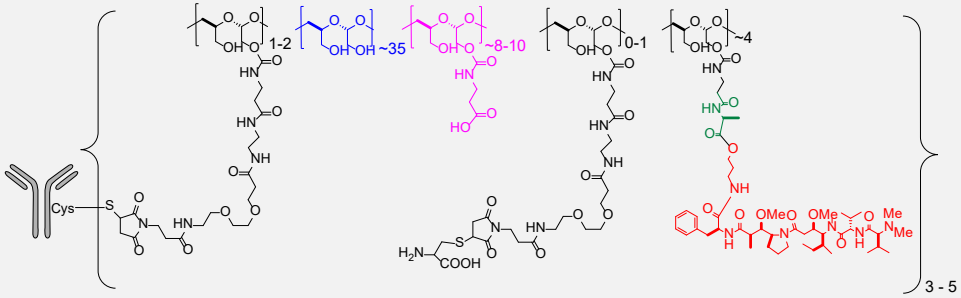


Fleximer® Polymer

- High DAR
- Optimal PK and drug-like properties
- Efficacy - against low antigen expressing tumors

DolaLock Payload

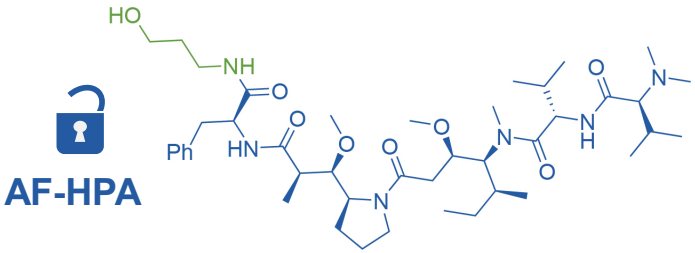
- Controlled bystander effect for **greater efficacy and tolerability**



A *biodegradable, biocompatible* scaffold providing *aqueous solubility*, *charge balance*, and a high *drug* to antibody ratio (ideally 10-12 per mAb) on average

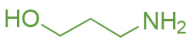
Proprietary Auristatin DolaLock Payload provides Unique Pharmacology – a Controlled Bystander Effect

Auristatin F-HPA (AF-HPA)

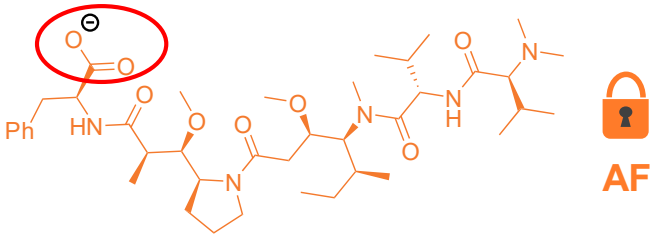


Bystander Killing
freely cell permeable

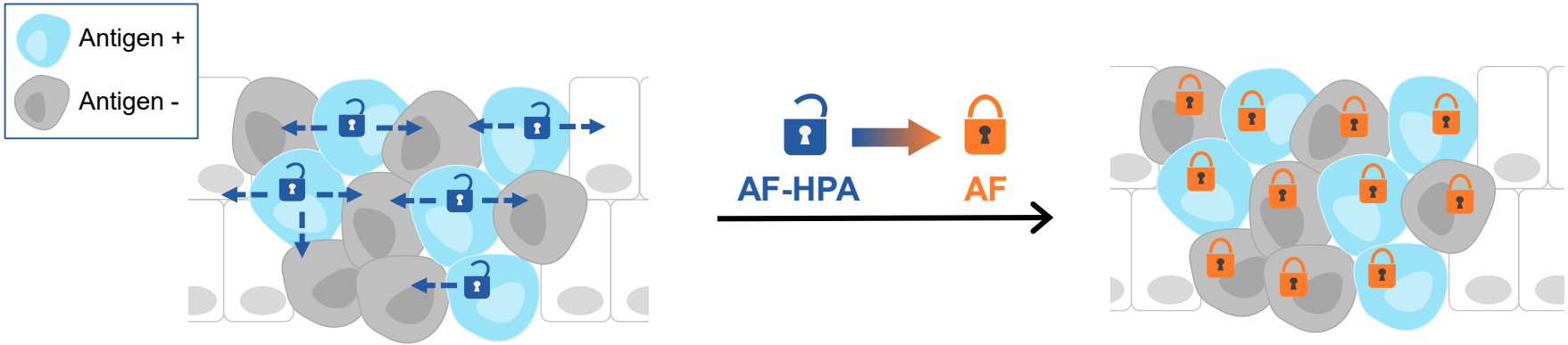
Metabolic Conversion in Tumor Cell



Auristatin F (AF)

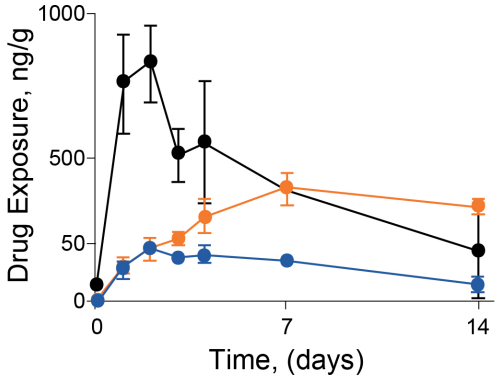


No Bystander Killing
Not cell permeable; *not a Pgp substrate*

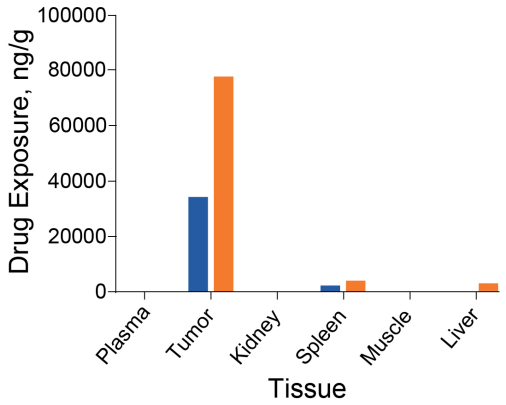


DolaLock Provides Prolonged Tumor Exposure and Improves Tolerability

Tumor Exposure
after single dose to tumor-bearing mice

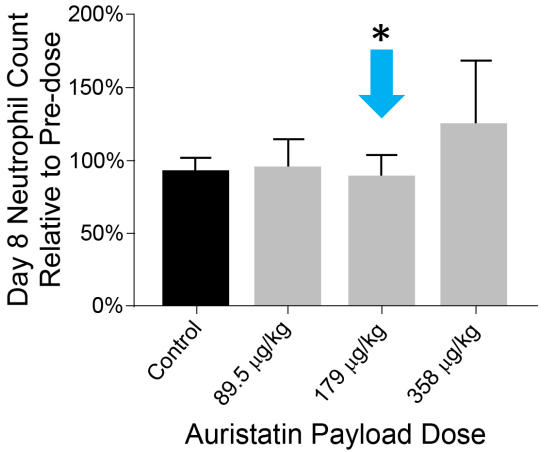


Tissue Exposure (AUC)
after single dose to tumor-bearing mice
Total exposure over 2 weeks



