Society for Immunotherapy of Cancer

# XMT-2056:
# A Her-2 Targeted Immunosynthen STING agonist antibody drug conjugate

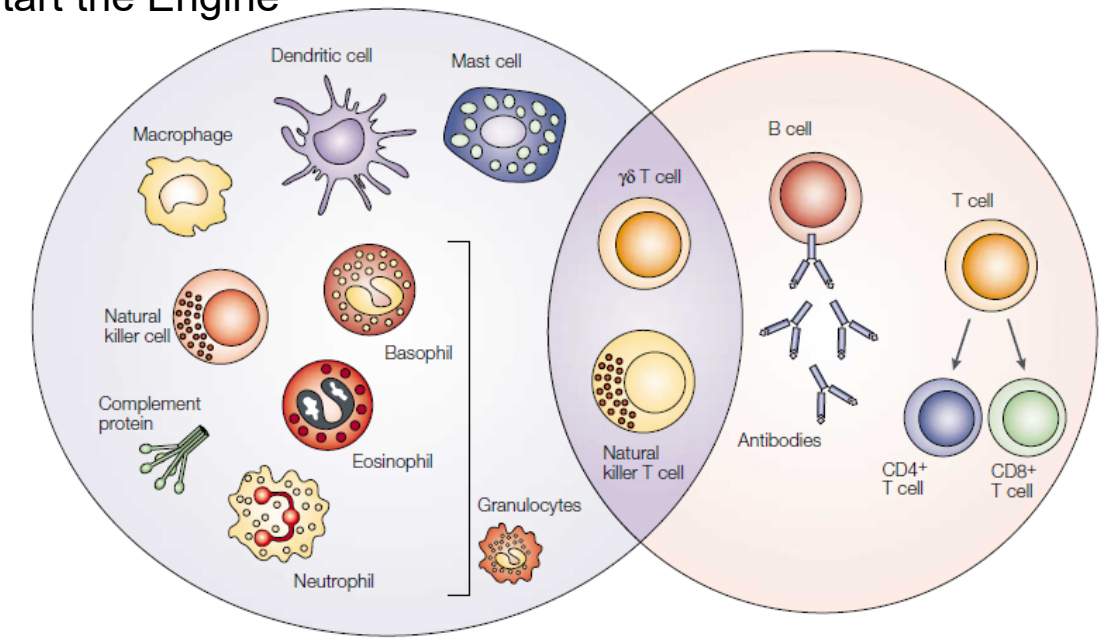
Timothy B. Lowinger, Ph.D.
Chief Science and Technology Officer, Mersana Therapeutics

Friday, August 26, 2022

# Targeted Stimulation of Innate Immunity has the Potential to Deliver Breakthroughs

Innate Immunity
- Includes STING
- “Start the Engine”

Adaptive Immunity
- Includes CTLA4, PD1/PD-L1
- “Release the brakes”

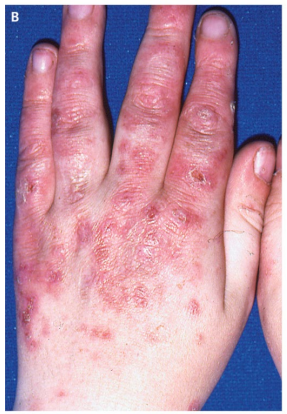



- The immunotherapy revolution has focused on adaptive immunity

- Innate immune stimulation could address unmet medical needs in:
  - Checkpoint refractory tumors
  - Checkpoint relapsed tumors
  - Tumor types where checkpoints have minimal activity

# STING Is a Fundamental Immune Pathway

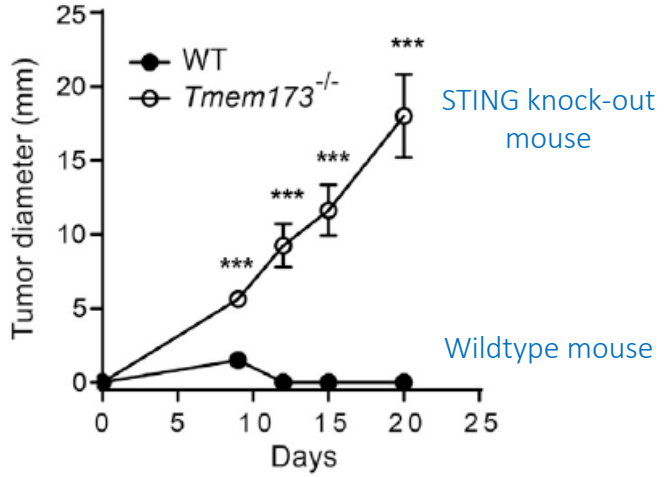
## Human Genetics




*Liu et al, NEJM, 2014*

Ligand-independent gain-of-function mutation in STING leading to pediatric STING-associated vasculopathy with onset in infancy (SAVI) - severe auto-inflammatory disease

## Mouse Genetics

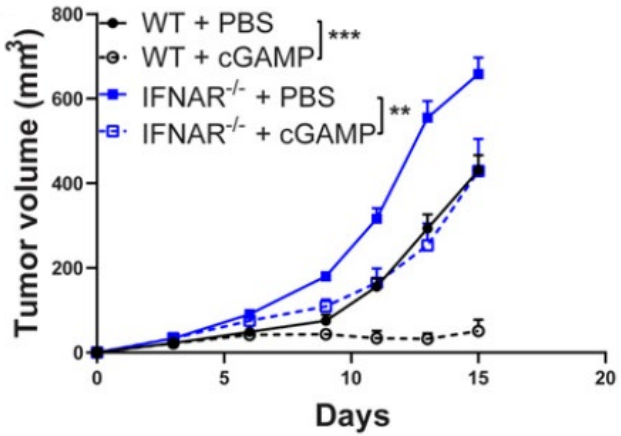



*Woo et al, Immunity, 2014*

STING knock-out (KO) mouse (*Tmem173*$^{-/-}$)

- Unable to mount immune-mediated anti-tumor response
- Sensitivity to HSV-1 virus infection
  (*Ishikawa et al, 2009, Nature*)

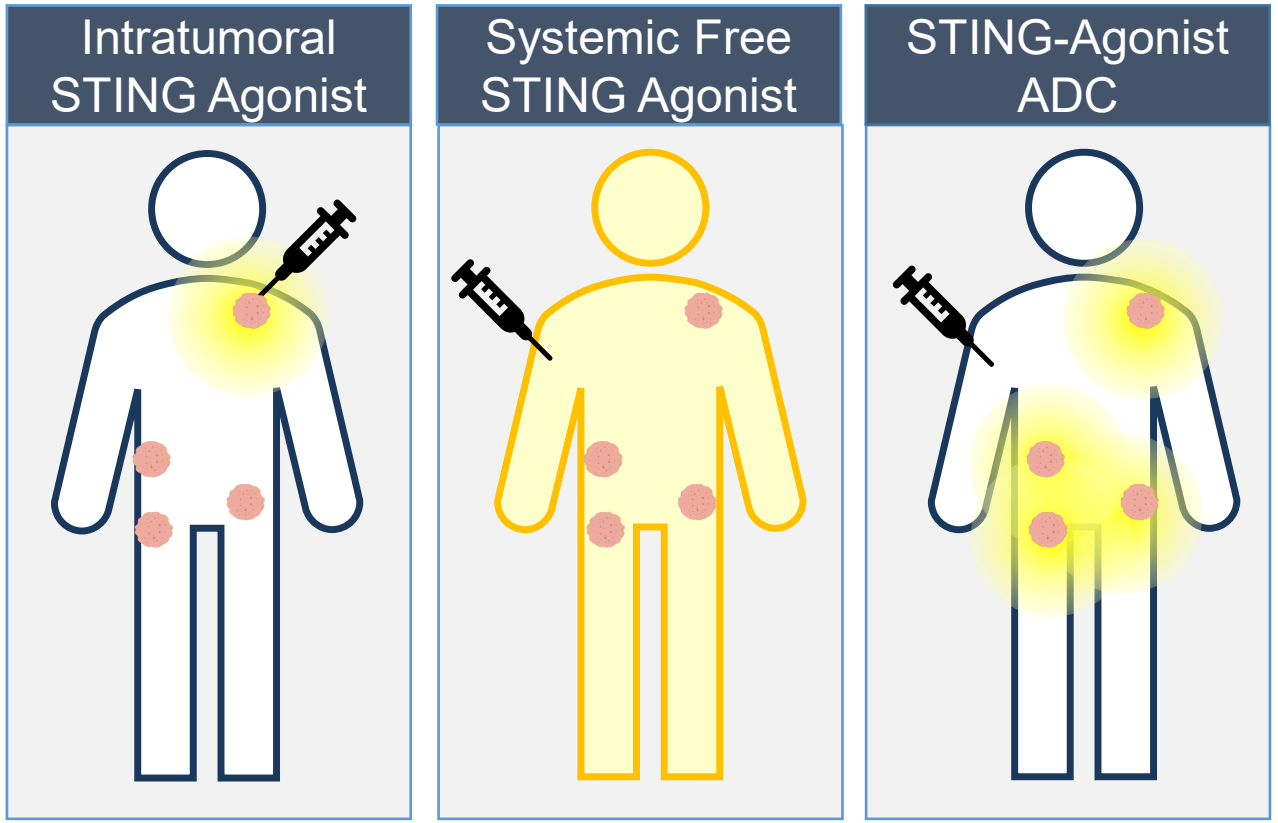
## Cancer Pharmacology




*Yum et al, PNAS, 2021*

STING agonist (cGAMP) inhibits tumor growth via an interferon response

# An ADC is an Ideal Approach for Targeted Innate Immune Activation with STING




- Systemic administration with targeted delivery to all tumor lesions while avoiding healthy tissues
- Improved anti-tumor activity compared to free agonist
- Improved tolerability compared to free agonist

