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XMT-2056, a HER2-targeted Immunosynthen STING-agonist antibody-drug conjugate, binds a novel epitope of HER2 and shows increased anti-tumor activity in combination with trastuzumab or pertuzumab

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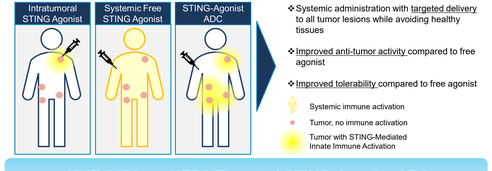
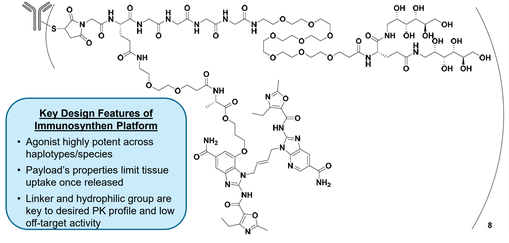
Abstract - We present here a novel therapeutic agent, XMT-2056, that results in robust anti-tumor activity mediated by an immune response through targeted delivery of a STING agonist to the tumor microenvironment. By leveraging an antibody-drug conjugate (ADC) strategy, systemic administration of a STING agonist with tumor-targeted delivery can be achieved, potentially overcoming limitations of either intratumoral or intravenous administrations of unconjugated, small molecule STING agonists. XMT-2056 was generated through conjugation of Immunosynthen, a platform that employs a novel STING agonist payload specifically designed for ADCs, to HT-19, a HER2-targeting antibody which binds to a novel epitope and does not compete for binding with either trastuzumab or pertuzumab. Initial results showed XMT-2056 has target-dependent anti-tumor activity in vivo and is well tolerated in non-human primates at significantly higher exposure levels than those required for anti-tumor activity.

To evaluate the impact of HER2 expression level on the activity of XMT-2056, in vivo studies in gastric and breast cancer models with varying HER2 expression levels were conducted, and XMT-2056 showed potent anti-tumor activity in a dose dependent and target dependent manner including in models with very low expression of HER2. Because the antibody employed in XMT-2056 does not compete for binding with trastuzumab or pertuzumab, we hypothesized that there could be benefit in combining with such approved HER2-targeted therapies. This advantage was demonstrated in vivo as the combination of XMT-2056 and trastuzumab, pertuzumab, or trastuzumab deruxtecan showed greater anti-tumor activity compared to the administration of either agent alone. The improved activity could be attributed to increased internalization due to binding to non-overlapping epitopes or Fc receptor clustering. Given the innate immune activation by XMT-2056, there is also a strong rationale for combination with immune checkpoint inhibitors. To this end, administration of an XMT-2056 surrogate ADC in combination with an anti-PD1 agent improved anti-tumor activity and improved immunological memory in a ratHER2-engineered EMT-6 syngeneic mouse model. Together these data support the potential of XMT-2056 both as a monotherapy and in combination with other HER2 targeted agents as well as checkpoint inhibitors.

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



XMT-2056 – a HER2-Targeted STING Agonist ADC



Key Design Features of Immunosynthen Platform

- Agonist highly potent across haplotypes/species
- Payload's properties limit tissue uptake once released
- Linker and hydrophilic group are key to desired PK profile and low off-target activity

Novel HER2-Targeted Antibody Binds to a Novel Epitope Compared to Approved HER2-Targeted Agents

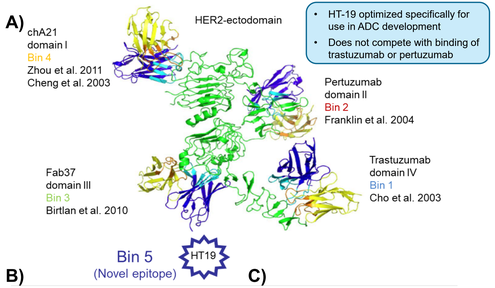


Figure 1. HT-19, the antibody component of XMT-2056, binds to a different epitope than that of trastuzumab or pertuzumab. A) Epitope mapping of HT-19 on HER2 ECD showing binding location compared to other known HER2 binding epitopes; **B)** and **C)** HER2 binding as assessed by Octet. HT-19 (as indicated by the second rise in the signal when the HT-19 is added) was still able to bind to HER2 ECD even after trastuzumab (B) or pertuzumab (C) was already bound to the protein.