AF-HPA AF

Neutrophil Count
after single dose to non-human primates



*dose that causes fatal neutropenia with Lifastuzumab vedotin – see Lin et al. *Clinical Cancer Research 2015*

XMT-1536

A NaPi2b-targeted Dolaflexin ADC

Mersana THERAPEUTICS

NaPi2b: An Attractive ADC Target Ideally-Suited for Mersana's Innovative Platforms

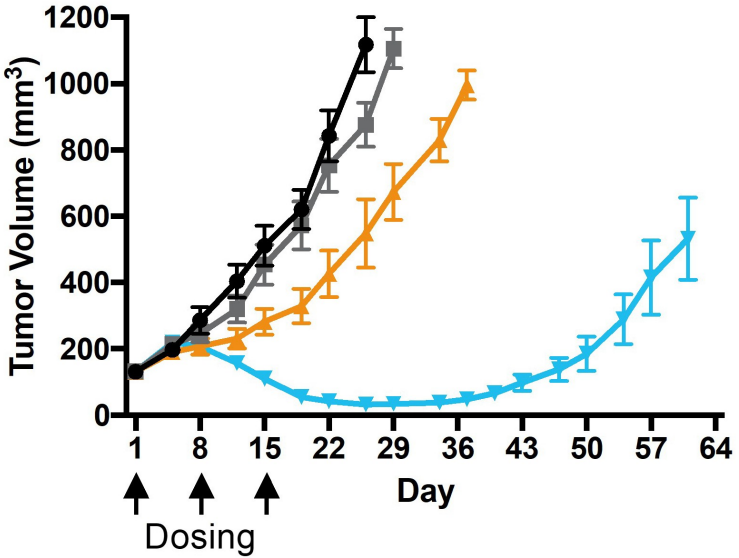
- Broadly expressed in ovarian cancer and NSCLC adenocarcinoma
  - No detectable expression in squamous NSCLC
  - Limited expression in healthy tissues on apical surface of polarized epithelium (inaccessible to bloodstream limiting potential for on-target toxicities)
- NaPi2b is a lineage marker (not an oncogene) that transports inorganic phosphate (Pi) into the cell
  - Not downregulated in response to treatment
  - High expression of NaPi2b is correlated with the presence of EGFR mutations in NSCLC adenocarcinoma
- Companion diagnostic can distinguish across low, medium, and high expression
  - Correlation between biomarker expression and response in preclinical and clinical settings

Mersana companion diagnostic discriminates across expression levels

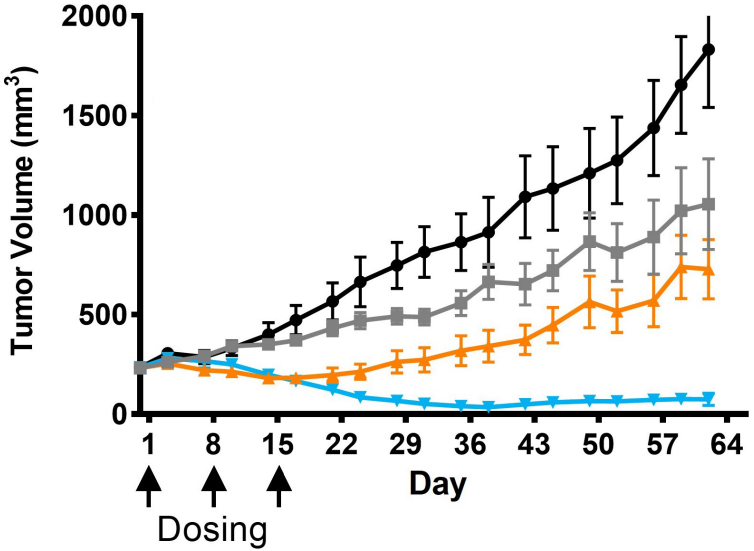
R. Mosher et al, AACR-NCI-EORTC International Conference, October 2017
D'Archangelo, et al. Abstract 194P ESMO 2014
ASCO 2019 Poster #3010; Phase 1 dose escalation study of XMT-1536, a novel NaPi2b-targeting antibody-drug conjugate (ADC), in patients (pts) with solid tumors likely to express NaPi2b; June 2019 , Data Cutoff May 10, 2019

XMT-1536 Data Show Improved Efficacy and Tolerability to vcMMAE ADC in Head to Head Preclinical Studies

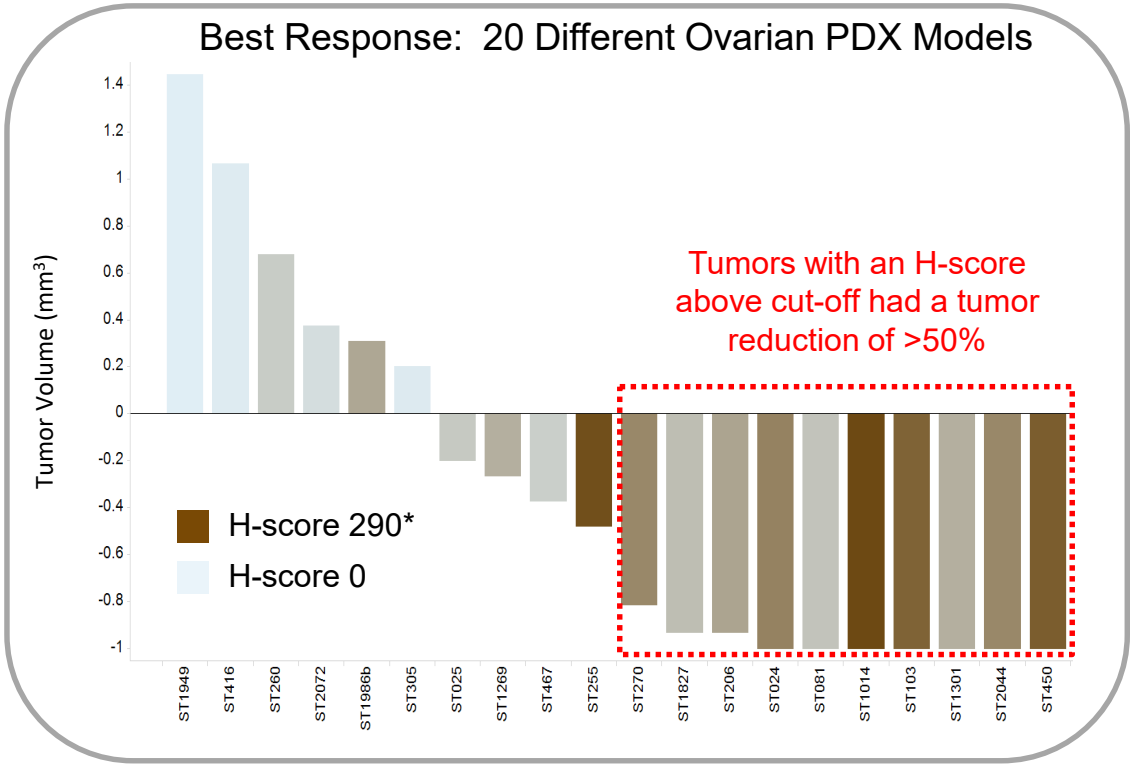
OVCAR3
Ovarian Xenograft



CTG-0852
NSCLC Patient Derived Xenograft



NaPi2b Expression Levels Have Been Predictive of Response to XMT-1536 in Ovarian Cancer Patient-Derived Models



