The DolaLock-based ADC Platforms: Dolaflexin & Dolasynthen

Timothy B. Lowinger, PhD
Chief Science & Technology Officer

World ADC Summit
October 2019
• Brief introduction to the Dolaflexin platform and the DolaLock payload
• Update on the clinical development of XMT-1536, a Dolaflexin ADC targeting NaPi2b
• Dolasynthen - a fully homogeneous ADC platform incorporating the DolaLock payload
• Immunosynthen – an immunostimulatory ADC platform
Dolaflexin and the DolaLock Payload
Novel Dolaflexin Platform Technology

Designed to Expand Therapeutic Index vs Other ADC Platforms

**Fleximer® Polymer**
- High DAR
- Optimal PK and drug-like properties
- Efficacy - against low antigen expressing tumors

**DolaLock Payload**
- Controlled bystander effect for greater efficacy and tolerability

A biodegradable, biocompatible scaffold providing aqueous solubility, charge balance, and a high drug to antibody ratio (ideally 10-12 per mAb) on average
Proprietary Auristatin DolaLock Payload provides Unique Pharmacology – a Controlled Bystander Effect

**Auristatin F-HPA (AF-HPA)**

- Bystander Killing freely cell permeable

**Auristatin F (AF)**

- No Bystander Killing
  - Not cell permeable; *not a Pgp substrate*

**Metabolic Conversion in Tumor Cell**

- AF-HPA → AF

**Antigen +**

**Antigen -**

**AF-HPA**

**AF**
DolaLock Provides Prolonged Tumor Exposure and Improves Tolerability

**Tumor Exposure**
after single dose to tumor-bearing mice

**Tissue Exposure (AUC)**
after single dose to tumor-bearing mice
Total exposure over 2 weeks

**Neutrophil Count**
after single dose to non-human primates

*dose that causes fatal neutropenia with Lifastuzumab vedotin – see Lin et al. Clinical Cancer Research 2015*
XMT-1536
A NaPi2b-targeted Dolaflexin ADC
NaPi2b: An Attractive ADC Target Ideally-Suited for Mersana’s Innovative Platforms

- Broadly expressed in ovarian cancer and NSCLC adenocarcinoma
  - No detectable expression in squamous NSCLC
  - Limited expression in healthy tissues on apical surface of polarized epithelium (inaccessible to bloodstream limiting potential for on-target toxicities)

- NaPi2b is a lineage marker (not an oncogene) that transports inorganic phosphate (Pi) into the cell
  - Not downregulated in response to treatment
  - High expression of NaPi2b is correlated with the presence of EGFR mutations in NSCLC adenocarcinoma

- Companion diagnostic can distinguish across low, medium, and high expression
  - Correlation between biomarker expression and response in preclinical and clinical settings

Mersana companion diagnostic discriminates across expression levels

R. Mosher et al, AACR-NCI-EORTC International Conference, October 2017
ASCO 2019 Poster #3010; Phase 1 dose escalation study of XMT-1536, a novel NaPi2b-targeting antibody-drug conjugate (ADC), in patients (pts) with solid tumors likely to express NaPi2b; June 2019, Data Cutoff May 10, 2019
XMT-1536 Data Show Improved Efficacy and Tolerability to vcMMAE ADC in Head to Head Preclinical Studies

**OVCAR3**
Ovarian Xenograft

**CTG-0852**
NSCLC Patient Derived Xenograft

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![Graph of Tumor Volume vs Day for OVCAR3 and CTG-0852](image)

- **Vehicle**
- **IgG1-dolaflexin 3 mg/kg weekly x3**
- **NaPi2b-vc-MMAE 3 mg/kg weekly x3**
- **XMT-1536 3 mg/kg weekly x3**
NaPi2b Expression Levels Have Been Predictive of Response to XMT-1536 in Ovarian Cancer Patient-Derived Models

- Proprietary research assay validated and used for retrospective evaluation of patients
- Preclinical data demonstrate NaPi2b expression highly correlated with response
- ~60% of ovarian cancer patients predicted to have NaPi2b score associated with deep responses in PDX models

