Abstract #227287

Phase 1 dose escalation of XMT-1522, a novel HER2-targeting antibody-drug conjugate (ADC), in patients with HER2-expressing breast, lung and gastric tumors

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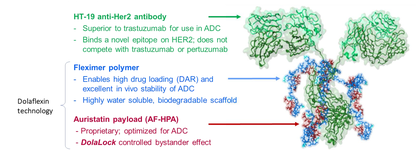
Introduction

Background

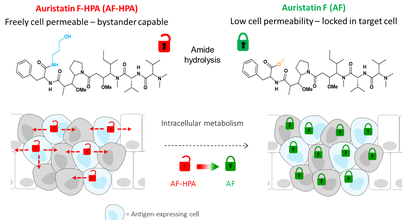
- There is unmet medical need for effective therapies for patients with HER2-positive breast cancer after treatment with trastuzumab, pertuzumab and T-DM1, and for HER2-positive gastric cancer after treatment with trastuzumab
- There are no approved HER2-directed therapies for HER2-low (HER2 IHC 1+/2+ without HER2 gene amplification) breast or gastric cancer or for HER2-expressing NSCLC
- XMT-1522 is a potent HER2-targeting ADC with a high drug-to-antibody ratio and a controlled bystander effect
- Preliminary safety and efficacy results are available from ongoing dose escalation in patients with HER2-expressing breast, gastric or lung cancer

XMT-1522, a Potent, HER2-targeted Dolaflexin ADC

- XMT-1522 is an antibody-drug conjugate (ADC)
  - Delivers auristatin payload specifically to HER2-expressing cells
  - Carries ~12 payloads per ADC molecule

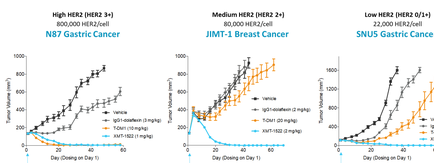


DolaLock – Controlled Bystander Effect



Preclinical Efficacy in Breast, Gastric & Lung Cancer

- Durable complete regressions across models with range of HER2 expression levels
- XMT-1522 outperforms Kadcyla (T-DM1) in vitro and in vivo in preclinical models of breast, gastric and lung cancer.



Methods

Study Design

www.ClinicalTrials.gov\NCT02952729

- Patients with HER2-expressing (by local assessment) breast, gastric, or lung cancers
- XMT-1522 dosed IV every 3 weeks in 21-day cycles until disease progression or unacceptable toxicity
- Dose escalation: "3 + 3" design with optional 4th patient at each dose level
- Intrapatient dose escalation allowed

Current dose level

Dose Escalation, Ongoing		
	Dose, mg/m²	Increase
DL1	2.0	100%
DL2	4.0	100%
DL3	8.0	100%
DL4	12.0	50%
DL5	16.0	33%
DL6	21.3	33%
DL7	**28.3**	**33%**
DL8	37.0	33%
DL9	49.0	33%
Escalation continues in ~33% increments		

→ MTD/RP2D →

Planned Expansion Cohorts
Breast Cancer, HER2+, post T-DM1 (N=30)
Breast Cancer, HER2-low (IHC 1+/2+, non-amplified) (N=30)
Gastric Cancer, HER2+ post-trastuzumab (N=30)
NSCLC, HER2 IHC 2+/3+ (N=30)
NSCLC, HER2 IHC 1+ (N=30)

Objectives – Dose Escalation

- Primary
  - Assess safety and tolerability of XMT-1522 administered IV every three weeks
  - Identify MTD and/or RP2D
- Secondary
  - Assess pharmacokinetic profile of XMT-1522 and its metabolites
  - Assess preliminary efficacy of XMT-1522
  - Assess development of antibodies to XMT-1522
- Exploratory
  - Retrospectively evaluate the relationship of tumor response with HER2 expression, expression of other genes, or patient subsets defined by gene mutations