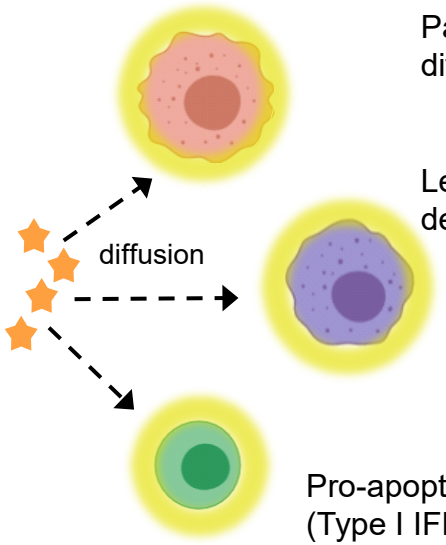
Systemic immune activation

Tumor, no immune activation

Tumor with STING-Mediated Innate Immune Activation

# How and Where You Deliver STING is Key to Maximizing the Therapeutic Index – a Major Advantage of an ADC

## Free STING Agonist




Passive, indiscriminate diffusion

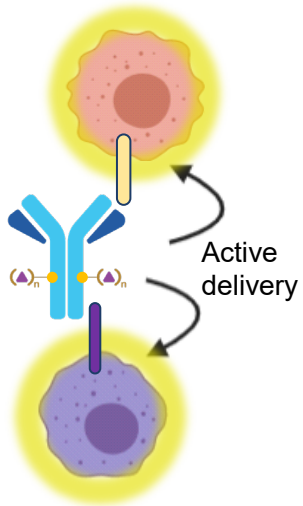
Less efficient delivery to desired cell types

Pro-apoptotic effect of T cells (Type I IFN independent)

Gulen et al. *Nature Comm*. 2017
Wu et al. *Immunity* 2020

## Immunosynthen ADC

✓ Antigen-dependent, active delivery into tumor cells



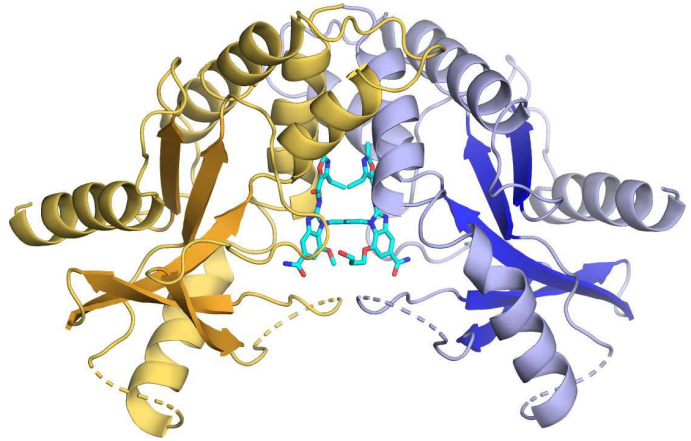

✓ FcgR-mediated, active delivery into tumor-resident myeloid and dendritic cells

✓ No delivery to T cells

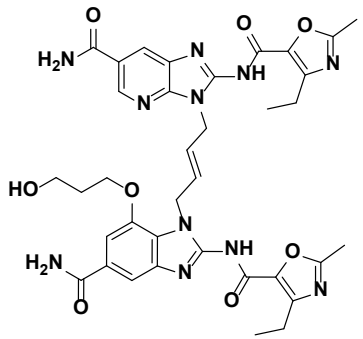
# Proprietary STING Payload Specifically Designed for an ADC

## Extensive Structure-based Medicinal Chemistry Effort

- Highly potent STING agonist
  - $K_D$ = 271 pM (SPR)
  - $EC_{50}$ = 4.4 nM (IRF3 reporter, WT haplotype)
  - Active against all major haplotypes
  - Active vs. mouse, rat, NHP, human
- Very low cell permeability
  - $P_{app} < 0.1 \times 10^{-6}$ cm/s
  - ADC >100-fold more active than free payload
- Short half-life
  - In vitro ½ life (human microsomes) = 28 minutes
  - In vivo ½ life (mouse) < 0.5 hour
- Physicochemical properties suitable for an ADC
  - Low cLogP, high tPSA

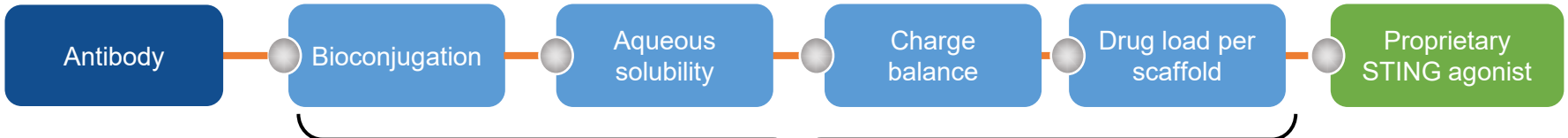


Co-crystal structure confirms agonist binds in an active, “closed” conformation of the protein

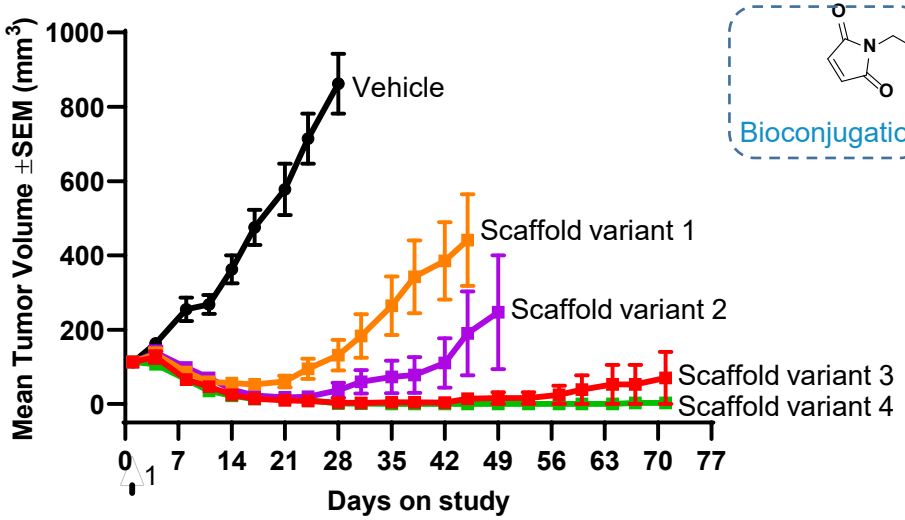


XMT-1616

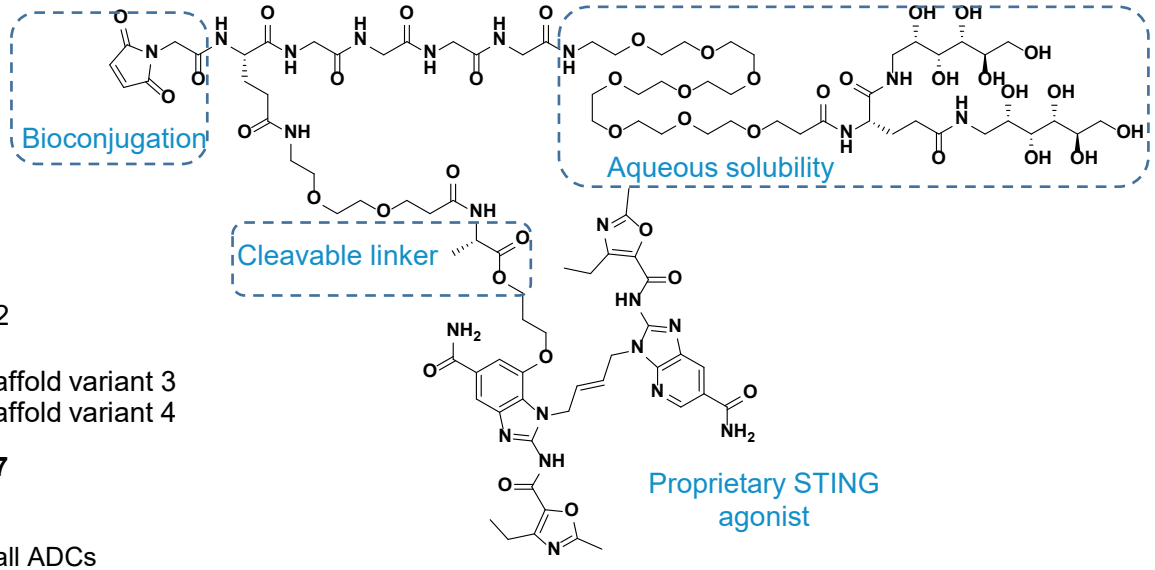
# Linker-Scaffold Specifically Optimized for the STING Agonist