Tumors with an H-score above cut-off had a tumor reduction of >50%

R. Mosher et al, AACR-NCI-EROTC International Conference, October 2017

*Semi-quantitative measure of antigen expression; ranges from 0-300
**XMT-1536 Phase 1 Dose Escalation Study Design**

*Data Presented at ASCO with a Data Cutoff of May 10, 2019*

- **Patient population:** patients with ovarian epithelial, non-squamous lung, endometrial, papillary renal, salivary duct, or papillary thyroid cancers, progressing after standard treatments

- **Dosing:** XMT-1536 administered IV initially every 3 weeks, amended to every 4 weeks, until disease progression or unacceptable toxicity

- **Dose escalation design:** single-patient cohorts for first two dose levels, followed by a standard “3 + 3” design

- **Assessments:** standard assessments including AEs, preliminary activity, concomitant medications, safety labs, PK

### Dosing: Q3 weeks

<table>
<thead>
<tr>
<th>DL</th>
<th>Dose (mg/m²)</th>
<th>Dose (mg/kg)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>DL 1</td>
<td>3 mg/m²</td>
<td>0.081 mg/kg</td>
<td>1</td>
</tr>
<tr>
<td>DL 2</td>
<td>6 mg/m²</td>
<td>0.162 mg/kg</td>
<td>1</td>
</tr>
<tr>
<td>DL 3</td>
<td>12 mg/m²</td>
<td>0.324 mg/kg</td>
<td>7</td>
</tr>
<tr>
<td>DL 4</td>
<td>20 mg/m²</td>
<td>0.54 mg/kg</td>
<td>6</td>
</tr>
<tr>
<td>DL 5</td>
<td>30 mg/m²</td>
<td>0.81 mg/kg</td>
<td>4</td>
</tr>
<tr>
<td>DL 6</td>
<td>40 mg/m²</td>
<td>1.08 mg/kg</td>
<td>1</td>
</tr>
</tbody>
</table>

### Dosing: Q4 weeks

<table>
<thead>
<tr>
<th>DL</th>
<th>Dose (mg/m²)</th>
<th>Dose (mg/kg)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>DL 4</td>
<td>20 mg/m²</td>
<td>0.54 mg/kg</td>
<td>1</td>
</tr>
<tr>
<td>DL 5</td>
<td>30 mg/m²</td>
<td>0.81 mg/kg</td>
<td>8</td>
</tr>
<tr>
<td>DL 6</td>
<td>36 mg/m²</td>
<td>0.97 mg/kg</td>
<td>1</td>
</tr>
<tr>
<td>DL 7</td>
<td>43 mg/m²</td>
<td>1.2 mg/kg</td>
<td>O</td>
</tr>
</tbody>
</table>

*Data from 36 mg/m² cohort and ongoing 43 mg/m² cohort were not included in the ASCO data presentation*

**ClinicalTrials.gov:** NCT03319628

**Presented at ASCO**
Patients Were Heavily Pretreated and **Unselected for NaPi2b**

As of May 10, 2019

<table>
<thead>
<tr>
<th>(N = 37)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>Median (range)</td>
</tr>
<tr>
<td><strong>Sex – N (%)</strong></td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td><strong>ECOG performance status – N (%)</strong></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Tumor type – N (%)</strong></td>
<td>Ovarian, fallopian tube, or primary peritoneal NSCLC</td>
</tr>
<tr>
<td></td>
<td>Endometrial</td>
</tr>
<tr>
<td></td>
<td>Papillary renal</td>
</tr>
<tr>
<td></td>
<td>Salivary duct</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prior lines of therapy for metastatic disease (N=37)</strong></td>
<td>Median (range)</td>
</tr>
<tr>
<td><strong>Prior lines of therapy, ovarian cancer only (N = 22)</strong></td>
<td>Median (range)</td>
</tr>
</tbody>
</table>
XMT-1536 was Well-Tolerated with Most AE’s Grade 1-2
As of May 10, 2019

Treatment-Related Adverse Events in ≥10% of Patients

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
</tr>
<tr>
<td>Nausea</td>
<td>12 (32%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>Aspartate aminotransferase (AST) increased</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Blood alkaline phosphatase increased</td>
<td>6 (16%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Gamma-glutamyltransferase (GGT) increased</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (8%)</td>
</tr>
</tbody>
</table>

