Mersana THERAPEUTICS

Abstract P4-14-28

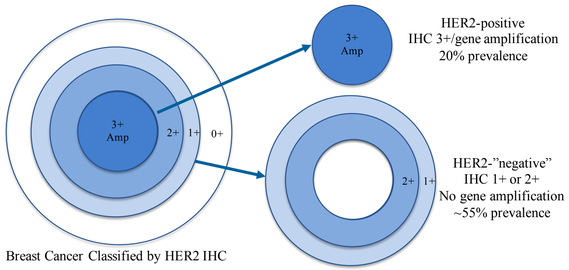
XMT-1522 induces tumor regressions in pre-clinical models representing HER2-positive and HER2 low-expressing breast cancer

Donald A. Bergstrom, Natalya Bodyak, Peter U. Park, Alex Yurkovetskiy, Michael DeVit, Mao Yin, Laura Poling, Joshua D. Thomas, Dmitry Gumerov, Dongmei Xiao, Elena Ter-Ovanesyan, LiuLiang Qin, Alex Uttard, Alex Johnson, Timothy B. Lowinger.

Mersana Therapeutics, Cambridge, MA

Background

- Advanced breast cancer remains an area of significant unmet medical need
- HER2+ breast cancer comprises a minority of breast cancer cases
  - The majority of cases express HER2 protein (IHC 1+ or 2+) without HER2 gene amplification and receive a diagnosis of HER2-negative breast cancer



HER2-positive
IHC 3+/gene amplification
20% prevalence

HER2-"negative"
IHC 1+ or 2+
No gene amplification
~55% prevalence

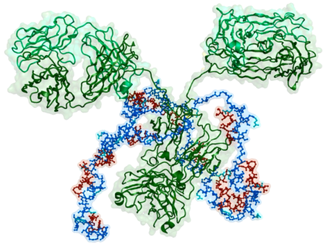
Breast Cancer Classified by HER2 IHC

- HER2-negative disease is heterogeneous with a diversity of oncogenic drivers
  - Cytotoxic chemotherapy has remained a mainstay of therapy for HER2-negative advanced breast cancer (HR- or R/R to endocrine therapy)
- Objective: develop a highly effective targeted therapy for the treatment of HER2 IHC 1+/2+ advanced breast cancer, and HER2-positive breast cancer after failure of ado-trastuzumab emtansine

XMT-1522: Potent HER2-targeted antibody-drug conjugate

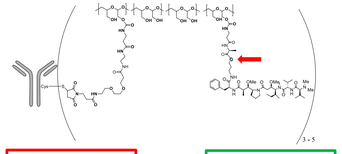
XMT-1522 Key features:

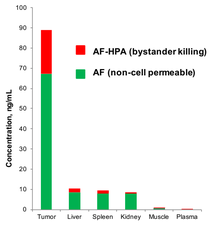
- Average of ~15 auristatin-derived payload molecules per antibody
- Drug-like properties enabled via Fleximer polymer conjugation
- Built on novel mAb (HT-19) optimized for ADC; binds to a unique epitope distinct from trastuzumab or pertuzumab
- 1-3 logs more potent then Kadcyla in vitro; single digit nanomolar potency in all cell lines with >10,000 HER2 receptors per cell
- Exploratory toxicology studies indicate exposure at tolerated dose in non-human primate is greater than exposure at 3 mg/kg dose in mouse (Bergstrom et. al., AACR Annual Meeting 2015, abstract LBA-231)
  - For translational relevance, top dose studied in PDX models is 3 mg/kg



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

XMT-1522 Bioactivation and Biodistribution





BT-474 Model Biodistribution Study

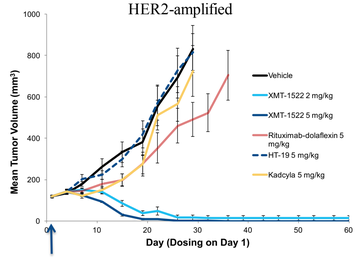
- Tissue accumulation of small molecule ADC release products 48h after dosing 5 mg/kg ADC
- Tumor AF-HPA > 20X IC_{50}
- AF-HPA in other tissues ≤ IC_{50}
- Tumor AF > 5X IC_{50}
- AF in other tissues < IC_{50}
- Experiment performed with trastuzumab-dolaflexin ADC

Tumor Xenograft Materials and Methods

- Tumors were implanted into nude mice and allowed to grow to ~200 mm^2 prior to randomization and dosing
- Mice were treated with XMT-1522 or the indicated controls or comparators:
  - Dosing days are indicated by arrows for iv or ip administration; lapatinib was dosed daily for 28 days
  - ADCs administered iv at the doses indicated
  - Comparator doses: gemcitabine 80 mg/kg ip; lapatinib 50 mg/kg po
- Tumor response criteria:
  - Partial Response (PR) = 50% tumor volume decrease from baseline over 3 consecutive measurements
  - Complete Response (CR) = tumor volume < 14 mm^2 for 3 consecutive measurements
  - Tumor-free survivors (TFS60) = animals alive with tumor volume < 14 mm^2 on study day 60