Key Dose Escalation Eligibility Criteria

- Advanced HER2 expressing tumors – by local assessment
  - Breast cancer: IHC 1+, 2+, or 3+; or amplified
  - NSCLC: IHC 1+, 2+ or 3+; or amplified
  - Gastric cancer: IHC 3+ or 2+/amplified
- Patients must have progressive disease after standard of care therapies
- Adequate organ function at baseline
- Measurable disease per RECIST 1.1
- ECOG performance status 0 or 1
- LVEF ≥ 50% or lower limit of normal and no history of significant cardiac dysfunction

Dose-limiting Toxicity (DLT) Criteria

- DLTs are defined as Grade 3 or higher drug-related adverse event occurring during Cycle 1, with exceptions or detailed criteria for gastrointestinal events, liver enzyme elevations, changes in electrolytes, neutropenia, and thrombocytopenia

Assessments

- Adverse events, concomitant medications
- PK, anti-drug antibodies, safety labs
- Ophthalmologic: slit lamp examination
- Cardiovascular: LVEF (MUGA or ECHO)
- Tumor imaging (MRI or CT): baseline and every 2nd cycle, with response assessed per RECIST 1.1

Results

Study Status

- 6 dose levels (2 to 21.3 mg/m²) have been completed; treatment in DL7 (28.3 mg/m²) is ongoing
- Data are shown here for DL 1-6 (22 patients) unless otherwise noted

Patient Characteristics, DL 1-6 (N = 22)

Age (years)	Median (range)	65 (31-79)
Sex – N (%)	Female	20 (91)
	Male	2 (9)
ECOG performance status – N (%)	0	8 (36)
	1	14 (64)
Tumor type – N (%)	Breast cancer	18 (82)
HER2 status by local assessment	HER2-positive	8 of 18 (44)
	HER2-low	10 of 18 (56)
	Prior trastuzumab	10 of 18 (56)
	Prior T-DM1	9 of 18 (50)
	Gastric cancer	3 (14)
	Prior trastuzumab	2 of 3 (67)
	Gallbladder cancer	1 (5)
Prior lines of therapy for metastatic disease	Median (range)	4 (0-10)

Completed Dose Levels (N=22)

	Dose Level 1	Dose Level 2	Dose Level 3	Dose Level 4	Dose Level 5	Dose Level 6
Dose, mg/m²	2.0	4.0	8.0	12.0	16.0	21.3
N	3	3	3	3	4[a]	6[b]
Tumor Type	Breast	Breast	Breast	Breast	3 Breast 1 Gastric	3 Breast 1 Gallbladder 2 Gastric
DLT	0	0	0	0	0	0

[a] Optional 4th patient enrolled.
[b] Gallbladder cancer patient (DL6) developed Grade 3 anemia, which was initially assessed as possibly related to study drug, leading to expansion of cohort because of suspected DLT. Negative rechallenge at the same dose and occurrence of a subsequent event of GI bleeding led the assessment to be changed to unlikely related to study drug, and the event was not considered a DLT.

Ongoing: Dose Level 7 (28.3 mg/m²)

- DLT occurred in the 4th patient enrolled:
  - A patient with HER2-positive breast cancer developed transient high fever, Grade 3 AST elevation (10.9 X ULN) and Grade 2 ALT elevation (4.6 X ULN) on C1D2. Bilirubin was normal. AST and ALT resolved to Grade 1 by C1D21 and the patient was treated in Cycle 2 at a reduced dose (21.3 mg/m²) with steroid pre-medication, without recurrence of symptoms.
- This dose level was expanded to 6 patients per the 3 + 3 design
- 5 patients have completed the DLT observation period, and the 6th patient has received treatment in Cycle 1
- 3 patients have completed the first post-baseline restaging tumor assessment, with progressive disease observed in one patient and stable disease in 2 patients

Safety (Through DL6; N = 22)

- Treatment was generally well-tolerated; most AEs were Grade 1-2
- The most common treatment-related AEs (>10%) were fatigue, nausea, vomiting, ALT increased, anemia, and AST increased
- Grade 3 treatment-related AEs are described individually below
- There were no Grade 4 or 5 AEs
- Limited evidence to date of toxicities often seen with other ADCs or microtubule-targeting agents such as neutropenia, ocular toxicities, peripheral neuropathy, or pneumonitis
- No cardiac AEs or reductions in LVEF requiring dose modification or discontinuation