ADC Optimization via Modular Approach




- Used same antibody and same STING agonist for all ADCs
- Single, equivalent IV dose for all ADCs

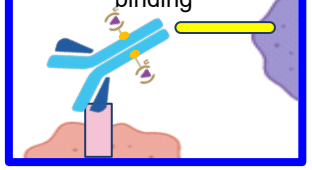



**Immunosynthen Platform (XMT-1621)**

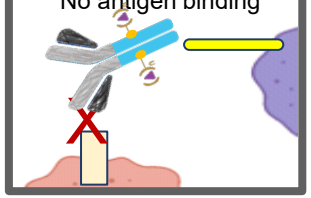
# Single, Low Dose of Prototype Trastuzumab-STING ADC Outperforms Comparators

**Vehicle**

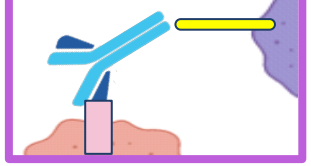
**Targeted ADC**
Antigen and FcγR binding



**Control ADC**
No antigen binding

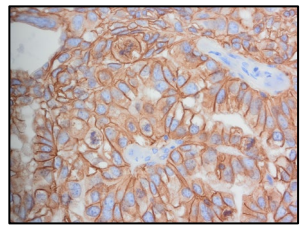


**Unconjugated**
No payload



**Free IV Agonist**

**SKOV3 (HER2 "high")**
**CB.17 SCID**
(220,000 receptors/cell; RNAseq[&]: 11.1)



HER2 IHC



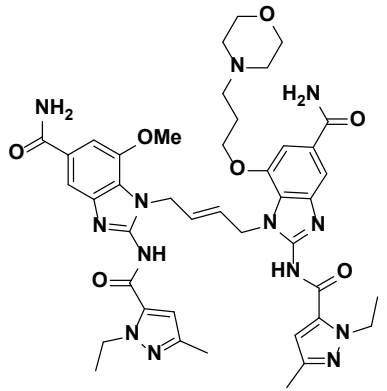

- Vehicle
- Non-binding Control STING ADC (3 / 0.09 mg/kg)
- Trastuzumab (3 mg/kg)
- diABZI IV STING agonist (5 mg/kg)*
- Trastuzumab-STING ADC (3 / 0.09 mg/kg)

  - All groups dosed IV
  - ADC doses reflect mAb / payload mg/kg

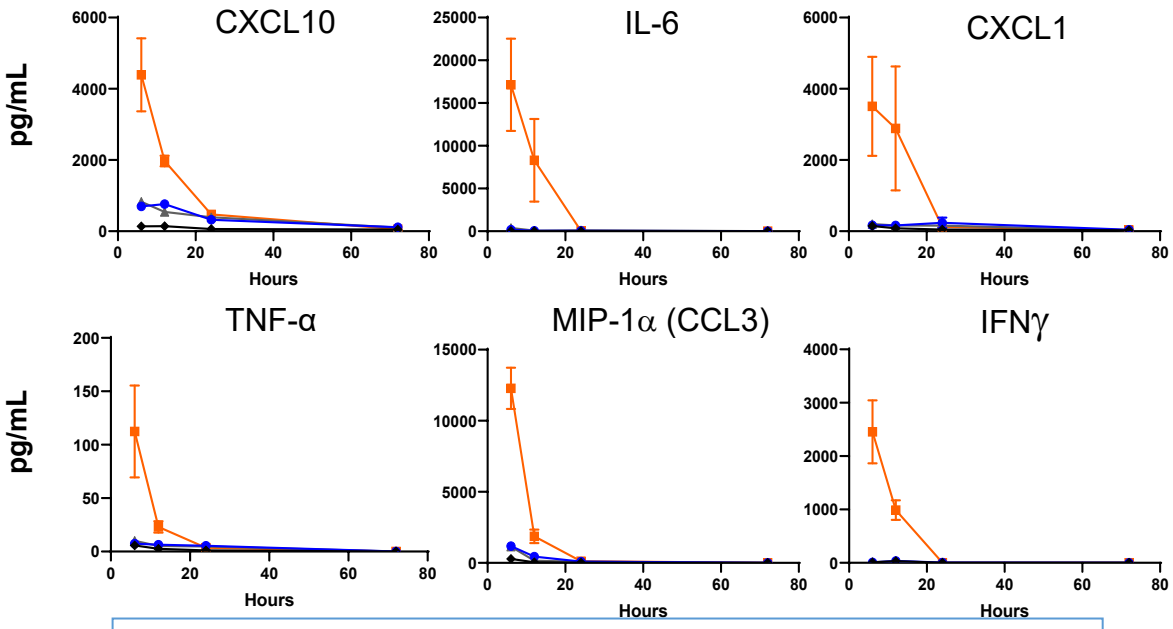
*diABZI IV STING agonist described in J.M. Ramanjulu *et al.* (2018) *Nature* (compound 3 in reference)

[&]CCLE RNAseq data from DepMap, Broad (2021): DepMap 21Q3 Public

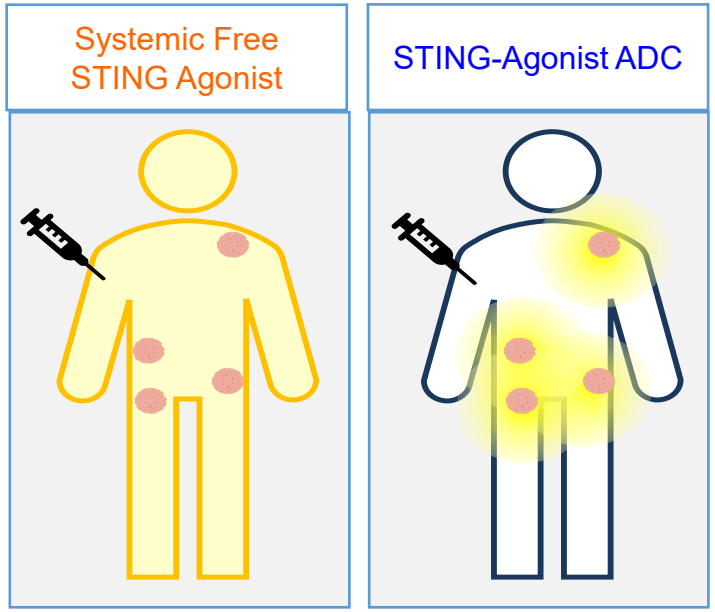
diABZI IV STING agonist*



# Dramatically Lower Systemic Cytokine Levels After IV Dosing of Prototype Trastuzumab–STING ADC Compared to diABZI Small Molecule STING Agonist




Serum cytokines measured with Luminex assay

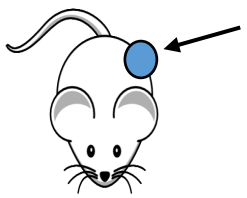



Systemic immune activation

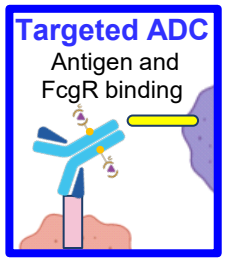
Tumor, no immune activation

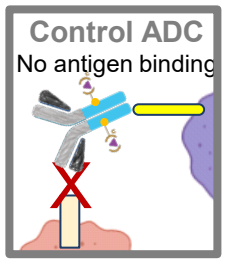
Tumor with STING-Mediated Innate Immune Activation