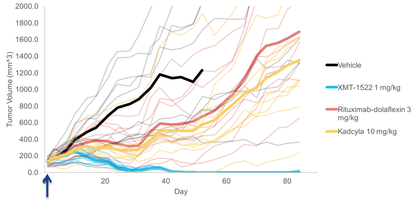
XMT-1522 Activity in HER2+ Models

BT-474
HER2 IHC 3+
HER2-amplified



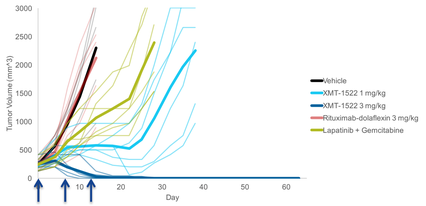
MAXF-1162
HER2 IHC 3+
HER2-amplified

N/PR/CR/TFS60	XMT-1522 1 mg/kg	Kadcyla 10 mg/kg
	10/0/10/10	10/0/1/0



ST-1360B (Wick et al., AACR/EORTC/NCI 2015, abstract #C74)
ER+, HER2 IHC 3+
HER2-amplified
Harvested from metastatic pleural effusion post Kadcyla
Next therapy after harvest: lapatinib + gemcitabine
Model insensitive to Kadcyla

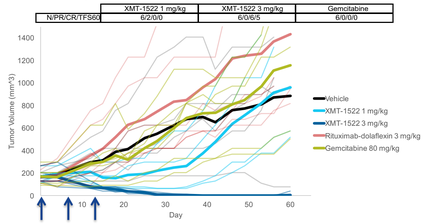
N/PR/CR/TFS60	XMT-1522 1 mg/kg	XMT-1522 3 mg/kg	Gemcitabine + Lapatinib
	6/0/0/0	6/0/6/6	6/0/0/0



XMT-1522 Activity in HER2 IHC 2+ PDX

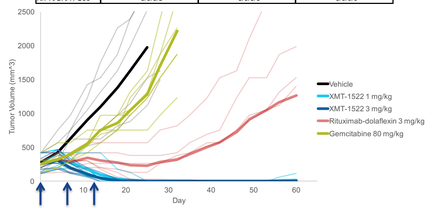
ST-565 (Wick et al., EORTC/AACR/NCI 2014, abstract #C104)
ER+, HER2 IHC 2+
HER2-wt; PIK3CA mut
Kadcyla insensitive; partially sensitive to docetaxel

N/PR/CR/TFS60	XMT-1522 1 mg/kg	XMT-1522 3 mg/kg	Gemcitabine
	6/2/0/0	6/0/6/5	6/0/0/0



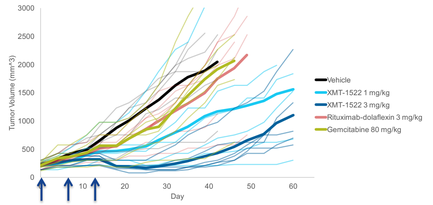
ST-313 (Wick et al., EORTC/AACR/NCI 2014, abstract #C104)
ER+, HER2 IHC 2+
HER2-wt; PIK3CA mut
Kadcyla insensitive; sensitive to docetaxel

N/PR/CR/TFS60	XMT-1522 1 mg/kg	XMT-1522 3 mg/kg	Gemcitabine
	6/0/6/5	6/0/6/6	6/0/0/0



ST-319 (Wick et al., EORTC/AACR/NCI 2014, abstract #C104)
Triple Negative, HER2 IHC 2+
HER2-wt
Kadcyla insensitive

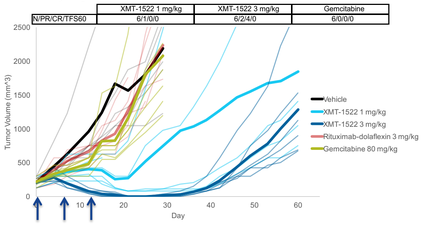
N/PR/CR/TFS60	XMT-1522 1 mg/kg	XMT-1522 3 mg/kg	Gemcitabine
	6/0/0/0	6/0/0/0	6/0/0/0



XMT-1522 Activity in HER2 IHC 1+ PDX

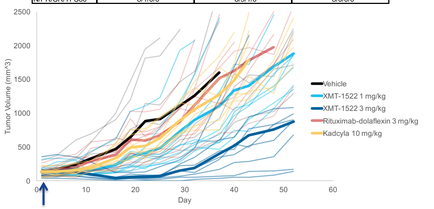
ST-455B (Wick et al., EORTC/AACR/NCI 2014, abstract #C104)
Triple Negative, HER2 IHC 1+
HER2-wt; p53 mut
Kadcyla partially sensitive; partially sensitive to paclitaxel

N/PR/CR/TFS60	XMT-1522 1 mg/kg	XMT-1522 3 mg/kg	Gemcitabine
	6/1/0/0	6/2/4/0	6/0/0/0



OD-BRE-333
HER2 IHC 1+
HER2-wt

N/PR/CR/TFS60	XMT-1522 1 mg/kg	XMT-1522 3 mg/kg	Kadcyla 10 mg/kg
	8/1/0/0	8/5/1/0	8/0/0/0



Conclusions

- HER2 is a validated breast cancer target that could be used for targeting HER2 IHC 1+ and 2+ populations with a sufficiently potent ADC
- XMT-1522 is significantly more potent that ado-trastuzumab emtansine (Kadcyla)
- XMT-1522 is active in a range of models representing HER2+ disease where HER2-targeted therapies (Kadcyla, lapatinib, trastuzumab) are not active
- XMT-1522 is also active in models representing HR+ and HR- HER2 IHC 1+ and 2+ disease
- Phase 1 evaluation of XMT-1522 in these breast cancer populations will begin in 2016

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