Safety:
- No Grade 4 or 5 treatment-related adverse events (TRAEs)
- Low rate of toxicities associated with microtubule-targeting agents or other ADC platforms, such as neutropenia, ocular toxicities, or peripheral neuropathy
Dolaflexin Safety Profile Easily Monitored; High Consistency between Early Clinical and Preclinical Data

Preclinical Data Demonstrate Transient AST Elevations Are Correlated with Kupffer Cell Hypertrophy

- Kupffer cells are involved in AST clearance
- Transient elevation is consistent with a change in clearance kinetics
- Transient elevations of AST were not associated with hepatocellular necrosis based on histopathology
- AST elevations peak at day 8 and return to normal along with Kupffer cell appearance

Clinical Data Mirror Preclinical Observations

- Repeatable and predictable pattern: transient AST peaking on Day 8, returning to baseline or Grade 1 by next dose (sawtooth pattern)
- Patients treated for over 34 weeks maintained predictable pattern
- No changes in bilirubin. No cases of Hy’s Law

AST: Aspartate aminotransferase; Also known as serum glutamic oxaloacetic transaminase (SGOT); CK: Creatine Kinase; ALT: Alanine aminotransferase
As of May 10, 2019

Response Evaluable Population, **Unselected for NaPi2b**

<table>
<thead>
<tr>
<th>Outcomes in Ovarian Cancer (OC) &amp; Non-small Cell Lung Cancer (NSCLC)</th>
<th>All OC</th>
<th>All NSCLC</th>
<th>OC ≥20 mg/m²</th>
<th>NSCLC ≥20 mg/m²</th>
<th>OC ≥30 mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>19</td>
<td>3</td>
<td>16</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>PR*</td>
<td>3 (16%)</td>
<td>0 (0%)</td>
<td>3 (19%)</td>
<td>0 (0%)</td>
<td>2 (28%)</td>
</tr>
<tr>
<td>SD*</td>
<td>8 (42%)</td>
<td>2 (67%)</td>
<td>6 (38%)</td>
<td>2 (100%)</td>
<td>3 (43%)</td>
</tr>
<tr>
<td>DCR (PR + SD)</td>
<td>11 (58%)</td>
<td>2 (67%)</td>
<td>9 (57%)</td>
<td>2 (100%)</td>
<td>5 (71%)</td>
</tr>
<tr>
<td>PD*</td>
<td>8 (42%)</td>
<td>1 (33%)</td>
<td>7 (43%)</td>
<td>0 (0%)</td>
<td>2 (28%)</td>
</tr>
</tbody>
</table>

- Based on objective responses and duration of treatment
- Clinical activity was observed at doses of 20 mg/m² and higher

*As measured by RECIST, version 1.1
Ovarian Cancer Patient with Confirmed PR at Cycle 3
As of May 10, 2019

- 70-year-old woman with platinum-resistant high-grade serous ovarian cancer treated at DL 4A (20 mg/m²)
- 11 prior lines of therapy, with progression on most recent therapy of cyclophosphamide and bevacizumab
- Target lesions of perihepatic and mid-abdominal metastases, 52 and 42 mm respectively
- Decrease of 40% in diameter of target lesions at the end of Cycle 2 (4-week cycles) and 75% at the end of Cycle 3
# Single Agent Activity in Platinum-Resistant Ovarian Cancer Based on Literature Review

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prior Lines of Therapy</th>
<th>ORR</th>
<th>PFS/TTP* Months</th>
<th>OS Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>1-2</td>
<td>13-37%</td>
<td>3.3-8</td>
<td>9-15</td>
</tr>
<tr>
<td>Topotecan</td>
<td>1</td>
<td>17-28%</td>
<td>3.1-5.3</td>
<td>10-14</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>1-2</td>
<td>16%</td>
<td>2.8</td>
<td>10</td>
</tr>
<tr>
<td>PLD</td>
<td>1-2</td>
<td>8-20%</td>
<td>2.1-5.8</td>
<td>8-19</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>1-2</td>
<td>9-29%</td>
<td>3.6-4.7</td>
<td>12-13</td>
</tr>
<tr>
<td>Treosulfan</td>
<td>1</td>
<td>16%</td>
<td>2.9</td>
<td>10</td>
</tr>
</tbody>
</table>