# Prototype Trastuzumab-STING ADC Induces STING Pathway Cytokines in Tumor-Resident Mouse Cells and Human Tumor Cells *In Vivo* in a Target-Dependent Manner

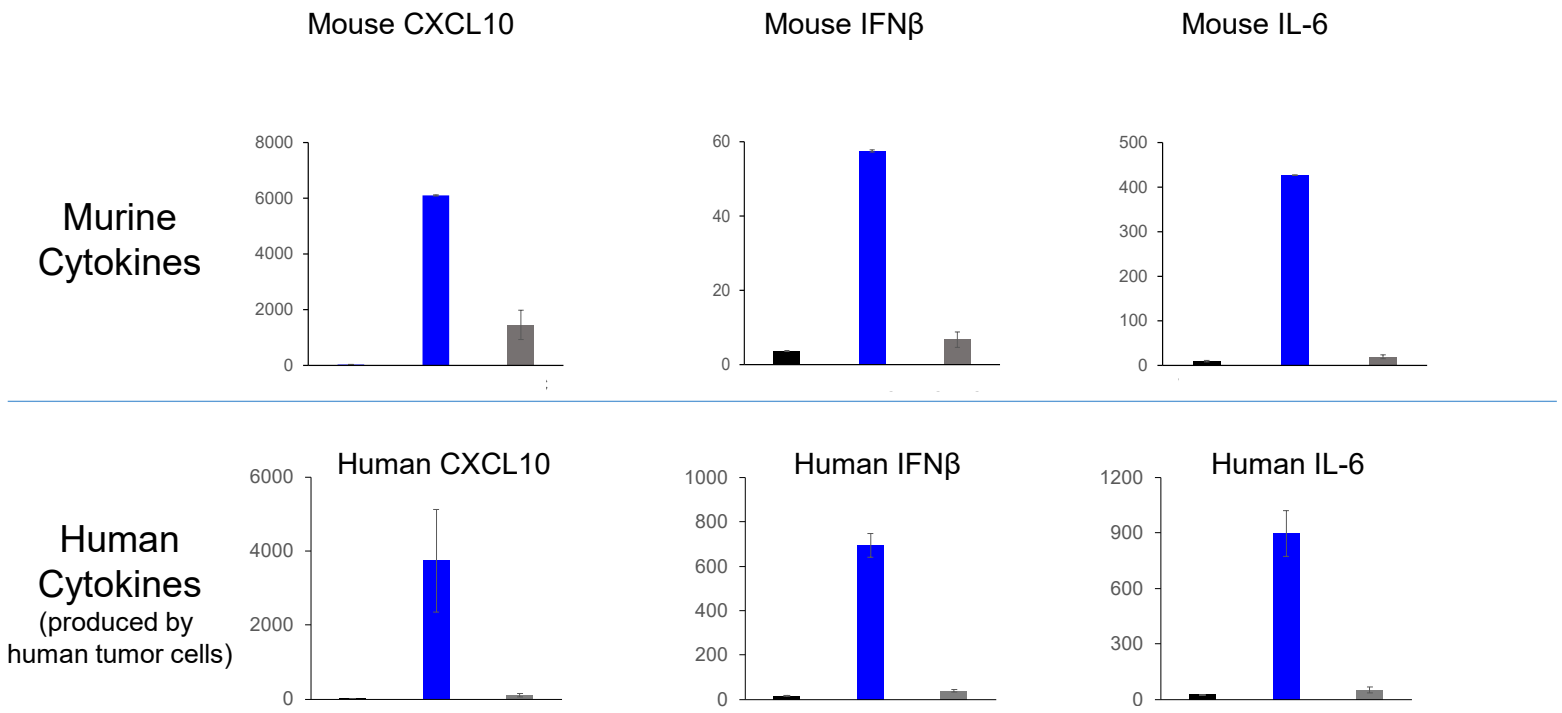



**Vehicle**

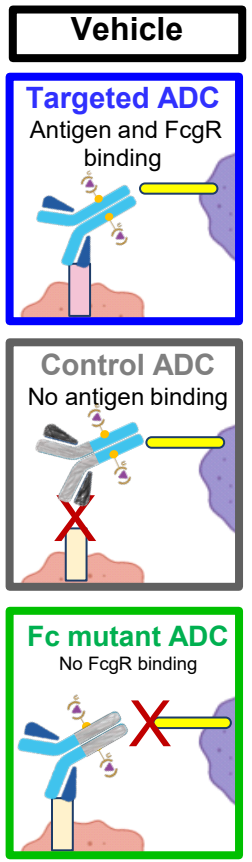


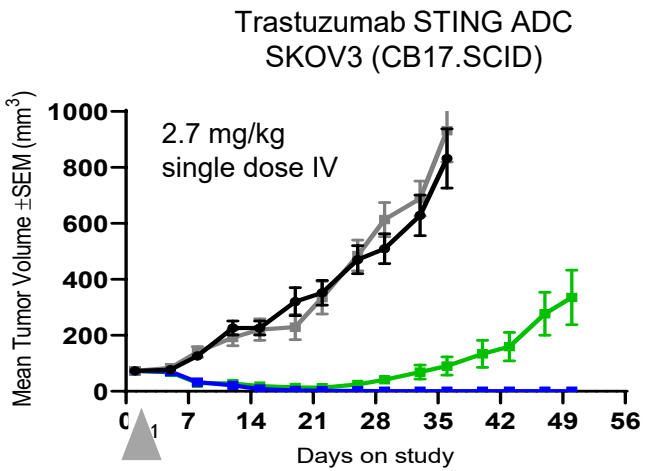

Cytokine Induction in the Tumor Microenvironment



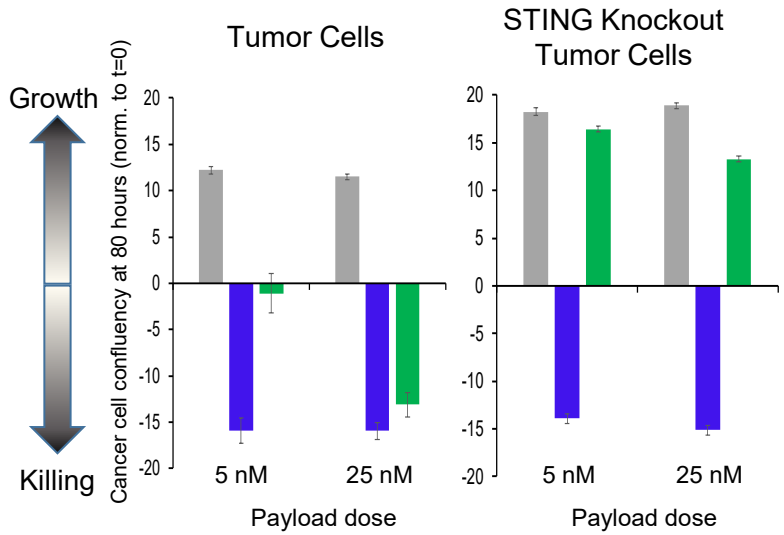
# Fc-Blocking Experiment Further Confirms Tumor Cell Contribution and Fc-mediated Uptake to Immune cells