XMT-2056 Activates STING in a Target-Dependent Manner Leading to Improved Cancer Cell Killing Over Free Payload

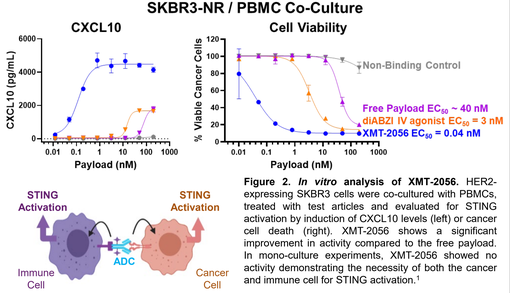


Figure 2. *In vitro* analysis of XMT-2056. HER2-expressing SKBR3 cells were co-cultured with PBMCs, treated with test articles and evaluated for STING activation by induction of CXCL10 levels (left) or cancer cell death (right). XMT-2056 shows a significant improvement in activity compared to the free payload. In mono-culture experiments, XMT-2056 showed no activity demonstrating the necessity of both the cancer and immune cell for STING activation.[1]

XMT-2056 Demonstrates Robust Anti-Tumor Activity in In Vivo Models with Varying HER2 Expression Levels

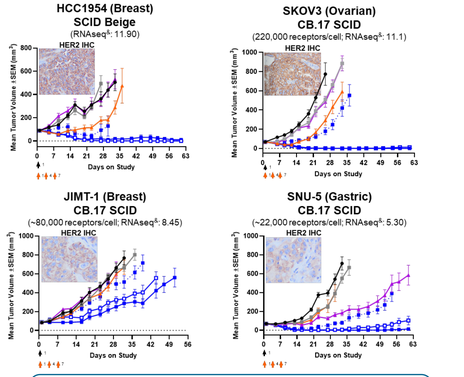


Figure 3. XMT-2056 induced durable and complete tumor regressions in xenograft mouse models at significantly lower doses by payload than the IV administered diABZI STING agonist.[2] Single doses of XMT-2056 administered intravenously resulted in tumor regression in a dose dependent manner. Control ADC and unconjugated mAb (HT-19) at equivalent doses show little to no effect demonstrating the advantage of the ADC. The diABZI IV agonist (administered as described in reference 2) showed only modest effect on tumor growth inhibition. IHC generated using a rabbit polyclonal HER2 concentrate.

XMT-2056 Induces Anti-Tumor Activity in Multiple Syngeneic Models

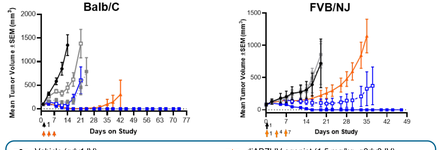


Figure 4. An XMT-2056 surrogate ADC induced durable and complete tumor regressions in syngeneic mouse models. Single doses of an XMT-2056 surrogate ADC administered intravenously resulted in tumor regression in a dose dependent manner. The XMT-2056 surrogate was made by substituting HT-19 with a mouse mAb targeting rat HER2. The EMT-6 model had been engineered to express rat HER2. mBR9013 is an MMTV-ratErbb2 GEMM derived tumor model shown to be refractory to immune checkpoint inhibitors.

Improved Anti-Tumor Activity When Combining XMT-2056 with Trastuzumab or Pertuzumab

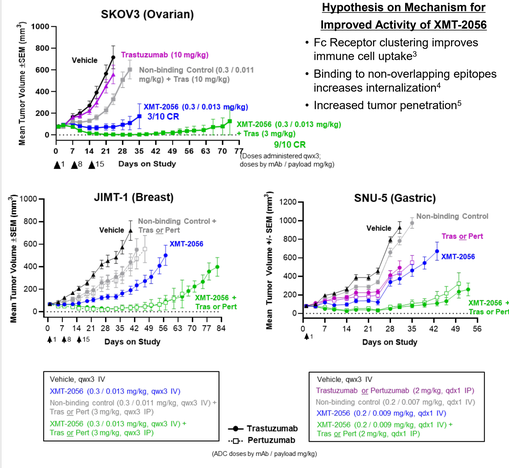


Figure 5. XMT-2056 in combination with trastuzumab or pertuzumab showed improved anti-tumor activity. XMT-2056 and trastuzumab or pertuzumab were administered in combination and led to improved anti-tumor activity in multiple tumor models compared to single agents. Dosing the non-binding control ADC in combination with trastuzumab or pertuzumab resulted in little activity demonstrating target dependence.