**Study (Control Arm) – Drug**

<table>
<thead>
<tr>
<th>Study (Control Arm) – Drug</th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AURELIA - Investigator’s Choice (PLD/Taxol/Topotecan)</td>
<td>1-2</td>
<td>12%</td>
<td>3.4</td>
<td>13.3</td>
</tr>
<tr>
<td>JAVELIN 200 – PLD</td>
<td>1-3</td>
<td>4.2%</td>
<td>3.5</td>
<td>13.1</td>
</tr>
<tr>
<td>FORWARD I - Investigator’s Choice (PLD/Taxol/Topotecan)</td>
<td>1-3</td>
<td>12%</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Forward I press release dated March 1, 2019  
PFS = Progression-Free Survival; TTP = Time to progression; NR = Not Reported.
<table>
<thead>
<tr>
<th>Line of Therapy*</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
<th>6th</th>
<th>7th</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR %</td>
<td>26-34%</td>
<td>12-20%</td>
<td>3-17%</td>
<td>5-11%</td>
<td>0-8%</td>
<td>0%</td>
</tr>
<tr>
<td>DCR %</td>
<td>59%</td>
<td>16-45%</td>
<td>9-33%</td>
<td>9-44%</td>
<td>0-23%</td>
<td>0-20%</td>
</tr>
</tbody>
</table>

XMT-1536 Dose Level ≥30 mg/m²
Lines of Therapy: Median 5 (3-8)

| ORR %       | 28%   |
| DCR %       | 71%   |

* Calculated according to P.J.Hoskins; Nhu Le, Gynecologic Oncology 2005; I. Bruchim et al, EJOGRB 2013
As of May 10, 2019

Ovarian Cancer and NSCLC Adenocarcinoma Duration

All Completed Dose Levels
OC and NSCLC Patients, N=26

- All dose levels are represented in the graph:
  - **Dose Level 1**: 3 mg/m² (n=1)
  - **Dose Level 2**: 6 mg/m² (n=1)
  - **Dose Level 3**: 12 mg/m² (n=3)
  - **Dose Levels 4 & 4A**: 20 mg/m² (n=12)
  - **Dose Levels 5 & 5A**: 30 mg/m² (n=8)
  - **Dose Level 6**: 40 mg/m² (n=1)

Ongoing: 40 mg/m²

Partial Remission = PR

Population UNSELECTED for NaPi2b Expression

~50% Treated above 20 mg/m² had Duration > 16 weeks
Study Designed to Confirm Profile and Inform Path to Approval in High Unmet Medical Need Populations

Expansion Study Initiated:
36 mg/m² dose on Q4W schedule

Expansion: Platinum-Resistant Ovarian Cancer
Eligibility criteria:
• High-grade serous histology
• 1-3 prior lines of therapy
• Platinum-resistant
• Archived tumor and fresh biopsy (if medically feasible)

Expansion: NSCLC Adenocarcinoma
Eligibility criteria:
• Adenocarcinoma histology
• Prior treatment with a platinum doublet and PD-1/L1 inhibitor
• No additional prior treatment with cytotoxics or immunotherapy
• Prior TKIs for patients with targetable abnormalities
• Archived tumor and fresh biopsy (if medically feasible)

Dose Escalation Continuation
• MTD not determined in dose escalation study
• Exploring 43 mg/m² dose (~1.2 mg/kg) in parallel to expansion study to inform future clinical development
Dolasynthen
A Precise, Fully Synthetic, Customizable and Homogeneous Approach

Precisely Optimized for a given target, DAR, mAb & payload

Many Factors Can Influence the Performance of an ADC:
- Drug-to-antibody ratio
- Site of bioconjugation
- Payload employed
- Linker – cleavable vs. non-cleavable
- Hydrophilicity / hydrophobicity
- Charge profile
- Means of bioconjugation – lysine, cysteine, thiomab, enzymatic, etc.
- Characteristics of Fc portion of mAb – e.g. Fcγ, FcRN binding

The optimal combination will likely differ based on the target, the antibody and the indication
Optimized Dolasynthen Trimeric Scaffold