- Proprietary research assay validated and used for retrospective evaluation of patients
- Preclinical data demonstrate NaPi2b expression highly correlated with response
- ~60% of ovarian cancer patients predicted to have NaPi2b score associated with deep responses in PDX models

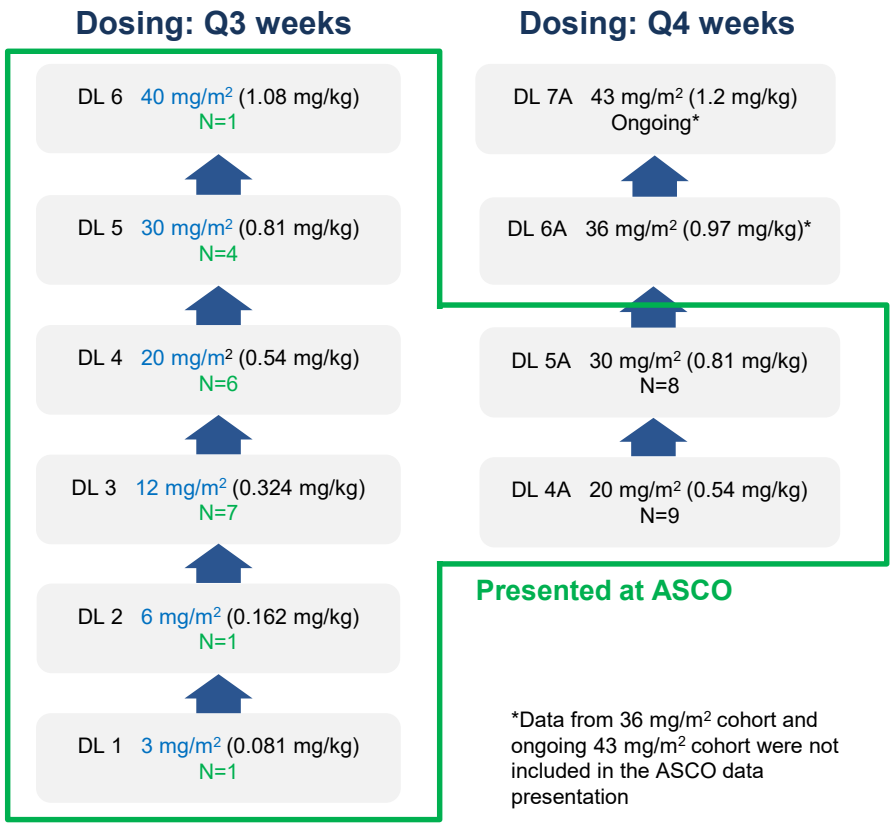
R. Mosher et al, AACR-NCI-EROTC International Conference, October 2017

*Semi-quantitative measure of antigen expression; ranges from 0-300

XMT-1536 Phase 1 Dose Escalation Study Design

Data Presented at ASCO with a Data Cutoff of May 10, 2019

- **Patient population:** patients with ovarian epithelial, non-squamous lung, endometrial, papillary renal, salivary duct, or papillary thyroid cancers, progressing after standard treatments
- **Dosing:** XMT-1536 administered IV initially every 3 weeks, amended to every 4 weeks, until disease progression or unacceptable toxicity
- **Dose escalation design:** single-patient cohorts for first two dose levels, followed by a standard “3 + 3” design
- **Assessments:** standard assessments including AEs, preliminary activity, concomitant medications, safety labs, PK



ClinicalTrials.gov: NCT03319628

Patients Were Heavily Pretreated and *Unselected for NaPi2b*

As of May 10, 2019

(N = 37)		
Age (years)	Median (range)	64 (39-93)
Sex – N (%)	Female Male	32 (86) 5 (14)
ECOG performance status – N (%)	0 1	11 (30) 26 (70)
Tumor type – N (%)	Ovarian, fallopian tube, or primary peritoneal NSCLC Endometrial Papillary renal Salivary duct	22 (59) 4 (11) 8 (22) 2 (5) 1 (3)
Prior lines of therapy for metastatic disease (N=37)	Median (range)	4 (1-13)
Prior lines of therapy, ovarian cancer only (N = 22)	Median (range)	5 (1-11)

XMT-1536 was Well-Tolerated with Most AE's Grade 1-2

As of May 10, 2019

Treatment-Related Adverse Events in ≥10% of Patients

N = 37	N (%)			
Preferred Term	**Grade 1**	**Grade 2**	**Grade 3**	**Total**
Nausea	12 (32)	2 (5)	0	14 (38)
Fatigue	4 (11)	7 (19)	0	11 (30)
Headache	5 (14)	5 (14)	0	10 (27)
Aspartate aminotransferase (AST) increased	3 (8)	2 (5)	4 (11)	9 (24)
Decreased appetite	1 (3)	6 (16)	0	7 (19)
Blood alkaline phosphatase increased	6 (16)	0	0	6 (16)
Vomiting	4 (11)	1 (3)	0	5 (14)
Gamma-glutamyltransferase (GGT) increased	3 (8)	1 (3)	0	4 (11)
Myalgia	3 (8)	0	1(3)	4 (11)
Pyrexia	3 (8)	1 (3)	0	4 (11)

Dose Escalation Continues

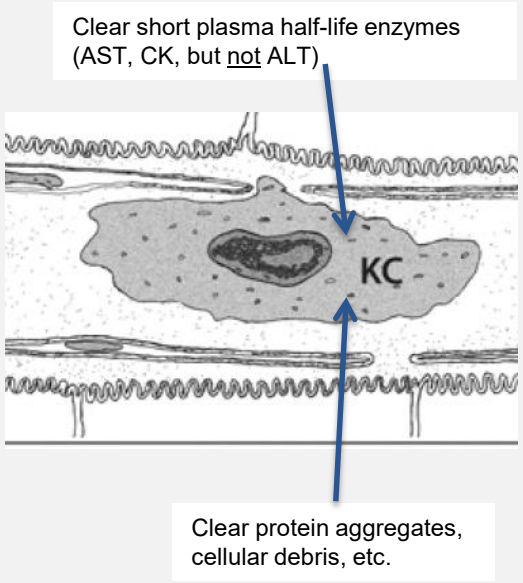
Safety:

- No Grade 4 or 5 treatment-related adverse events (TRAEs)
- Low rate of toxicities associated with microtubule-targeting agents or other ADC platforms, such as neutropenia, ocular toxicities, or peripheral neuropathy

Dolaflexin Safety Profile Easily Monitored; High Consistency between Early Clinical and Preclinical Data

Preclinical Data Demonstrate Transient AST Elevations Are Correlated with Kupffer Cell Hypertrophy

- Kupffer cells are involved in AST clearance
- Transient elevation is consistent with a change in clearance kinetics
- Transient elevations of AST were not associated with hepatocellular necrosis based on histopathology
- AST elevations peak at day 8 and return to normal along with Kupffer cell appearance