**In Vivo Efficacy**




**Tumor Cell Killing in PBMC Co-Culture**

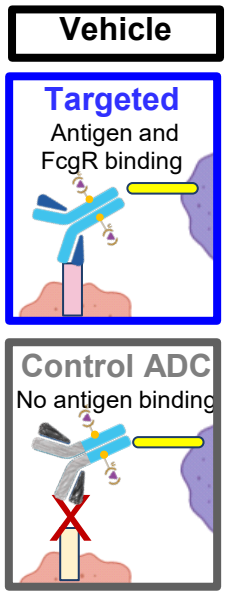


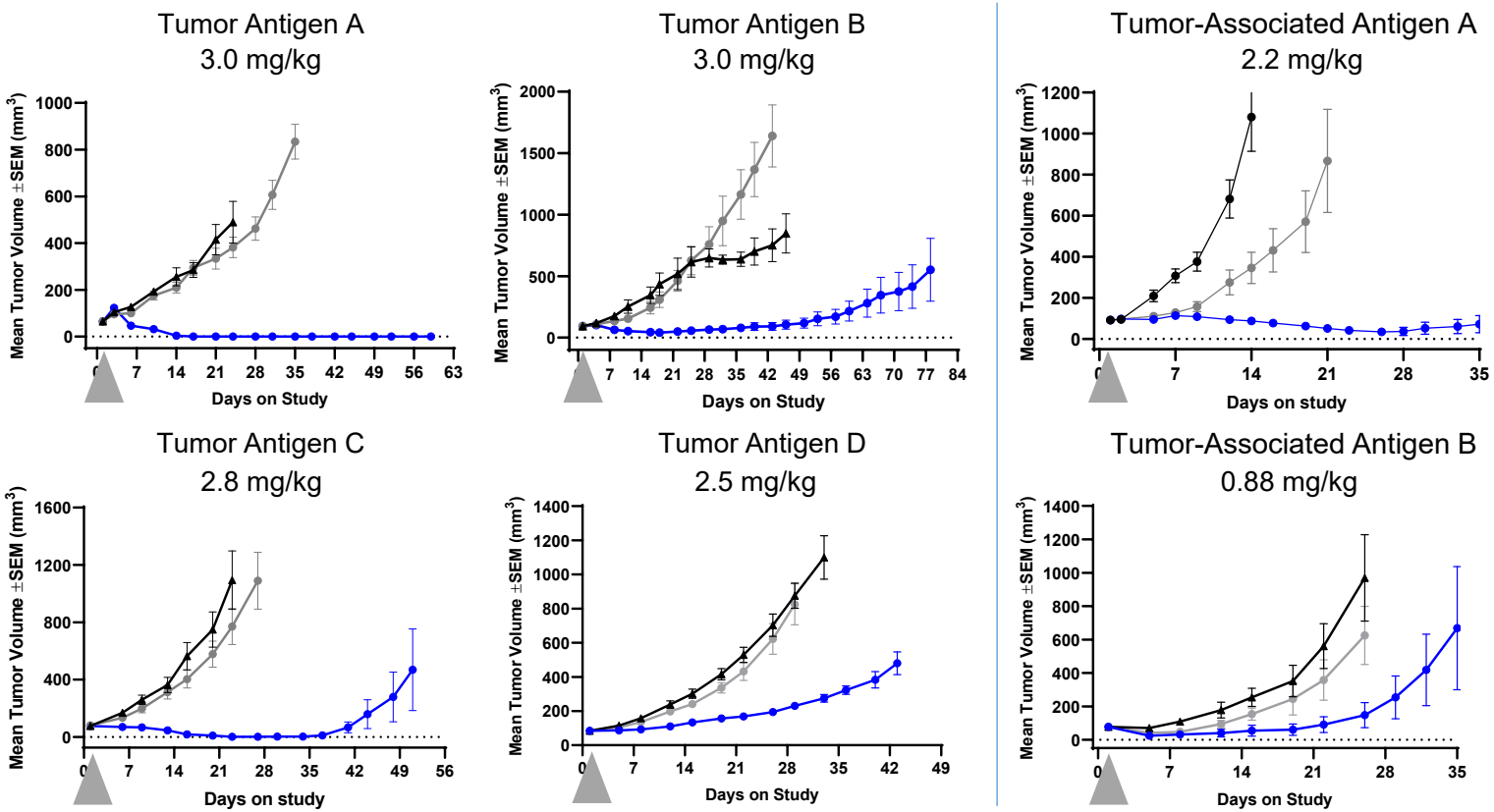

Significant anti-tumor activity in vivo & tumor cell killing in vitro is maintained by the Fc-mutant ADC, which cannot internalize into the immune cells

- Demonstrates the contribution of immune cell STING to activity
- Demonstrates the direct contribution of tumor-intrinsic STING activation

*Mersana Therapeutics, SITC 2020 & AACR 2021*

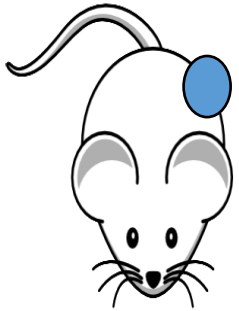
# Immunosynthen ADCs Active Against Diverse Tumor Antigens and Tumor-Associated Antigens in Multiple Models After Single, Low IV Dose



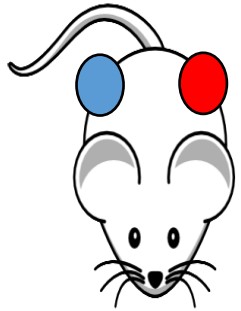
# Immunosynthen ADC Triggers Tumor-Specific Immunological Memory

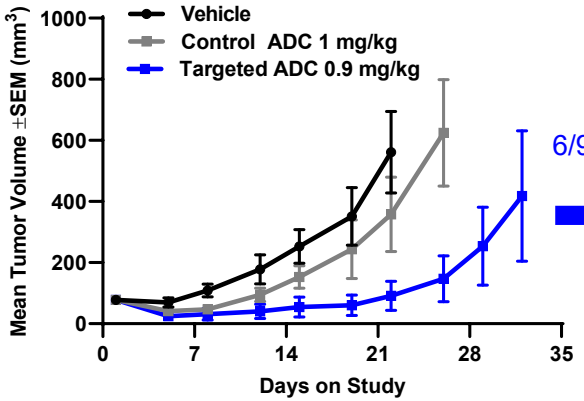
**Tumor Growth Inhibition Study**



- Tumor free mice re-implanted with targeted tumor on one flank (blue) and a non targeted tumor on the other flank (red).
- Untreated age matched mice also implanted as a control (black line).

**Tumor Rechallenge Study (Dual Flank)**

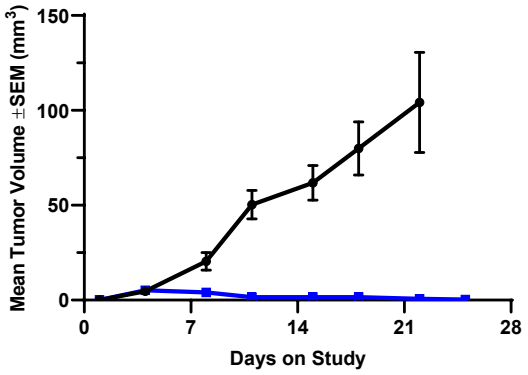




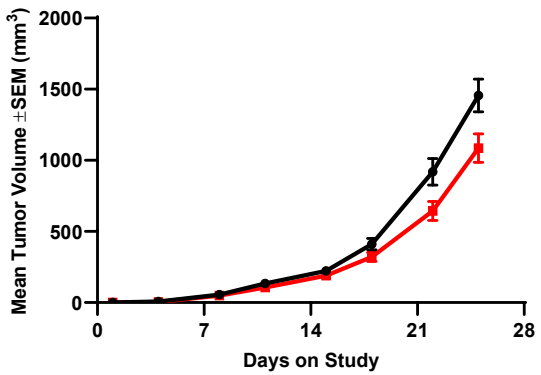

single IV dose

6/9 tumor-free animals

**Targeted-tumor**




**Non-targeted tumor**




Untreated Control Mouse (age matched)
Previously Treated with Targeted ADC

Untreated Control Mouse (age matched)
Previously Treated with Targeted ADC

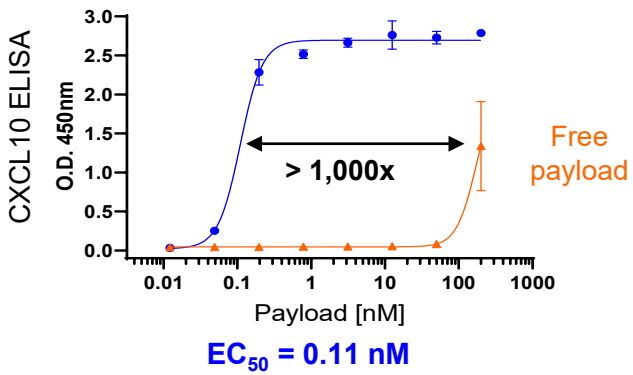
# Targeting HER2:
## XMT-2056 Provides a Differentiated Approach to a Well-validated Target

- HER2 is a well-validated target with multiple potential indications
  - Breast cancer, gastric cancer, NSCLC, colorectal cancer
  - Patient selection assays readily available
- Mersana developed a differentiated anti-HER2 antibody with Adimab
  - Specifically optimized for use in an ADC
  - Does not compete with trastuzumab or pertuzumab for HER2 binding
    - Rationale and opportunity for therapeutic combinations
- STING pathway is differentiated from other innate immune pathways
  - Activation in tumor cells and tumor-resident immune cells

# XMT-2056: Mersana's First Immunosynthen Development Candidate

### In Vitro – Tumor cells with PBMCs

**Greater than 1000 fold increase in potency of ADC vs. free payload**

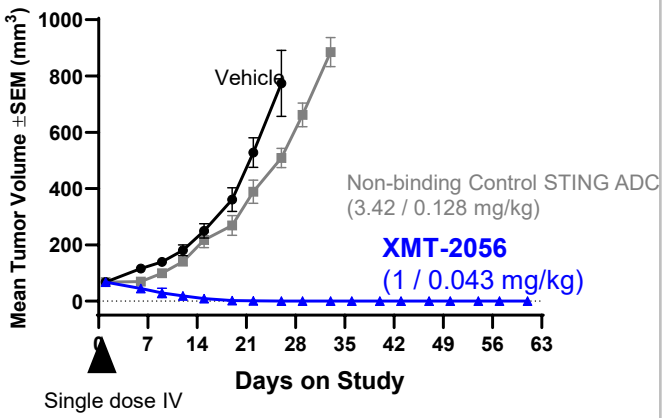



$EC_{50}$ = 0.11 nM

- ADC-mediated active delivery of STING payload to HER2 expressing tumor cells and PBMCs

