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XMT-2056, a HER2-targeted Immunosynthen STING agonist antibody-drug conjugate, induces anti-tumor activity at low doses in preclinical models

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ABSTRACT

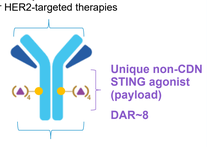
Activation of innate immune signaling within tumors has the potential to be effective against tumors, including those that are refractory or resistant to checkpoint inhibitors. We hypothesized that using an antibody-drug conjugate (ADC) bearing an innate immune activator payload would target delivery of the immune agonist to antigen-expressing tumor lesions after systemic administration, resulting in tumor-specific immune activation while minimizing toxicities associated with peripheral immune responses. We previously described XMT-2056, a systemically administered Immunosynthen STING agonist ADC that binds to a novel HER2 epitope and activates STING signaling in tumor cells and tumor-resident immune cells, thereby inducing an anti-tumor immune response. Here, we extend the body of preclinical data on XMT-2056 and discuss the potential implications for its clinical development strategy. We demonstrate that XMT-2056 effectively induces cytokine production and cancer cell-killing in PBMC co-cultures with cancer cells that express very low levels of HER2. These data complement previous results in higher HER2-expressing models and emphasize the potential for treating HER2-low tumors with XMT-2056. We further demonstrate that XMT-2056, when administered to mice at very low doses, activates STING signaling in tumors and upregulates immune pathway genes, including PD-L1, resulting in significant tumor growth inhibition. Together, these results underscore the therapeutic potential of XMT-2056 in treating tumors with various levels of HER2-expression and support its ongoing clinical exploration in a Phase 1 dose escalation study in patients with solid tumors expressing HER2 (NCT05514717).

BACKGROUND

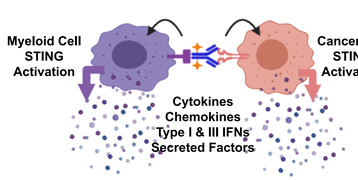
XMT-2056: a HER2-Directed STING Agonist ADC

- Proprietary Immunosynthen ADC platform
- Systemically administered
- Tumor-targeted delivery of STING agonist
- Potent target-dependent anti-tumor activity in tumor models[1]
- Improved efficacy and reduced systemic cytokines compared to a systemically administered diABZI STING agonist[2] in mice
- Well-tolerated in repeat dose toxicology studies in NHP
- A Phase I dose escalation clinical trial is ongoing (NCT05514717)

Binds to a novel epitope of HER2
Does not compete with trastuzumab or pertuzumab
Opportunity to combine with other HER2-targeted therapies



XMT-2056 Activates STING in Both Tumor Cells and Tumor-Resident Myeloid Cells

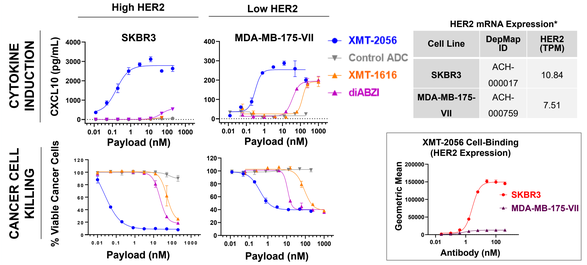


XMT-2056 binds to HER2 on tumor cells and Fcγ receptors on tumor-resident myeloid cells, leading to internalization and STING activation in both cell types. Subsequent release of type I & type III interferons, as well as other key chemokines and cytokines mediate the anti-tumor activity of XMT-2056 (see reference 3 for detailed mechanism of action of tumor cell-targeted STING agonist ADCs).