Clinical Data Mirror Preclinical Observations

- Repeatable and predictable pattern: transient AST peaking on Day 8, returning to baseline or Grade 1 by next dose (sawtooth pattern)
- Patients treated for over 34 weeks maintained predictable pattern
- No changes in bilirubin. No cases of Hy's Law

AST: Aspartate aminotransferase; Also known as serum glutamic oxaloacetic transaminase (SGOT); CK: Creatine Kinase; ALT: Alanine aminotransferase

Response Evaluable Population, *Unselected for NaPi2b*

As of May 10, 2019

Outcomes in Ovarian Cancer (OC) & Non-small Cell Lung Cancer (NSCLC)	All OC	All NSCLC	OC ≥20 mg/m^2	NSCLC ≥20 mg/m^2	OC ≥30 mg/m^2
N	19	3	16	2	7
PR*	3 (16%)	0 (0%)	3 (19%)	0 (0%)	2 (28%)
SD*	8 (42%)	2 (67%)	6 (38%)	2 (100%)	3 (43%)
DCR (PR + SD)	11 (58%)	2 (67%)	9 (57%)	2 (100%)	5 (71%)
PD*	8 (42%)	1 (33%)	7 (43%)	0 (0%)	2 (28%)

- Based on objective responses and duration of treatment
- Clinical activity was observed at doses of 20 mg/m^2 and higher

*As measured by RECIST, version 1.1

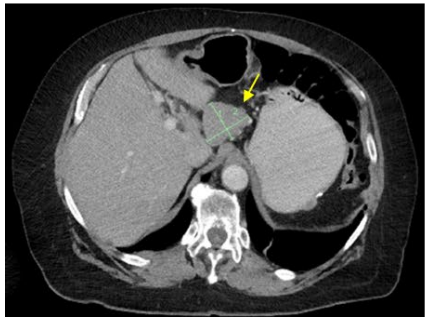
Ovarian Cancer Patient with Confirmed PR at Cycle 3

As of May 10, 2019

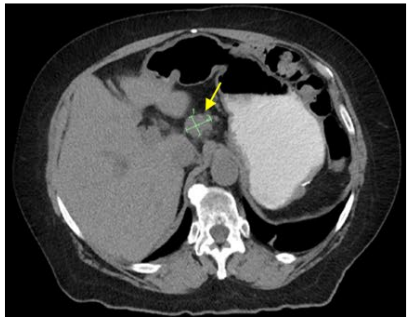
- 70-year-old woman with platinum-resistant high-grade serous ovarian cancer treated at DL 4A (20 mg/m^2)
- 11 prior lines of therapy, with progression on most recent therapy of cyclophosphamide and bevacizumab
- Target lesions of perihepatic and mid-abdominal metastases, 52 and 42 mm respectively
- Decrease of 40% in diameter of target lesions at the end of Cycle 2 (4-week cycles) and 75% at the end of Cycle 3

Lesion 1

Baseline

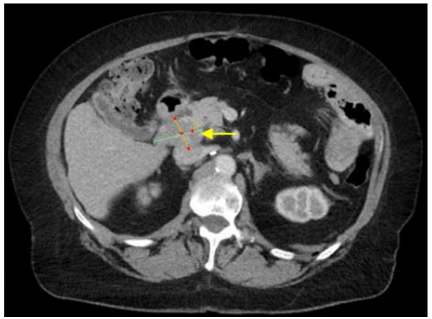


Cycle 3

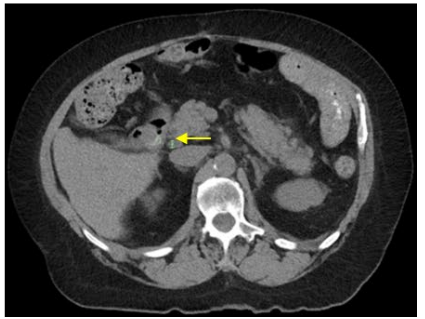


Lesion 2

Baseline



Cycle 3



Single Agent Activity in Platinum-Resistant Ovarian Cancer Based on Literature Review

Drug	Prior Lines of Therapy	ORR	PFS/TTP* Months	OS Months
Paclitaxel	1-2	13-37%	3.3-8	9-15
Topotecan	1	17-28%	3.1-5.3	10-14
Oxaliplatin	1-2	16%	2.8	10
PLD	1-2	8-20%	2.1-5.8	8-19
Gemcitabine	1-2	9-29%	3.6-4.7	12-13
Treosulfan	1	16%	2.9	10
Study (Control Arm) – Drug				
AURELIA - Investigator's Choice (PLD/Taxol/Topotecan)	1-2	12%	3.4	13.3
JAVELIN 200 – PLD	1-3	4.2%	3.5	13.1
FORWARD I - Investigator's Choice (PLD/Taxol/Topotecan)	1-3	12%	NR	NR

Ten Bokkel Huinink JCO 1997, Rosenberg P Acta Oncol. 2002, Piccart MJ JCO 2000, Gordon AN JCO 2001, Ferrandina G JCO 2008, Meier W Gynecol Oncol. 2009, Mutch DG JCO 2007, Vergote I Int J Gynecol Cancer 2010, Monk BJ JCO 2010, Pignata S Lancet Oncol; Pujade-Lauraine, E, et al. Javelin 200 Study SGO 2019 LBA; Pujade-Lauraine, E, JCO 2014.
Forward I press release dated March 1, 2019
*PFS = Progression-Free Survival; TTP = Time to progression; NR = Not Reported

XMT-1536 Ovarian Cancer Data in Context, *Unselected for NaPi2b Expression*

	Line of Therapy*					
	2nd	3rd	4th	5th	6th	7th
ORR %	26-34%	12-20%	3-17%	5-11%	0-8%	0%
DCR %	59%	16-45%	9-33%	9-44%	0-23%	0-20%
	XMT-1536 Dose Level ≥30 mg/m² Lines of Therapy: Median 5 (3-8)					
ORR %				28%		
DCR %				71%		

* Calculated according to P.J.Hoskins; Nhu Le, Gynecologic Oncology 2005; I. Bruchim et al, EJOGRB 2013

