A novel, highly potent HER2-targeted antibody-drug conjugate (ADC) for the treatment of low HER2-expressing tumors and combination with trastuzumab-based regimens in HER2-driven tumors

Mersana THERAPEUTICS

Abstract LBA-231

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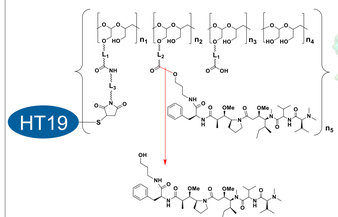
Abstract

Antibody-drug conjugates are effective in the treatment of HER2-amplified breast cancer and Hodgkin's lymphoma, but current ADC technologies have faced limitations expanding the addressable patient population and target space. Ado-trastuzumab emtansine (T-DM1) is an ADC with 3-4 cytotoxic drugs per antibody that was recently approved for HER2 IHC 3+ or HER2-amplified breast cancer. Even within this high HER2-expressing population, several studies have now shown greater T-DM1 benefit in patients with HER2 mRNA expression above the median. These data suggest the need for more potent anti-HER2 ADCs to maximize benefit for HER2 IHC 3+ or amplified patients, and to extend HER2 ADC therapy to low HER2-expressing patients (HER2 IHC 1+/2+). XMT-1522 is an anti-HER2 ADC that uses a novel, human anti-HER2 antibody optimized for cytotoxic payload delivery, and is non-competitive with trastuzumab or pertuzumab for HER2 binding. Each antibody is conjugated to ~15 proprietary auristatin molecules using Fleximer, a biodegradable hydrophilic polymer. XMT-1522 shows nanomolar potency in cultured tumor cells with HER2 receptor densities as low as 10,000 per cell, and is typically 1-3 logs more potent than T-DM1 across a panel of 25 tumor cell lines. In mouse xenograft studies XMT-1522 has excellent pharmacokinetic properties and achieves complete tumor regressions at well-tolerated doses. In the high HER2-expressing N87 gastric cancer model (800,000 HER2 receptors/cell), complete regressions are achieved with a single 1 mg/kg dose of XMT-1522, while 10 mg/kg T-DM1 is required for comparable activity. In the same model, the XMT-1522/trastuzumab/pertuzumab triple combination results in tumor regressions where the same doses of XMT-1522 alone or the trastuzumab/pertuzumab doublet result in tumor stasis. In the low HER2-expressing JIMT-1 breast cancer (79,000 HER2/cell) and SNU5 gastric cancer (22,000 HER2/cell) models, complete regressions are achieved with single 1 mg/kg or 0.67 mg/kg doses of XMT-1522, respectively, while T-DM1 is inactive at doses ≥10 mg/kg. In non-human primates XMT-1522 demonstrates good stability of drug conjugate in plasma with t1/2 ~5 days (comparable to antibody t1/2) and minimal exposure to free payload. Despite the high potency of XMT-1522 in low HER2 tumor models, there is no XMT-1522-related toxicity observed in critical HER2-expressing tissues including heart and lung. The preclinical data support testing XMT-1522 as a single agent in tumors with low HER2 expression where current HER2-directed therapies are not indicated. Furthermore, combination of XMT-1522 with trastuzumab and/or pertuzumab achieves efficient cytotoxic payload delivery while retaining the potential for full inhibition of HER2 signaling, which may be necessary to improve on current regimens in HER2-driven tumors.

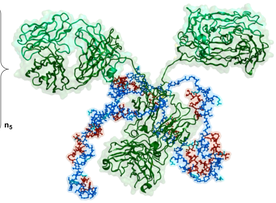
XMT-1522 Structure

XMT-1522 Key features:

- Average of ~15 auristatin-derived payload molecules per antibody
- Drug-like properties enabled via Fleximer polymer conjugation
- Built on novel mAb (HT-19) optimized for ADC; binds to a unique epitope distinct from trastuzumab or pertuzumab



Release product: Auristatin F-HPA

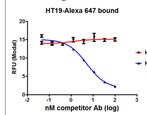


Green = mAb
Blue = Fleximer polymer
Red = Auristatin F-HPA payload

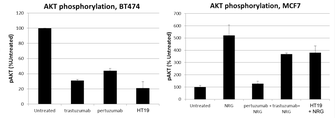
- Molecular weight of each polymer is ~8 to ~14 kDa by SEC
- 4-5 Auristatin F-HPA payload molecules loaded per polymer
- Intracellular cleavage of drug-polymer linker
- 3-5 polymers conjugated primarily to hinge region cysteines