RESULTS

XMT-2056 is Active in Both High-HER2 and Low-HER2 Tumor Models

Cancer Cell / PBMC Co-Cultures In Vitro



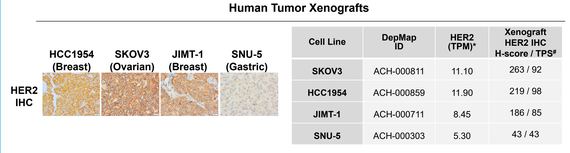
HER2 mRNA Expression*

Cell Line	DepMap ID	HER2 (TPM)
SKBR3	ACH-000017	10.84
MDA-MB-175-VII	ACH-000759	7.51

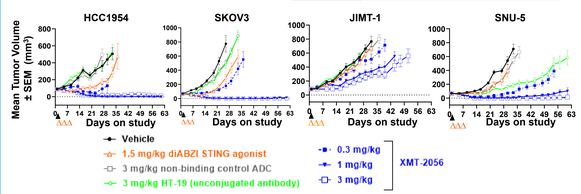
XMT-2056 induces significant levels of cytokines and cancer cell death in co-cultures of PBMCs and cancer cells expressing high HER2 (SKBR3) or low HER2 (MDA-MB-175-VII) in vitro (HER2 antigen-dependent), outperforming the systemically administered diABZI STING agonist or the XMT-1616 (free payload of XMT-2056).
* RSEM; Log2 transformed. Obtained from DepMap 21Q2 (public), Broad Institute (2021).

Mouse Tumor Models with Varying HER2 Expression Levels In Vivo

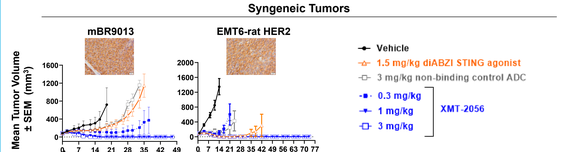
Human Tumor Xenografts



Cell Line	DepMap ID	HER2 (TPM)*	Xenograft HER2 IHC H-score / TPS#
SKOV3	ACH-000811	11.10	263 / 92
HCC1954	ACH-000859	11.90	219 / 98
JIMT-1	ACH-000711	8.45	186 / 85
SNU-5	ACH-000303	5.30	43 / 43



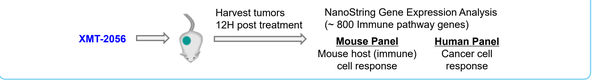
Syngeneic Tumors



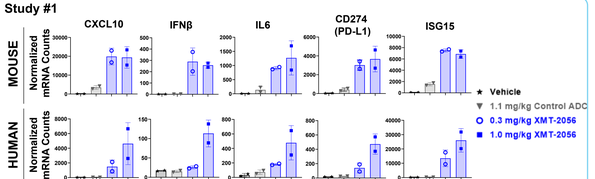
A single dose of intravenous XMT-2056 treatment leads to tumor regressions in multiple tumor models expressing various levels of HER2 in vivo. XMT-2056 surrogate ADC targeting rat HER2 was used in the syngeneic mBR9013 (rat HER2-expressing GEMM-derived tumor model) and in the EMT6-rat HER2 (EMT6 engineered to express rat HER2) models. ADC & HT-19 (unconjugated antibody) doses are based on antibody.
* mRNA expression based on RSEM; Log2 transformed. Obtained from DepMap 21Q2 (public), Broad Institute (2021).
# Image analysis was conducted with HER2 algorithms built with HALO multiplex IHC software. TPS = Tumor Proportion Score.

XMT-2056 Activates STING Pathway in Tumors at Low Doses In Vivo

Tumor PD Study Design (SKOV3 (HER2) / CB.17 SCID Xenograft Model)