Ovarian Cancer and NSCLC Adenocarcinoma Duration

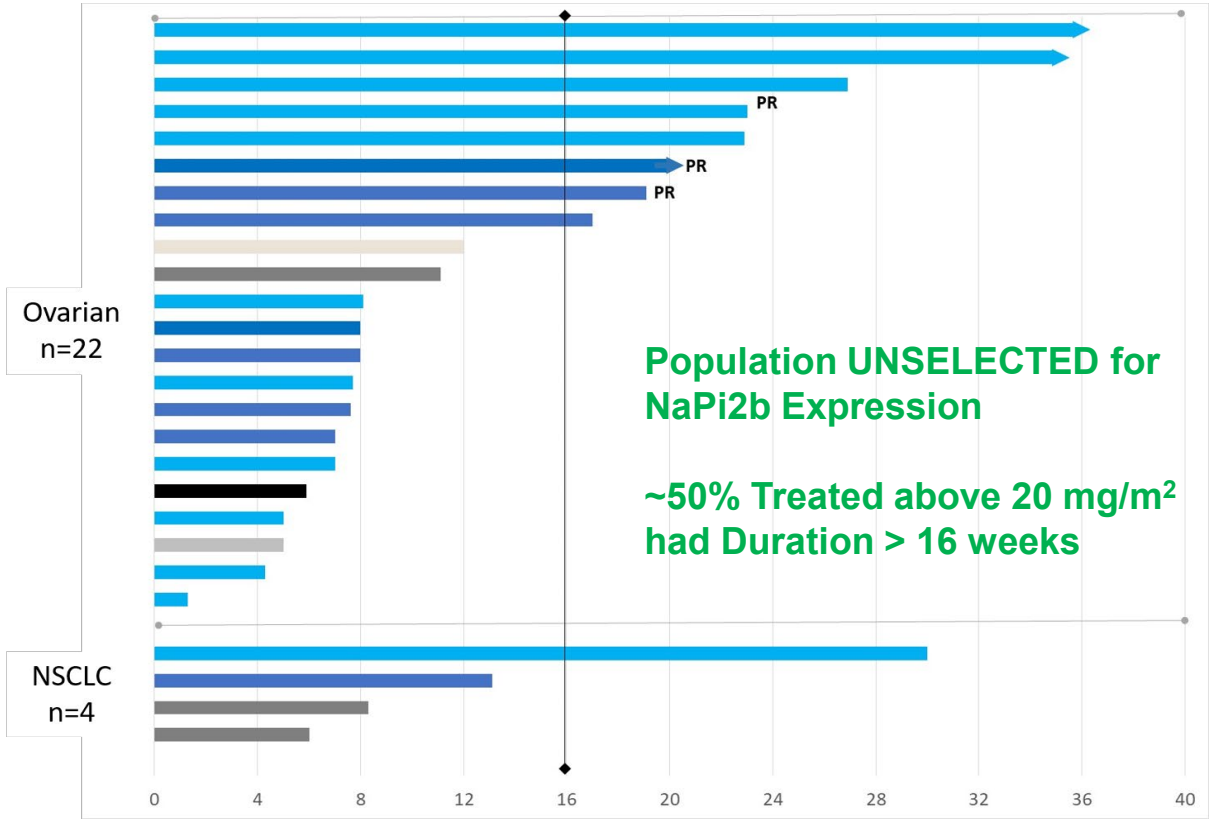
As of May 10, 2019

All Completed Dose Levels
OC and NSCLC Patients, N=26

n=1	3 mg/m^2 Dose Level 1
n=1	6 mg/m^2 Dose Level 2
n=3	12 mg/m^2 Dose Level 3
n=12	20 mg/m^2 Dose Levels 4 & 4A
n=8	30 mg/m^2 Dose Levels 5 & 5A
n=1	40 mg/m^2 Dose Level 6

Ongoing →

Partial Remission = **PR**



XMT-1536 Phase I Expansion Study Initiated

Study Designed to Confirm Profile and Inform Path to Approval in High Unmet Medical Need Populations

Expansion Study Initiated:
36 mg/m^2 dose on Q4W schedule

Expansion: Platinum-Resistant Ovarian Cancer

Eligibility criteria:

- High-grade serous histology
- 1-3 prior lines of therapy
- Platinum-resistant
- Archived tumor and fresh biopsy (if medically feasible)

Expansion: NSCLC Adenocarcinoma

Eligibility criteria:

- Adenocarcinoma histology
- Prior treatment with a platinum doublet and PD-1/L1 inhibitor
- No additional prior treatment with cytotoxics or immunotherapy
- Prior TKIs for patients with targetable abnormalities
- Archived tumor and fresh biopsy (if medically feasible)

Dose Escalation Continuation

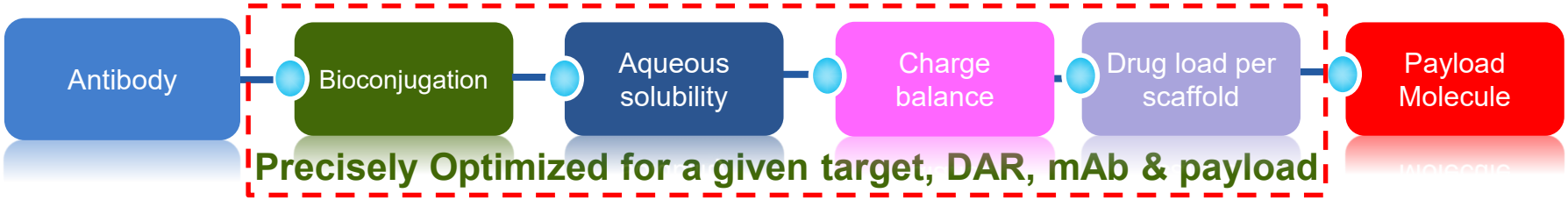
- MTD not determined in dose escalation study
- Exploring 43 mg/m^2 dose (~1.2 mg/kg) in parallel to expansion study to inform future clinical development

Dolasynthen

Mersana THERAPEUTICS

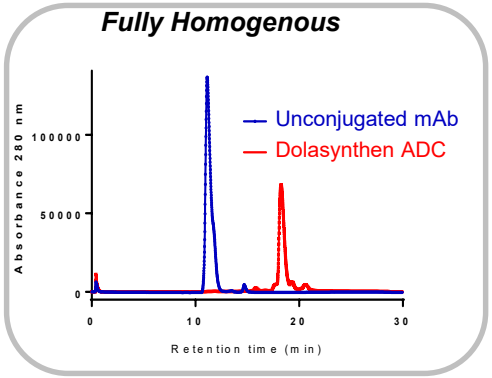
Dolasynthen

A Precise, Fully Synthetic, Customizable and Homogeneous Approach



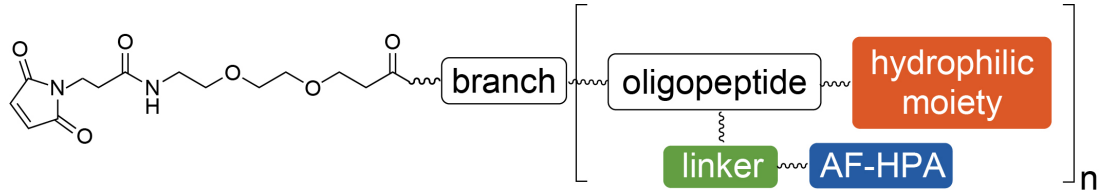
Many Factors Can Influence the Performance of an ADC:

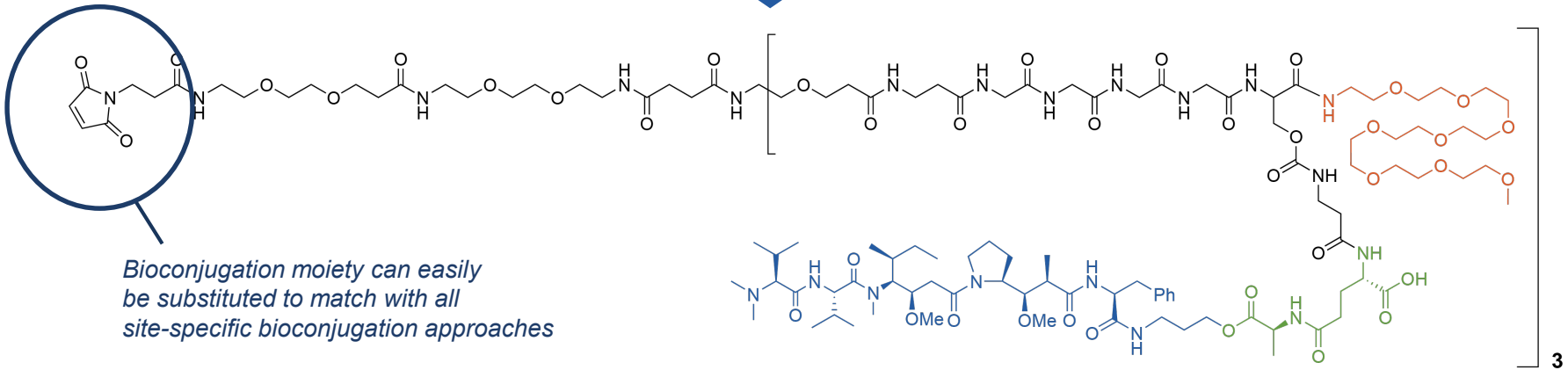
- *Drug-to-antibody ratio*
- *Site of bioconjugation*
- *Payload employed*
- *Linker – cleavable vs. non-cleavable*
- *Hydrophilicity / hydrophobicity*
- *Charge profile*
- *Means of bioconjugation – lysine, cysteine, thiomab, enzymatic, etc.*
- *Characteristics of Fc portion of mAb – e.g. Fcγ, FcRN binding*



The optimal combination will likely differ based on the target, the antibody and the indication

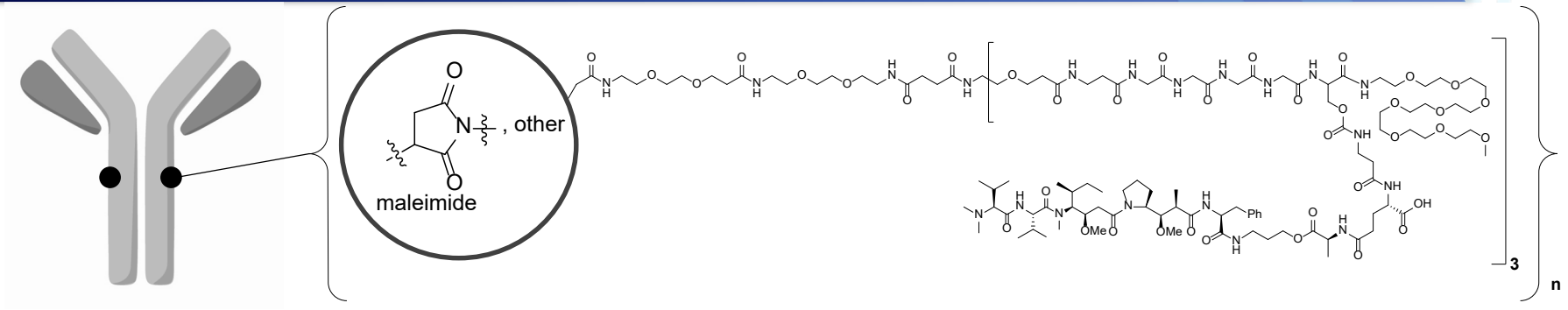
Optimized Dolasynthen Trimeric Scaffold





Bioconjugation moiety can easily be substituted to match with all site-specific bioconjugation approaches

Applying Dolasynthen: SAR at the ADC Level

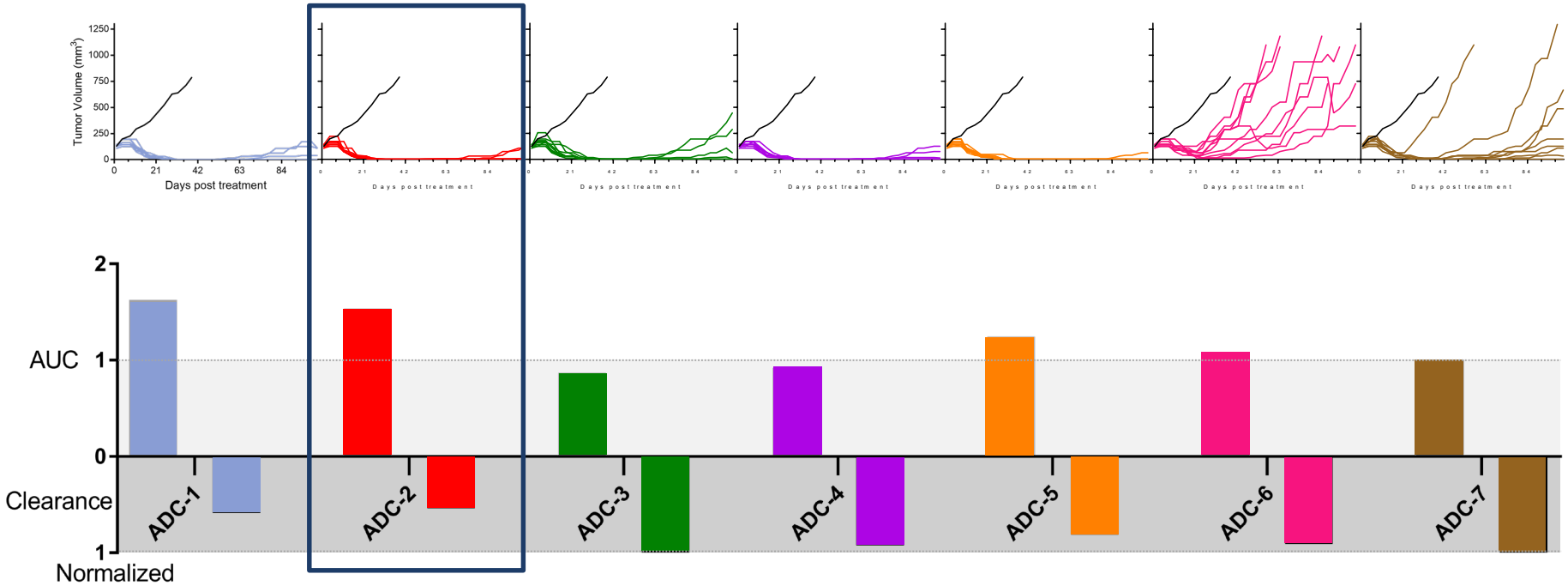


- Trastuzumab was used as a model to synthesize ADCs with variations in:
  - DAR (6, 12)
  - Bioconjugation site(s)
  - Bioconjugation technology

	ADC 1	ADC 2	ADC 3	ADC 4	ADC 5	ADC 6	ADC 7
Bioconjugation	A	B	A	C	C	D	A
DAR	6	6	6	6	6	12	12
Site specific	●	●		● (site 1)	● (site 2)	●	

Efficacy and PK Reveal the Optimal Candidate

Efficacy JIMT1 Breast Xenograft Model (0.067 mg/kg payload single dose)



PK in tumor bearing mice (0.133 mg/kg payload single dose)