Treatment Related Adverse Events Occurring in > 10% of Patients Through DL6 (N = 22)

Data cutoff: April 21, 2018

Preferred Term, Highest Grade of AE		DL 1 2.0 mg/m² N=3, n(%)	DL 2 4.0 mg/m² N=3, n(%)	DL 3 8.0 mg/m² N=3, n(%)	DL 4 12.0 mg/m² N=3, n(%)	DL 5 16.0 mg/m² N=4, n(%)	DL 6 21.3mg/m² N=6, n(%)	Total N=22 n(%)
Patients with any TRAE		1 (33)	1 (33)	2 (67)	2 (67)	4 (100)	4 (67)	14 (64)
Fatigue	All Grades	0	0	2 (67)	1 (33)	2 (50)	1 (17)	6 (27)
	Gr 1	0	0	2 (67)	0	1 (25)	0	3 (14)
	Gr 2	0	0	0	1 (33)	1 (25)	1 (17)	3 (14)
	Gr 3	0	0	0	0	0	0	0
Nausea	All Grades	0	0	1 (33)	0	2 (50)	3 (50)	6 (27)
	Gr 1	0	0	1 (33)	0	1 (25)	2 (33)	4 (18)
	Gr 2	0	0	0	0	1 (25)	1 (17)	2 (9)
	Gr 3	0	0	0	0	0	0	0
Vomiting	All Grades	0	1 (33)	0	0	1 (25)	2 (33)	4 (18)
	Gr 1	0	1 (33)	0	0	1 (25)	1 (17)	3 (14)
	Gr 2	0	0	0	0	0	1 (17)	1 (5)
	Gr 3	0	0	0	0	0	0	0
ALT Increased	All Grades	0	0	0	1 (33)	1 (25)	1 (17)	3 (14)
	Gr 1	0	0	0	1 (33)	1 (25)	1 (17)	3 (14)
	Gr 2	0	0	0	0	0	0	0
	Gr 3	0	0	0	0	0	0	0
Anemia	All Grades	1 (33)	0	0	0	0	2 (33)	3 (14)
	Gr 1	0	0	0	0	0	0	0
	Gr 2	0	0	0	0	0	2 (33)	2 (9)
	Gr 3	1 (33)	0	0	0	0	0	1 (5)
AST Increased	All Grades	0	0	0	1 (33)	0	2 (33)	3 (14)
	Gr 1	0	0	0	1 (33)	0	1 (17)	2 (9)
	Gr 2	0	0	0	0	0	0	0
	Gr 3	0	0	0	0	0	1 (17)	1 (5)

TRAEs in < 10% of Patients Through DL6 (N = 22)

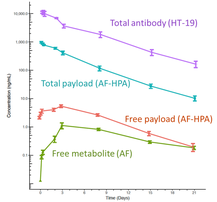
- All events Grade 1 or 2 except as noted (* = Grade 3, described below)

# pts (%)	Event Terms
2 (9)	Blood alkaline phosphatase increased, constipation, decreased appetite, dry eye, dysgeusia, dyspnea, headache, hypokalemia
1 (5)	Alopecia, blepharitis, bone pain, dehydration, early satiety, gastrointestinal pain, hepatotoxicity*, hypoalbuminemia, hyponatremia, infusion related reaction, neutrophil count decreased, pruritis, stomatitis, urinary tract infection, weight decreased, white blood cell count decreased

Grade 3 Treatment-Related Adverse Events (Through DL6)

