A NaPi2b Antibody-Drug Conjugate Induces Durable Complete Tumor Regressions in Patient-Derived Xenograft Models of NSCLC

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Disclosure:
Donald Bergstrom is an Employee of Mersana Therapeutics
NaPi2b Expression in Normal Lung and NSCLC

Normal Lung
- Type 2 pneumocytes
- Bronchial epithelium

NSCLC Adenocarcinoma
- 57% (20/35) NaPi2b positive (Mersana data)
- 87% NaPi2b positive (Genentech data\(^1\))
- High rate of positive staining in nonmucinous ovarian tumors and papillary thyroid tumors\(^1\)

\(^1\)Lin et al., Clinical Cancer Research 2015
XMT-1536: A Novel Antibody-Drug Conjugate Targeting NaPi2b

XMT-1536 utilizes Dolaflexin ADC platform
  • First Dolaflexin IND cleared October, 2016

12-15 payload molecules per antibody, increasing efficacy without impacting PK or physical/chemical properties

Proprietary auristatin metabolism allows for detoxification of release products in tumor, increasing tolerability and therapeutic index
XMT-1536 Drives Complete Regressions in Patient-Derived NSCLC Models

CTG-0852:
EML4-ALK translocation
TP53 F134L

Best Tumor Response in 8 Adenocarcinoma PDX Models
3 mg/kg dose, weekly x3

** statistically significant tumor growth delay, p < 0.01

Weekly dosing x3 (Days 0, 7, 14)

EGFR mut/amp
ALK translocation
KRAS/BRAF mut

** statistically significant tumor growth delay, p < 0.01
**XMT-1536 Regressions Show Good Durability**

Mouse PDX Experimental Design
3 mg/kg dose, weekly x3

<table>
<thead>
<tr>
<th>Tumor-free @ Days 60</th>
<th>1/6</th>
<th>3/8</th>
<th>5/6</th>
<th>6/6</th>
<th>6/6*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 60 TV relative to Day 0 (%)</td>
<td>258</td>
<td>-82</td>
<td>100</td>
<td>100</td>
<td>100*</td>
</tr>
</tbody>
</table>

*ST1976B achieves CR durable to Day 60 at 1 mg/kg dose level

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**Day 60 Tumor Volume in 5 PDX with Regressions**

- **Tumor Volume (mm³)**
  - 0
  - 500
  - 1000
  - 1500

- **Tumor Volume in 5 PDX with Regressions**
  - **ST1437**
  - **CTG-0852**
  - **ST742**
  - **ST1906**
  - **ST1976B**

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**Weekly dosing x3 (Days 0, 7, 14)**

- **No Treatment Interval (Days 15-60)**
- **End-of-Study (Day 60)**
XMT-1536 Well-Tolerated with Good Exposure in Cynomolgus Monkey

Single dose exploratory study at 1.25, 2.5 and 5 mg/kg ADC Dose
No body weight loss or ADC-related clinical observations
No neutropenia or anemia

<table>
<thead>
<tr>
<th>Dose</th>
<th>Terminal Necropsy</th>
<th>Recovery Necropsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Liver</td>
<td>None</td>
<td>Minimal hepatocyte apoptosis</td>
</tr>
<tr>
<td>Lung</td>
<td>None</td>
<td>Minimal mixed inflammatory cell infiltrate</td>
</tr>
<tr>
<td>Urinary Bladder</td>
<td>None</td>
<td>Minimal mucosal apoptosis; occasional mitotic figures</td>
</tr>
<tr>
<td>Stomach</td>
<td>None</td>
<td>Mild focal ulceration</td>
</tr>
</tbody>
</table>

ADC PK at 5 mg/kg ADC Dose
(358 μg/kg auristatin payload equivalents)

13.1 drug payload molecules conjugated per antibody
Molar ratio of conjugated drug payload:antibody in plasma: ~10-20X
Free drug payload not detected at any time point (1.25 nM LLOQ)
• NaPi2b is an attractive ADC target for lung cancer due to frequent expression in non-squamous NSCLC and limited normal tissue expression

• XMT-1536, an antibody-drug conjugate targeting NaPi2b, carries 12-15 auristatin payload molecules per antibody molecule

• XMT-1536 induced deep tumor regressions in 5/8 patient derived adenocarcinoma xenograft models
  • Tumor response to XMT-1536 was independent of tumor genotype

• Tumor responses to XMT-1536 were durable, with tumor regressions sustained >45 days following cessation of treatment in 4/5 models with regression as best response

• XMT-1536 had good plasma exposure and was well-tolerated in cynomolgus monkey after a single 5 mg/kg ADC dose, with no evidence of significant toxicity

• IND-enabling studies are underway with IND anticipated in the second half of 2017