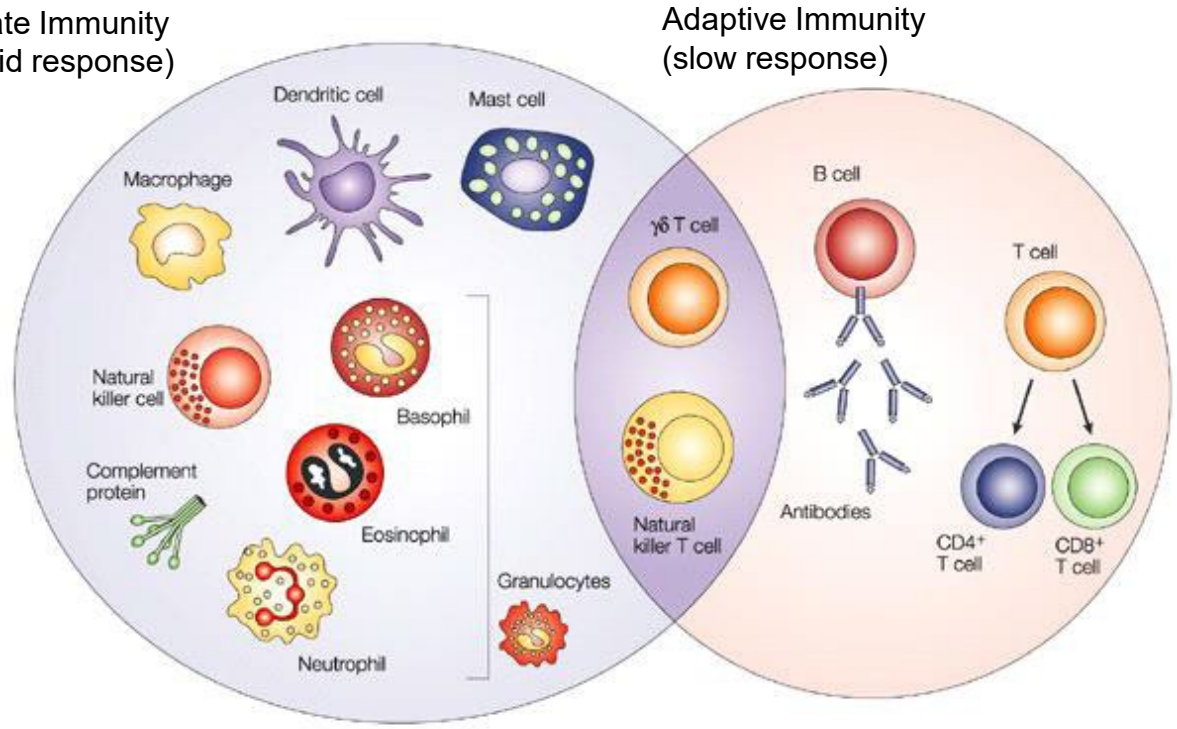
Immunosynthen

Mersana THERAPEUTICS

Expanding Immuno-Oncology Approaches

Innate Immunity Targets

→ *activation: hitting the gas pedal on the immune system*



Adaptive Immunity Targets

ex. checkpoint inhibitors, CAR-T

→ *inhibition: taking the brake off of the immune system*

Nature Reviews Cancer 4, 11–22 (2004)

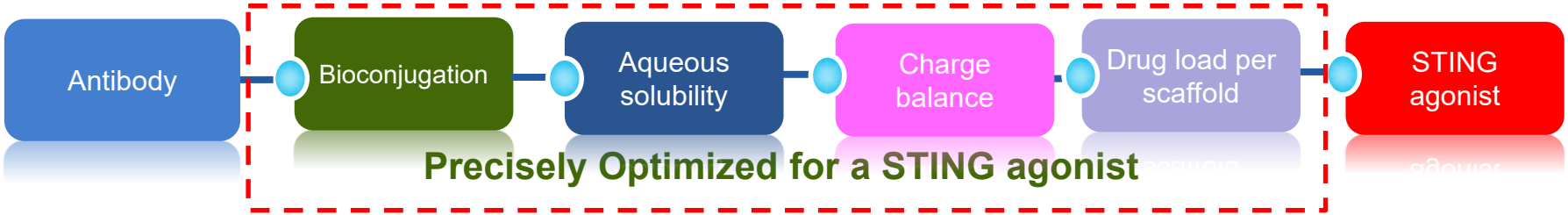
Why Pursue Systemic Delivery of STING as an ADC?

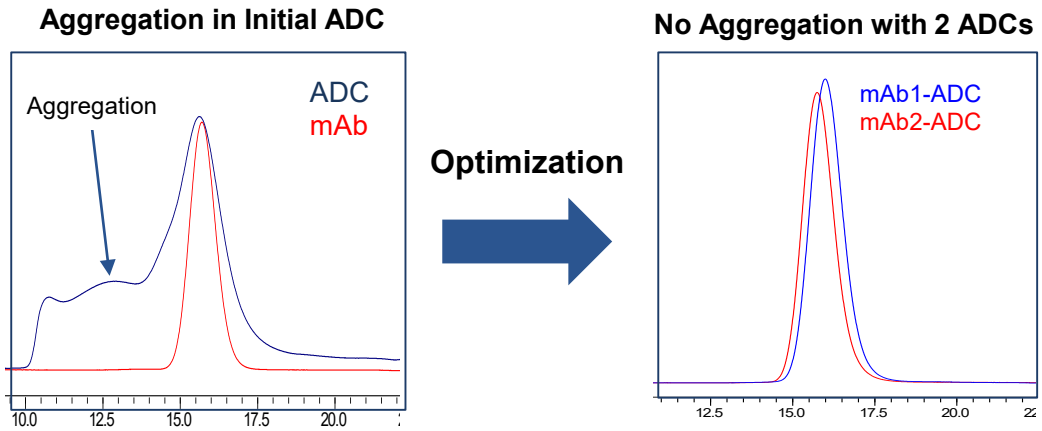
- Current clinical STING compounds limited to intra-tumoral injection due to concern of systemic toxicity as well as PK limitations
  - Limits clinical indications and tumors accessible to injection
  - Debate over effect on distal tumors/metastases (abscopal effect)
    - No clinical evidence of abscopal effect yet to date
  - Recent report by GSK of free agonist delivered systemically; Fast clearance and potential for limited TI

- ADCs are suited to overcome limitations with free agonists
  - Accessibility to primary and metastatic tumors
  - Amenable to antigen specific targeting on tumor resident immune cells
  - Longer exposure at lower doses- promotes systemic adaptive immunity
  - Active intracellular delivery to cytoplasmic STING