### In Vivo – Mouse

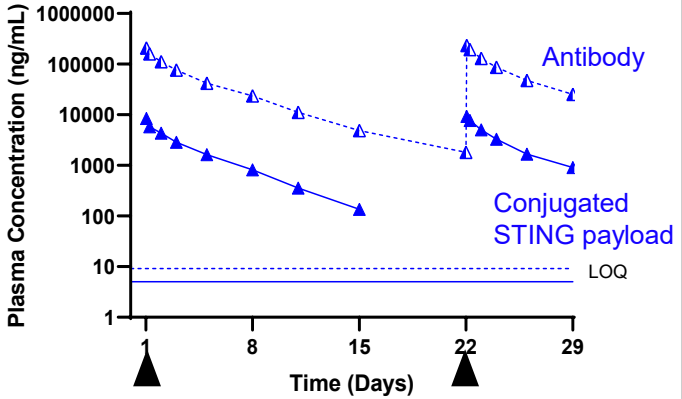
**Highly efficacious in various human xenograft models**




- Target dependent anti-tumor activity after a single dose of 1 mg/kg ADC

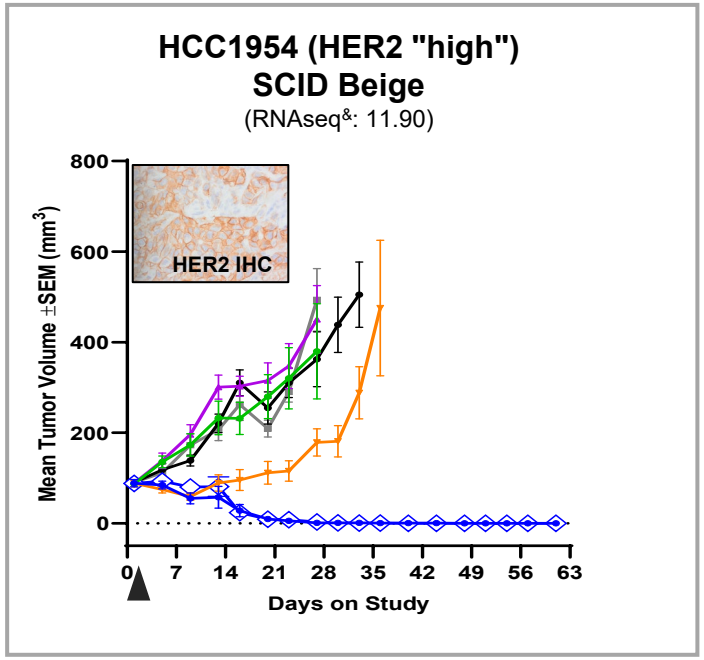
### In Vivo – Non-Human Primate (NHP)

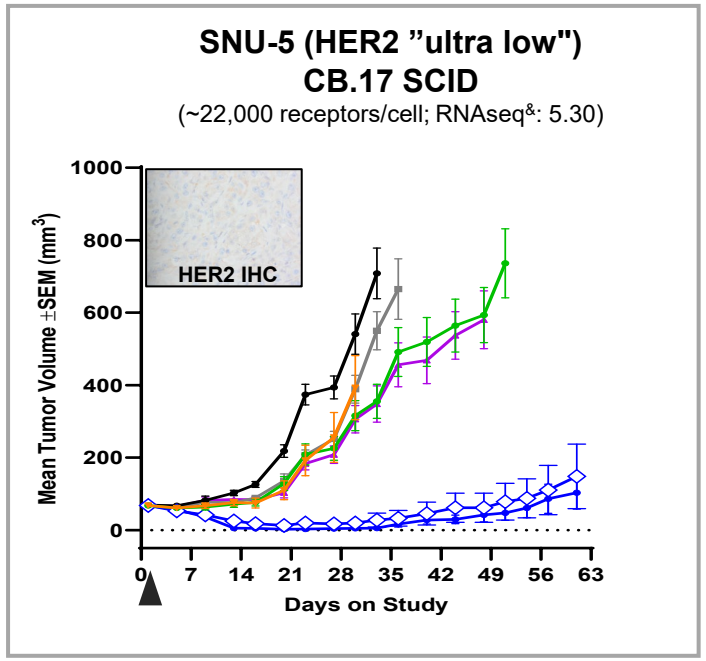
**High, consistent exposures after repeat IV doses**




- High stability as indicated by parallel curves of antibody and conjugated drug
- Comparable PK profiles after 1st and 2nd dose

# XMT-2056 Outperforms diABZI IV STING Agonist and Trastuzumab TLR7/8 ISAC in Her2$^{high}$ and HER2$^{low}$ Models




**Vehicle**

**diABZI IV STING agonist (1.5 mg/kg; q3dx3, IV)***

**Trastuzumab (10 mg/kg; qdx1, IP)**

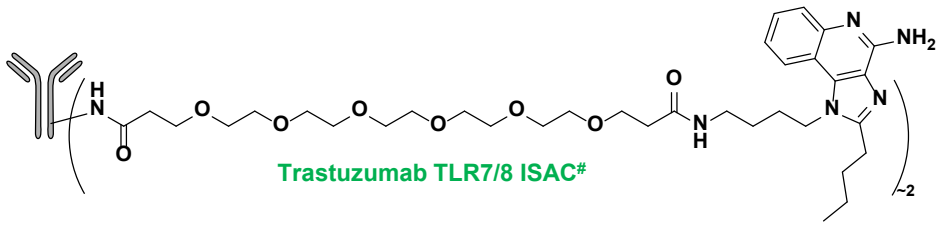
**Non-binding Control STING ADC (3 / 0.112 mg/kg; qdx1, IV)**

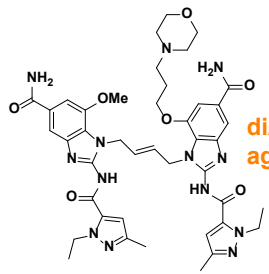
**Trastuzumab TLR7/8 ISAC (5 / 0.033 mg/kg; q5dx6, IP)#**

**XMT-2056**

- **(1.0 / 0.043 mg/kg; qdx1, IV)**
- **◇ (0.3 / 0.013 mg/kg; q5dx6, IP)**

(Doses reflect mAb / payload mg/kg)



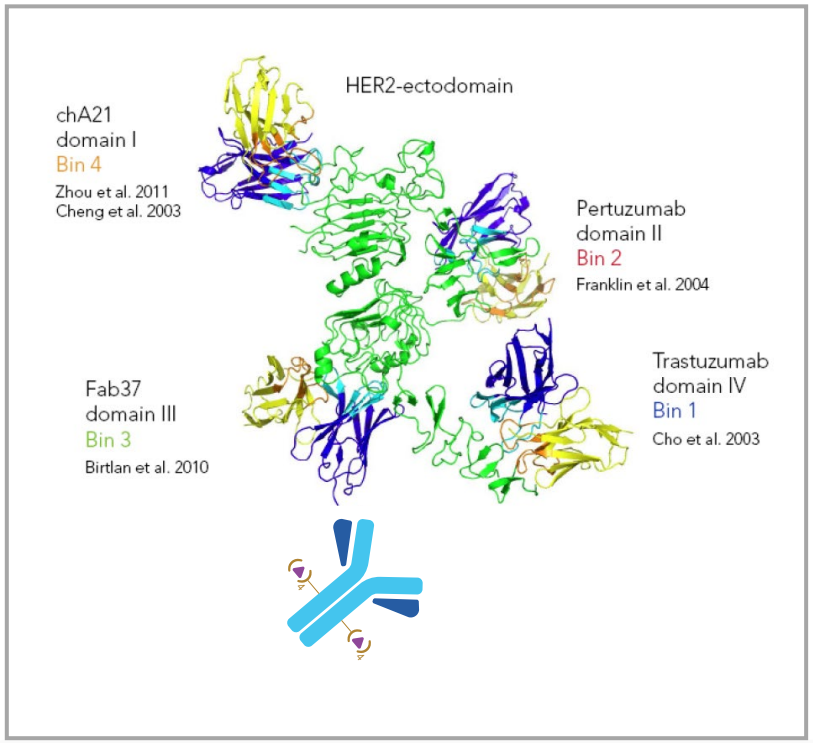

*agonist described in Ramanjulu *et al.* (2018) *Nature* (compd 3 in reference)