Characterization of HT-19 mAb

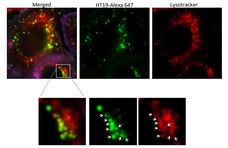
(A) HT-19 does not compete with trastuzumab for HER2-binding



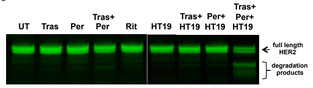
(B) HT-19 is comparable to trastuzumab for inhibition of HER2 signaling



(C) HT-19 efficiently internalizes



(D) HT-19 enhances HER2 degradation in combination with trastuzumab and pertuzumab

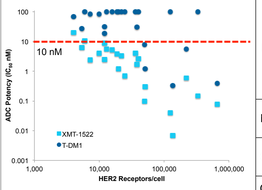


(A) JIMT-1 cells were incubated with 30nM of HT-19 conjugated to Alexa-fluor 647 and increasing concentrations of trastuzumab or unlabeled HT-19. The cells were washed, fixed and the amount of bound fluorescence was determined by flow cytometry. HT-19 binds to recombinant human HER2 with half maximal binding (EC50) of 0.03 nM based on ELISA method (data not shown).
(B) Inhibition of ligand-independent signaling (BT474, left panel) and ligand-dependent signaling (MCF7 + neuregulin, right panel).
(C) SKBR3 cells were incubated with 5 ug/ml HT-19-Alexa fluor 647 for 1 hour on ice, washed, and incubated for 24 hours. The cells were stained with Lysotracker and Cell Mask Orange and imaged microscopically.
(D) SKBR3 cells were incubated with 10 ug/ml of each antibody for 3 hours. The cells were then harvested and cell lysates were fractionated by gel electrophoresis and HER2 detected by western analysis. The percent of full-length HER2 remaining relative to untreated control is shown for each antibody treatment.

XMT-1522 *in vitro* Potency

XMT-1522 shows sub-nanomolar potency in cell lines with ~25,000 HER2 receptors per cell and is 1-3 logs more potent than Kadcyla *in vitro*

ADC potency vs HER2 expression



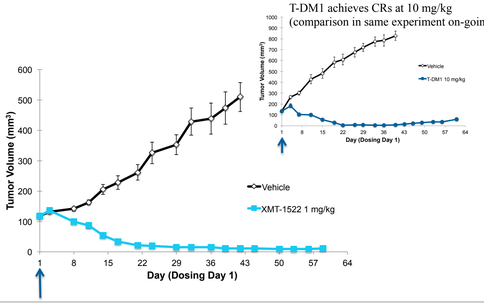
Tumor Type	Cell line	HER2 Receptors/cell	XMT-1522 Fold Potency Increase
Breast	MDA-MB-361	135,000	47X
	MDA-MB-453	125,000	>2500X
	MDA-MB-175VII	51,000	4X
	CAMA-1	50,000	78X
	ZR75-1	40,000	>37X
	HCC1187	38,000	18X
	HCC38	36,000	>25X
	T47D	20,000	>83X
NSCLC	NCI-H2170	660,000	5X
	CALU3	330,000	>667X
	NCI-H522	25,000	>143X
Gastric	SNU5	22,000	>30X
	KATOIII	19,000	>26X
	MKN45	16,000	>19X
Ovarian	SKOV3	220,000	9X
	TOV21G	12,000	3X

XMT-1522 consistently demonstrates single digit nanomolar potency in cell lines with greater than 10,000 HER2 receptors per cell. In contrast, T-DM1 achieves sub-nanomolar potency only in cell lines with greater than 100,000 HER2 receptors per cell and is inactive ($IC_{50} \geq 100$nM) in a majority of cell lines with fewer than 100,000 HER2 receptors per cell.