AE Term	Dose Level	Cycle	Relationship to Study Drug	Patient, Details
Anemia	1 (2 mg/m²)	11	Possibly related	HER2-positive breast cancer; prior treatments included doxorubicin, cyclophosphamide, docetaxel, fulvestrant, letrozole, Abraxane, trastuzumab, pertuzumab, and T-DM1; Grade 1 anemia at baseline.
AST increased	6 (21.3 mg/m²)	2	Definitely related	HER2-low breast cancer; liver metastases present; history of Grade 1 AST elevation. Grade 3 AST elevation in Cycle 2 resolved to Grade 1 before dosing in Cycle 3 at a reduced dose. Repeated Grade 3 AST elevation in subsequent cycles led to further dose reduction.
Hepatotoxicity	6 (21.3 mg/m²)	3	Possibly related	HER2-positive gastric cancer; history of Grade 1 anorexia, Grade 1 AST elevation, Grade 1 ascites, and Grade 2 hypoalbuminemia. Hospitalized for confusion at Cycle 3, Day 15 and found to have AST 1.9X ULN, alkaline phosphatase 1.3X ULN, normal ALT and bilirubin, and plasma ammonia 1.7X ULN. Treated with IV fluids and lactulose, with resolution of the mental status changes within 1-2 days. The patient was planned to have further treatment at a reduced dose, but was taken off study because of disease progression.

Pharmacokinetics (Cycle 1)

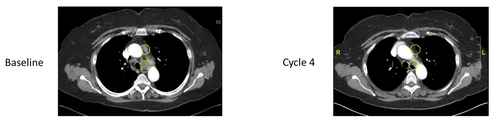


- PK profiles of XMT-1522 for each analyte shown for patients treated at DL6 (21.3 mg/m²)
- Within the tested dose range up to 21.3 mg/m²:
  - Increased exposure with increasing dose for each analyte
  - PK characteristics consistent with other ADCs approved or in clinical development
  - Low systemic exposure of free payload (AF-HPA) and its metabolite (AF)

Efficacy

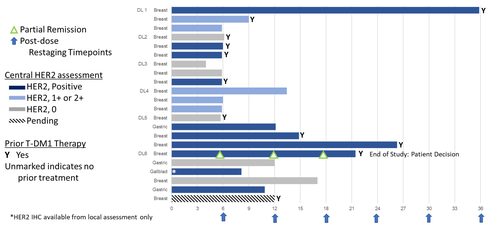
- Disease control (SD or better at the first restaging scan) was achieved in 11 of 13 patients treated at ≥ 16 mg/m² (DL5) who had at least one restaging scan (including 3 patients in DL7), including 6 breast cancer, 4 gastric cancer, and 1 gallbladder cancer patient
- One confirmed partial response, described below

HER2+ breast cancer patient with confirmed PR at Cycle 4

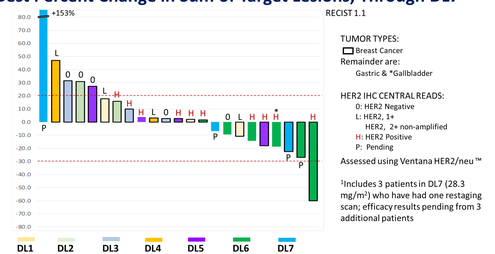


A 69-year-old woman with HER2-positive breast cancer (IHC 3+ by central assessment) and a history of treatment with trastuzumab, pertuzumab and T-DM1 had target (circled) and non-target thoracic lymph node lesions, with a decrease of 45% in diameter of target lesions at the end of Cycle 2 and 60% at the end of Cycle 4 (shown above). PR was ongoing at Cycle 6 with a 58% reduction from baseline.

Time on Study, Through DL6 (N = 22)



Best Percent Change in Sum of Target Lesions, Through DL7[1]



Assessed using Ventana HER2/neu ™

[1]Includes 3 patients in DL7 (28.3 mg/m²) who have had one restaging scan; efficacy results pending from 3 additional patients

Conclusions

- XMT-1522 is the first ADC on the Dolaflexin platform to enter the clinic
- Treatment has been well-tolerated, with most AEs being low grade and manageable; the most common treatment-related AEs were fatigue, nausea, vomiting, anemia, and transient elevations of AST and ALT
- Preliminary signs of efficacy have been seen at doses ≥ 16 mg/m² with overall best response of SD or better in 11 of 13 patients and one confirmed PR at DL6 (21.3 mg/m²)
- MTD has not been reached; enrollment in the dose escalation phase is ongoing at DL 7 (28.3 mg/m²)