#TLR7/8 ISAC described in Ackerman *et al*, (2020) *Nature Cancer*

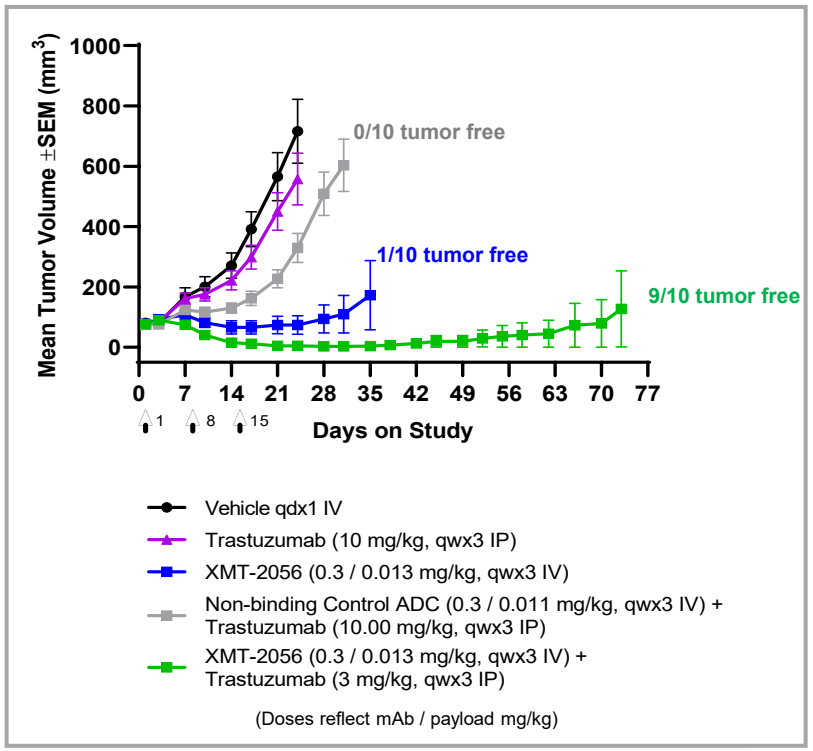
&CCLE RNAseq data from DepMap, Broad (2021): DepMap 21Q3 Public

# XMT-2056 Targets a Novel HER2 Epitope Distinct from Trastuzumab and Pertuzumab Allowing for Combinability

## XMT-2056 Binds to a Novel Epitope

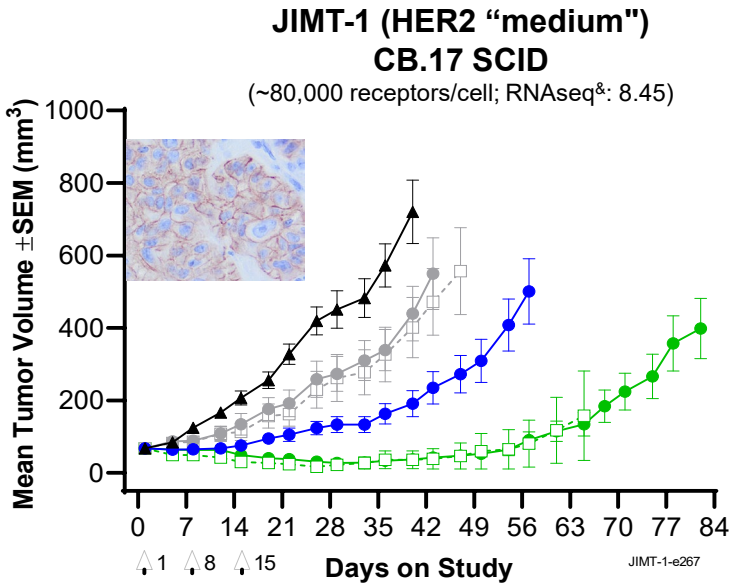



## HER2 (SKOV3) QWx3 regimen




**XMT-2056 Offers a Potentially Differentiated and Complementary Approach to the Treatment of HER2-Expressing Tumors**

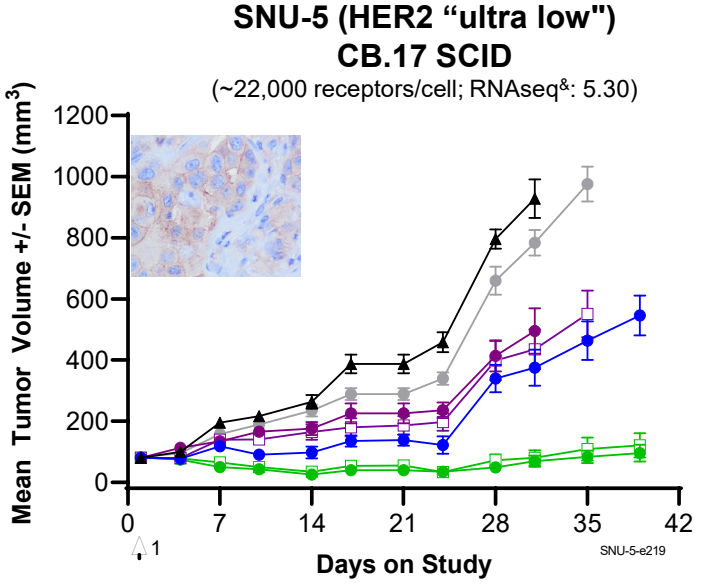
# Combination of XMT-2056 with Trastuzumab Or Pertuzumab Shows Benefit *In Vivo*




Vehicle
XMT-2056 (0.3 / 0.013 mg/kg, IV)
Non-binding control ADC (0.3 / 0.011 mg/kg, IV) + Tras or Pert (3 mg/kg, IP)
XMT-2056 (0.3 / 0.013 mg/kg, IV) + Tras or Pert (3 mg/kg, IP)

(ADC doses by mAb / payload mg/kg)

Trastuzumab
Pertuzumab



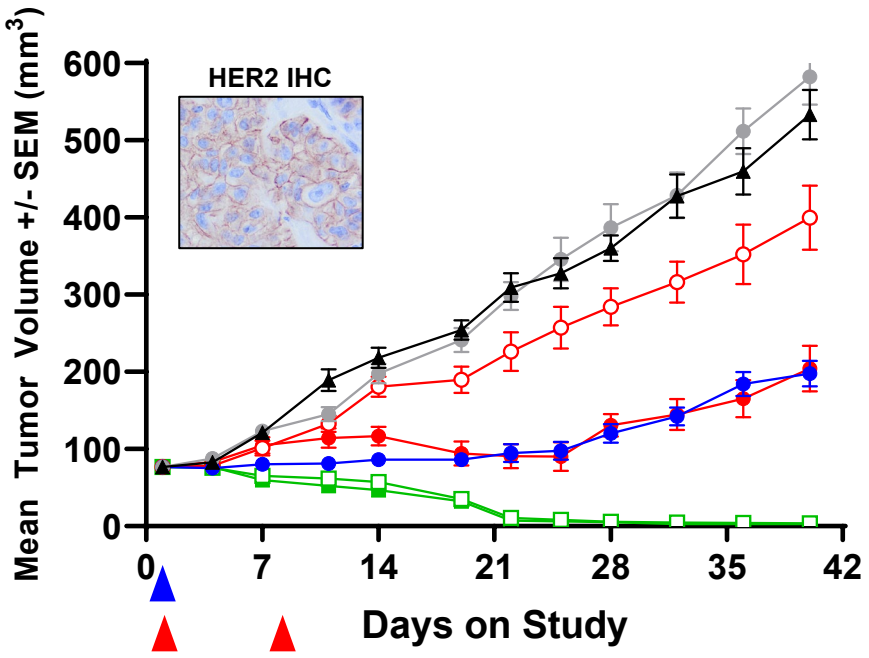

Vehicle
Trastuzumab or Pertuzumab (2 mg/kg, IP)
Non-binding control ADC (0.2 / 0.007 mg/kg, IV)
XMT-2056 (0.2 / 0.009 mg/kg, IV)
XMT-2056 (0.2 / 0.009 mg/kg, IV) + Tras or Pert (2 mg/kg, IP)

(ADC doses by mAb / payload mg/kg)