Bioconjugation moiety can easily be substituted to match with all site-specific bioconjugation approaches
Trastuzumab was used as a model to synthesize ADCs with variations in:
- DAR (6, 12)
- Bioconjugation site(s)
- Bioconjugation technology

### Table

<table>
<thead>
<tr>
<th>Bioconjugation</th>
<th>ADC 1</th>
<th>ADC 2</th>
<th>ADC 3</th>
<th>ADC 4</th>
<th>ADC 5</th>
<th>ADC 6</th>
<th>ADC 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maleimide</td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>C</td>
<td>C</td>
<td>D</td>
<td>A</td>
</tr>
<tr>
<td>DAR</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Site specific</td>
<td><img src="image" alt="Site 1" /></td>
<td><img src="image" alt="Site 2" /></td>
<td><img src="image" alt="Site 1" /></td>
<td><img src="image" alt="Site 1" /></td>
<td><img src="image" alt="Site 1" /></td>
<td><img src="image" alt="Site 1" /></td>
<td><img src="image" alt="Site 1" /></td>
</tr>
</tbody>
</table>
Efficacy and PK Reveal the Optimal Candidate

Efficacy JIMT1 Breast Xenograft Model (0.067 mg/kg payload single dose)

PK in tumor bearing mice (0.133 mg/kg payload single dose)
Expanding Immuno-Oncology Approaches

Innate Immunity (rapid response)

Adaptive Immunity (slow response)

Innate Immunity Targets → activation: hitting the gas pedal on the immune system

Adaptive Immunity Targets
ex. checkpoint inhibitors, CAR-T → inhibition: taking the brake off of the immune system

Why Pursue Systemic Delivery of STING as an ADC?

• Current clinical STING compounds limited to intra-tumoral injection due to concern of systemic toxicity as well as PK limitations
  − Limits clinical indications and tumors accessible to injection
  − Debate over effect on distal tumors/metastases (abscopal effect)
    − No clinical evidence of abscopal effect yet to date
  − Recent report by GSK of free agonist delivered systemically; Fast clearance and potential for limited TI

• ADCs are suited to overcome limitations with free agonists
  − Accessibility to primary and metastatic tumors
  − Amenable to antigen specific targeting on tumor resident immune cells
  − Longer exposure at lower doses- promotes systemic adaptive immunity
  − Active intracellular delivery to cytoplasmic STING
Leveraging Mersana’s Synthemer Platform Approach for STING

Critical Attributes Matched to Payload and Target

- Precisely Optimized for a STING agonist

- Initial ADC with STING agonist resulted in aggregation due to lipophilic payload

- Linker/scaffold optimization effort tailored to particular STING agonist
100x Increased Potency of ADC over Free Agonist

Killing assay: cancer cells / PBMC co-culture
- Cancer cells expressing a fluorescent red protein in the nucleus (stable)
- Cancer cell has minimal STING activity

- Vehicle
- Control ADC
- Free payload
- Targeted ADC

Graph showing % Red Object Confluency vs. Hours Post Treatment with different concentrations of Agonist [nM].
Durable Tumor Regressions in 10/10 Animals at 3 mg/kg
STING ADC at Significantly Lower Dose Outperforms Systemically Administered Agonist

Tumor Growth Inhibition

<table>
<thead>
<tr>
<th>Tumor Volume (mm³)</th>
<th>Mean +/- SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td></td>
</tr>
<tr>
<td>Control STING ADC</td>
<td>(3 mg/kg Mab / 0.1 mg/kg payload)</td>
</tr>
<tr>
<td>STING agonist benchmark</td>
<td>(5 mg/kg payload)</td>
</tr>
<tr>
<td>Targeted STING ADC</td>
<td>(3 mg/kg mAb / 0.03 mg/kg payload)</td>
</tr>
<tr>
<td>Targeted STING ADC</td>
<td>(3 mg/kg mAb / 0.1 mg/kg payload)</td>
</tr>
</tbody>
</table>

Tumor Cytokine Profile Consistent with STING Activation

Change in Body Weights

Days on Study

% Body Weight Change

Single dose
Day 1

4/5 tumor free

10/10 tumor free

mCXCL10

mIL-6

Vehicle
Targeted-ADC
Control-ADC
A special thank you to all of the patients involved in our clinical trial, and their families