XMT-1522 Achieves Complete Tumor Regressions Across HER2 Expression Levels with Single Doses ≤ 1 mg/kg

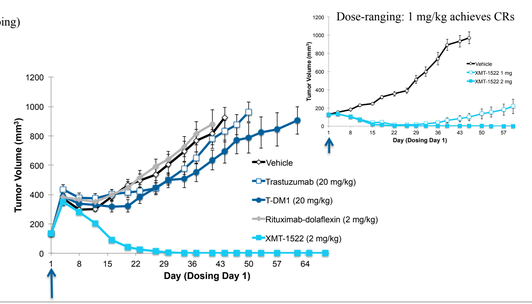
HER2 3+: N87 gastric cancer xenograft
~800,000 HER2 receptors per cell
HER2-amplified
T-DM1 sensitive

T-DM1 achieves CRs at 10 mg/kg (comparison in same experiment on-going)

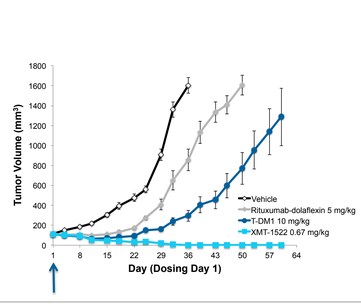


HER2 2+: JIMT-1 breast cancer xenograft
~79,000 HER2 receptors per cell
HER2-amplified
T-DM1 and trastuzumab insensitive

Dose-ranging: 1 mg/kg achieves CRs

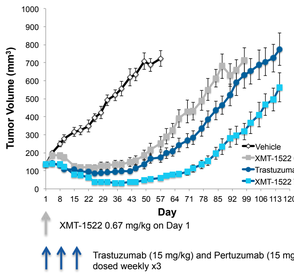


HER2 1+: SNU5 gastric cancer xenograft
~22,000 HER2 receptors per cell
HER2 non-amplified
T-DM1 insensitive

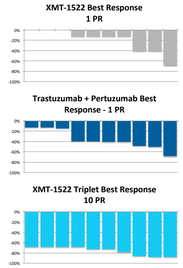


XMT-1522 Combines with Trastuzumab + Pertuzumab

(A) Significantly longer survival ($p<.05$) for XMT-1522 triplet compared to XMT-1522 monotherapy or trastuzumab + pertuzumab doublet



(B) Increased rate of tumor regressions for XMT-1522 triplet compared to XMT-1522 monotherapy or trastuzumab + pertuzumab doublet

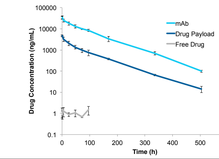


(A) N87 tumor cell xenografts were randomized and treated after reaching volumes of 100-200 mm^3. Treatment began on day 1 with a tumor static dose of XMT-1522 (0.67 mg/kg single dose) or fully active dose of the trastuzumab + pertuzumab combination (15 mg/kg of each antibody dosed weekly for 3 weeks). Tumors were allowed to grow to an endpoint voulme of 800 mm^3. The logrank test was used to evaluate the significance of the survival benefit of the triplet compared to the other therapies.
(B) Best tumor response over the course of the study presented as a waterfall plot. Partial response is defined as regression to less than 50% of baseline tumor volume sustained over at least 3 sequential tumor measurements. The XMT-1522 triplet had a numerically higher rate of partial responses, and led to a significantly greater reduction in tumor volume ($p<.05$, Mann-Whitney test) compared to either XMT-1522 monotherapy or the trastuzumab + pertuzumab doublet.

XMT-1522 Has a Favorable Therapeutic Index in Exploratory Studies

XMT-1522 dosed at 2.5 mg/kg (2465 μg/m^2 auristatin payload dose) is well-tolerated in cyno

PK of mAb and drug payload at 2.5 mg/kg dose in cyno



Total antibody measured by ELISA, with total drug payload and free drug measured by mass spectroscopy. Good conjugate stability is indicated by very low free drug exposure (<0.02% of total drug) and long drug conjugate half-life (~5 days, comparable to antibody).

Drug payload exposure at the tolerated 2.5 mg/kg dose in cyno is **~5X higher** than drug payload exposure at the 1 mg/kg dose in mouse. This dose is associated with complete tumor responses across multiple tumor models representing high and low HER2-expressing tumors.

Conclusions

- XMT-1522 is highly active in HER2-positive tumor models that are insensitive to ado-trastuzumab emtansine
- XMT-1522 is highly active in low HER2-expressing tumor models (representing HER2 1+ and 2+ tumors) where there are currently no approved HER2-targeted therapies
- The ability to combine XMT-1522 with trastuzumab or trastuzumab-containing regimens gives the potential of achieving full HER2 pathway inhibition combined with efficient delivery of cytotoxic payload
- Exploratory toxicity studies with XMT-1522 indicate a favorable therapeutic index with a manageable toxicity profile; IND filing is anticipated in 2015

Acknowledgement

Adimab

Mersana acknowledges Adimab, our partner for antibody discovery for HT-19.

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