&CCLE RNAseq data from DepMap, Broad (2021): DepMap 21Q3 Public

# Benefit from Combination of XMT-2056 with Enhertu (trastuzumab deruxtecan) in a Tras$^{R}$ Model

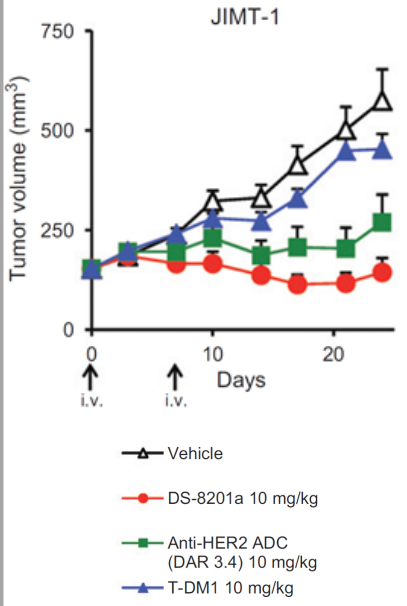
**JIMT-1 (HER2 "med")**
**XMT-2056 + Enhertu**




- Vehicle (qwx2 IV)
- Non-binding Control ADC (1.00 / 0.037 mg/kg, qdx1 IV)
- XMT-2056 (1.00 / 0.043 mg/kg, qdx1 IV)
- Enhertu (3.00 / 0.078 mg/kg, qwx2 IV)
- **Enhertu (10.00 / 0.261 mg/kg, qwx2 IV)** — Published regimen
- XMT-2056 (1.00 / 0.043 mg/kg, qdx1 IV) + Enhertu (3.00 / 0.078 mg/kg, qwx2 IV)
- XMT-2056 (1.00 / 0.043 mg/kg, qdx1 IV) + Enhertu (10.00 / 0.261 mg/kg, qwx2 IV)

(Doses by mAb / payload mg/kg)

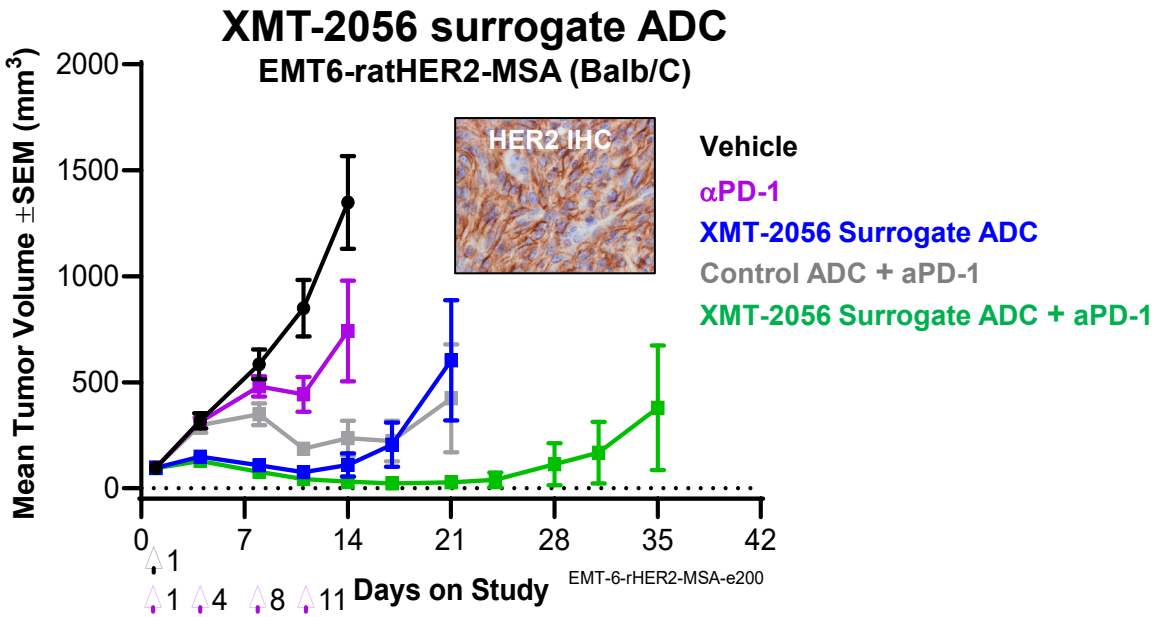
Daiichi published data




Clin Cancer Res; 22(20) October 15, 2016

# Benefit from Combining XMT-2056 Surrogate with αPD1, and No Adverse Clinical Signs, in a ratHER2 Engineered Syngeneic Tumor

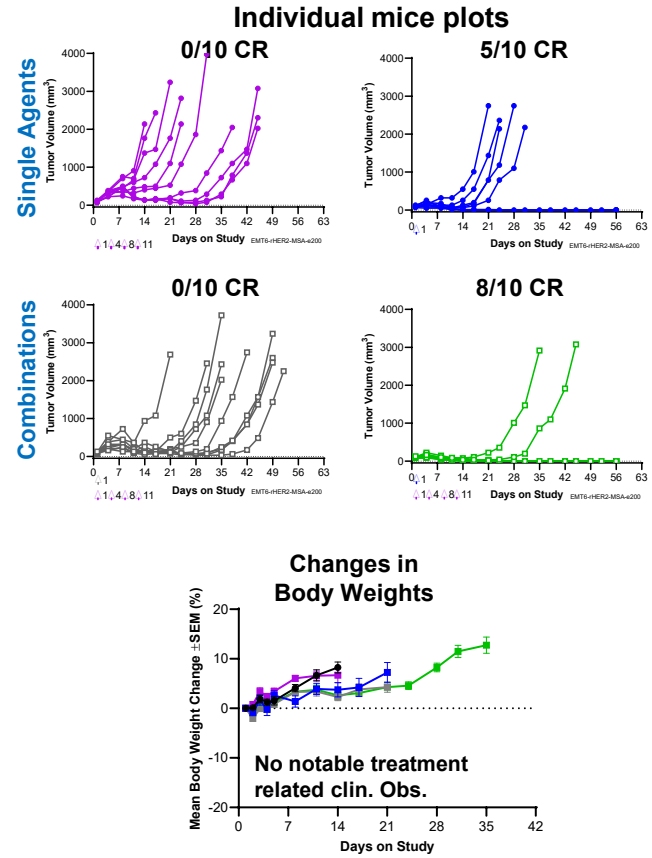
Rat HER2 expressed in EMT-6 mouse breast cancer model




αPD1 (5 mg/kg), biwx2, IP

Control ADC (0.3 / 0.012 mg/kg), single IV dose

XMT-2056 Surrogate ADC (0.3 / 0.01 mg/kg), single IV dose
(mAb = murine IgG2a targeting ratHER2)



# XMT-2056 Displays a Wide Therapeutic Index Based on Exposure in Relevant Pre-clinical Species

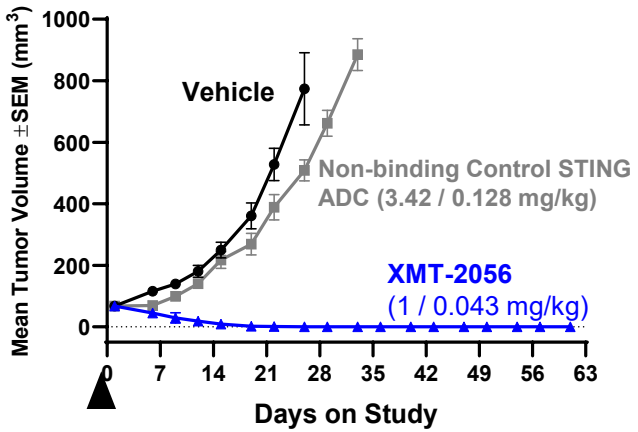
## NHP Results

Repeat dose studies at <u>36 mg/kg antibody i.v.</u>

- No clinical signs, no mortality (NOAEL)
- High exposure, high ADC stability in circulation
- Transient elevation of 5 cytokines out of 24 tested
- No adverse changes in clinical pathology
- No adverse findings in histopathology

**In Vivo – Mouse**

**Highly efficacious in various human xenograft models**




Target dependent anti-tumor activity after a single dose of 1 mg/kg ADC

# XMT-2056 - Summary

XMT-2056 offers a novel approach to the treatment of HER2-expressing tumors

Preclinical data to date shows it:

- Utilizes a novel antibody that is non-competitive with trastuzumab and pertuzumab
- Demonstrates target-dependent STING activation of tumor cells and tumor-resident immune cells, both of which can contribute to the anti-tumor effect
- Is highly efficacious as single agent and in combination with trastuzumab
- Is well-tolerated with no adverse events in NHPs after repeat doses at exposures far exceeding those required for efficacy in mouse

IND has cleared and dosing to begin in the near future

# Acknowledgements

I would very much like to acknowledge the tireless efforts of the multi-disciplinary team at Mersana, including Research, CMC, Clinical Development, Regulatory, and many others, to bring XMT-2056 to the clinic, as well as our collaborators as we continue to advance it for the potential benefit of patients