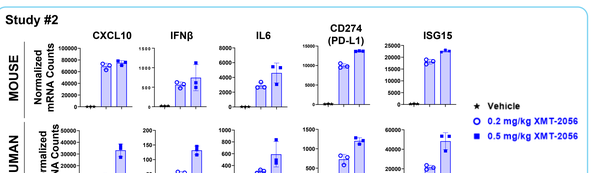


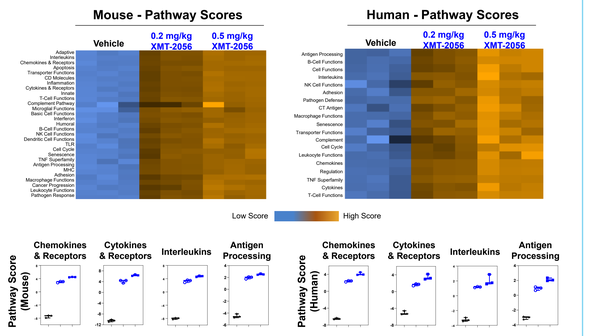
Study #1



XMT-2056 at 0.3 mg/kg dose induces significant levels of mouse and human STING pathway genes in the SKOV3 tumors, demonstrating activation in both tumor cells and tumor-resident mouse cells. Non-binding control ADC in general induces minimal gene expression at 1 mg/kg dose, indicating that STING activation in tumors by XMT-2056 is target-dependent.

Study #2

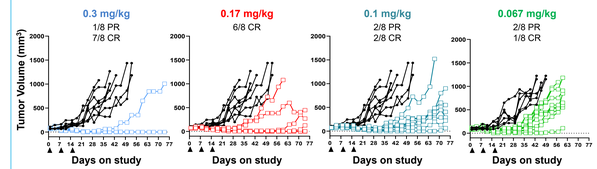




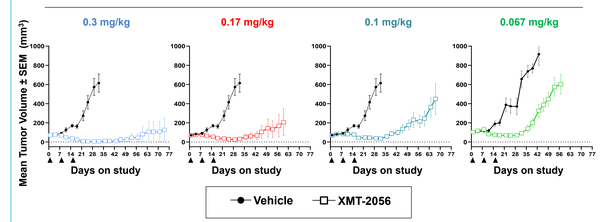
In this independent tumor PD study, a lower dose of XMT-2056 (0.2 mg/kg) also induced significant levels of STING pathway genes in SKOV3 tumors. Heat maps of immune pathway scores demonstrate that XMT-2056 treatment even at 0.2 mg/kg low dose leads to marked changes in immune pathways in SKOV3 tumors. (Orange → high scores, blue → low scores) Graphs shown in the bottom panel are the example pathway scores vs treatment.

XMT-2056 is Efficacious at Low Doses In Vivo

Individual Tumor Volumes



Mean Tumor Volumes



Three weekly administrations (IV) of XMT-2056 at doses as low as 0.067 mg/kg result in partial and complete responses in SKOV3 / CB.17 SCID human tumor xenograft model in vivo. XMT-2056 dose is based on antibody.

CONCLUSIONS

- We have previously shown that XMT-2056, a HER2-targeted STING agonist ADC, activates STING in cancer cells and myeloid cells in a HER2-dependent manner, resulting in potent anti-tumor activity in multiple tumor models.
- In this study, we demonstrated:
  - XMT-2056 induces STING pathway and cancer cell killing activity in co-cultures of PBMCs and cancer cells expressing both high and very low levels of HER2 in vitro.
  - XMT-2056 is efficacious in multiple human tumor xenograft (CDX) and syngeneic mouse models expressing varying levels of HER2 in vivo.
  - Low doses of XMT-2056 activate STING and immune pathways in human tumor xenografts and inhibit tumor growth in vivo.
- These results underscore the therapeutic potential of XMT-2056 in treating tumors with various levels of HER2-expression and support its ongoing clinical exploration in a Phase 1 dose escalation study in patients with solid tumors expressing HER2 (NCT05514717).

References:

1. Duvall et al. AACR 2022 https://www.mersana.com/publications/
2. Ramanjulu et al. Nature 2018 PMID: 30405246
3. Malli Cetinbas et al. Nature Communications 2024 PMID: 38992037
4. Cartoons were generated using biorender.com.