Leveraging Mersana's Synthemer Platform Approach for STING

Critical Attributes Matched to Payload and Target

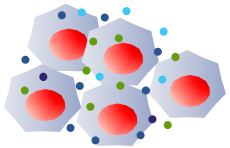




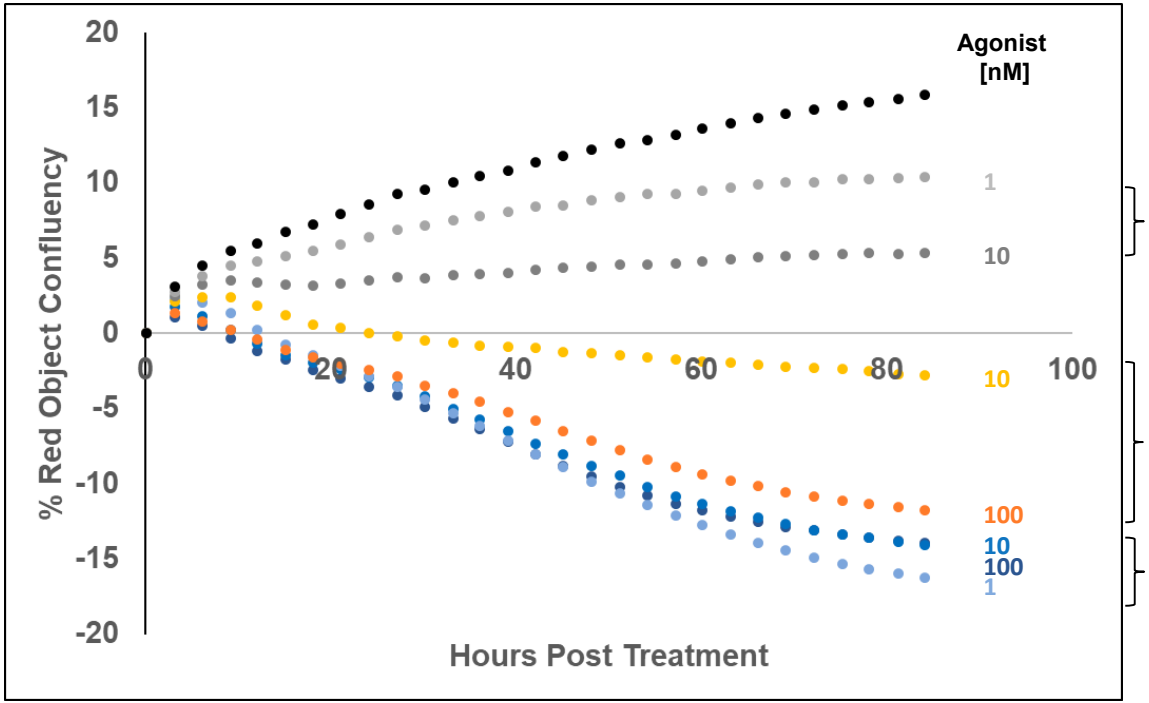
- Initial ADC with STING agonist resulted in aggregation due to lipophilic payload
- **Linker/scaffold optimization effort tailored to particular STING agonist**

100x Increased Potency of ADC over Free Agonist

Killing assay: cancer cells / PBMC co-culture

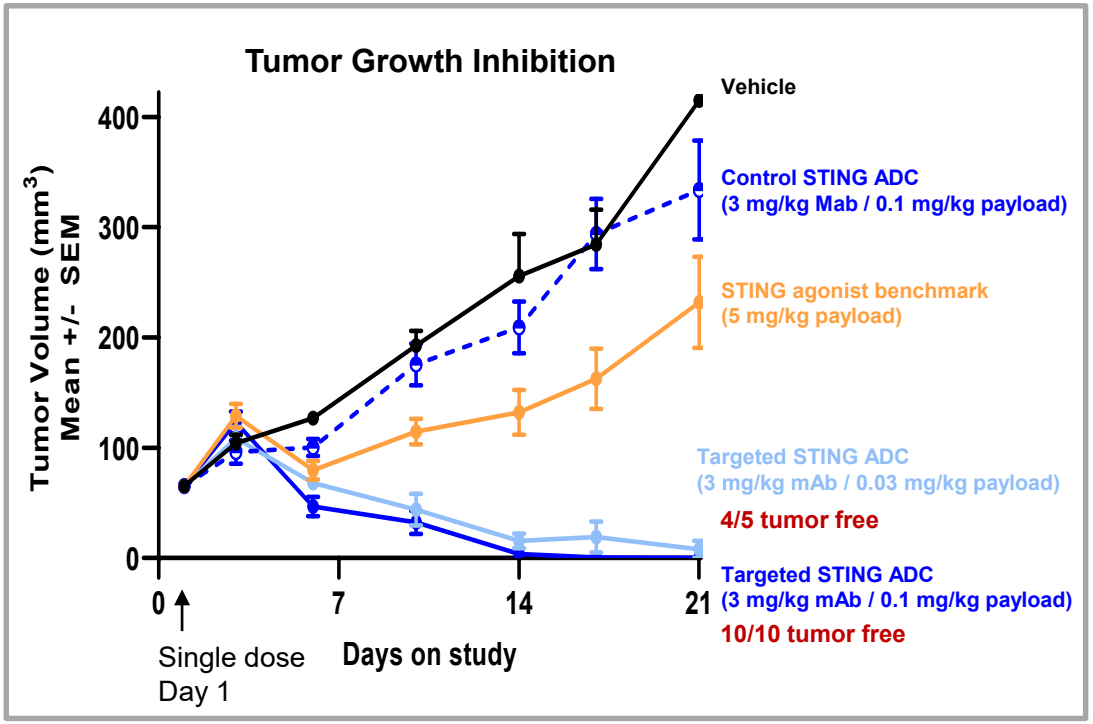


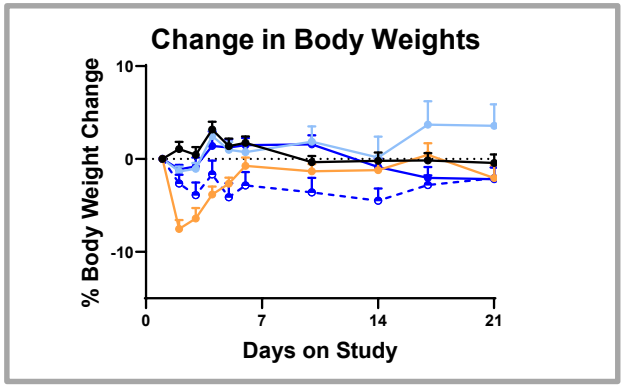
- Cancer cells expressing a fluorescent red protein in the nucleus (stable)
- Cancer cell has minimal STING activity

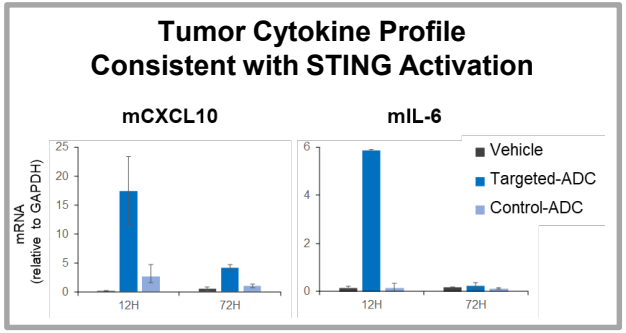


Durable Tumor Regressions in 10/10 Animals at 3 mg/k

STING ADC at Significantly Lower Dose Outperforms Systemically Administered Agonist







A special thank you to all of the patients involved in our clinical trial, and their families

Mersana
THERAPEUTICS