Trastuzumab Deruxtecan Activity Improved when Combined with XMT-2056

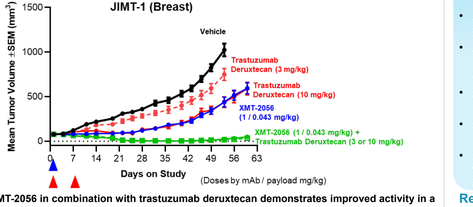


Figure 6. XMT-2056 in combination with trastuzumab deruxtecan demonstrates improved activity in a trastuzumab resistant breast cancer model. XMT-2056 and trastuzumab deruxtecan were administered in combination (XMT-2056 dosed once IV; trastuzumab deruxtecan dosed weekly for 2 weeks IP) and led to improved anti-tumor activity in a breast (JIMT-1) model. Monotherapy results for trastuzumab deruxtecan at 10 mg/kg dose were consistent with that previously published.[6]

Anti-PD1 Activity Improved When Combined with XMT-2056 in a Syngeneic Mouse Model

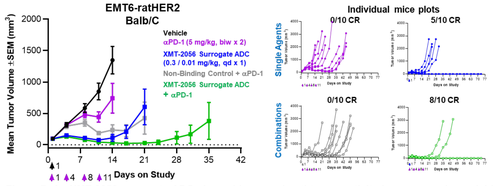


Figure 7. An XMT-2056 surrogate ADC showed improved anti-tumor activity in a syngeneic model in combination with a mouse αPD1. XMT-2056 surrogate ADC and αPD-1 were administered in combination (XMT-2056 surrogate dosed IV; αPD-1 dosed IP) and led to improved anti-tumor activity in an EMT-6 model engineered to express rat HER2. The XMT-2056 surrogate was made by substituting HT-19 with a mouse mAb targeting rat HER2.

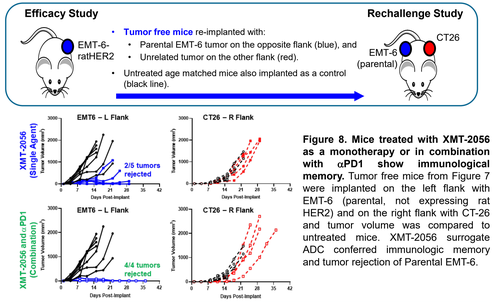


Figure 8. Mice treated with XMT-2056 as a monotherapy or in combination with αPD1 show immunological memory. Tumor free mice from Figure 7 were implanted on the left flank with EMT-6 (parental, not expressing rat HER2) and on the right flank with CT-26 and tumor volume was compared to untreated mice. XMT-2056 surrogate ADC conferred immunologic memory and tumor rejection of Parental EMT-6.

Conclusions

- XMT-2056, an Immunosynthen STING-agonist ADC targeting HER2, leverages an antibody that binds to a different epitope compared to that of trastuzumab and pertuzumab.
- XMT-2056 showed robust anti-tumor activity after a single IV dose in xenograft and syngeneic models, including a low HER2-expressing model.
- XMT-2056 showed improved anti-tumor activity when combined with trastuzumab, pertuzumab, or trastuzumab deruxtecan due to binding to non-overlapping epitopes of HER2 and complimentary mechanisms of anti-tumor activity.
- XMT-2056 in combination with an αPD-1 showed improved anti-tumor activity in a syngeneic mouse model.
- XMT-2056 as a monotherapy or in combination with an αPD-1 conferred immunologic memory when tumor free mice were rechallenged.
- XMT-2056 offers a differentiated approach for targeted innate immune activation with STING, with greater ability to target all tumor lesions than intratumoral delivery, and potential for significantly improved anti-tumor activity and tolerability compared to free agonist.

References:

1. For a more in-depth discussion on the mechanism of XMT-2056, please refer to abstract #4873.
2. Ramanjulu et al. ***Nature*** 2018, 564: 438-443.
3. Brandsma et al. ***Sci Signal.*** 2018, 11: eeaq0891.
4. Pedersen et al. ***Mol Cancer Ther.*** 2015, 14: 669-680.
5. Cilliers et al. ***Cancer Res.*** 2018, 78: 758-768.
6. Ogitani et al. ***Clin. Cancer Res.*** 2016, 22: 5097-5108.