I have the following financial relationships to disclose:

Employee of: Merrimack Pharmaceuticals™

- and -

I will not discuss off label use and/or investigational use in my presentation.
Nanoliposomal Targeting of Ephrin Receptor A2 (EphA2): Preclinical In Vitro and In Vivo Rationale

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MM-310

• ADN: Antibody-Directed Nanotherapeutics
• MM-310: EphA2-targeted docetaxel ADN
• Evidence of EphA2 targeting
• Translation to efficacy
Antibody-Targeted Therapeutic Platforms

**Antibody Drug Conjugate (ADC)**

- One < multiple copies of the antibody
  - Bypass the need for high affinity antibodies

- $n < n \times 10^4$ cytotoxic molecules
  - Bypass the need for high potency drugs
  - Non-covalent association

- Preferential deposition in tumor through the enhanced permeability and retention effect

**Antibody-Directed Nanotherapeutic ADN**

- Bypass the need for high affinity antibodies

References:
- Muggia M et al. 1999 Clin Cancer Res
- Mamot C et al. 2003 Drug Resist Update
MM-310: EphA2-Targeted Docetaxel ADN

EphA2 Targeting

Docetaxel prodrug
[Approximately 30,000 per Ls]
- Broad spectrum activity
- Dose-limiting toxicities

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Steep Dose-Response Relationship of Docetaxel

Table 4. Patients With Grade 3 to 4 Hematologic Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Docetaxel Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60 mg/m² (n = 149)</td>
</tr>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>73</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>113</td>
</tr>
<tr>
<td>Fever/neutropenia</td>
<td>7</td>
</tr>
<tr>
<td>Infection</td>
<td>3</td>
</tr>
<tr>
<td>Anemia</td>
<td>9</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
</tr>
</tbody>
</table>

*One hundred forty-eight patients were assessable (had blood count between days 2 and 19 of at least one cycle).
†One hundred eighty-two patients were assessable (had blood count between days 2 and 19 of at least one cycle).
‡P = .002 using Cochran-Mantel-Haenszel test of overall proportions.
§P = .035 using Cochran-Mantel-Haenszel test of overall proportions.

MM-310 Nanoliposomal Encapsulation Protects Against Docetaxel-Induced Hematologic Toxicity in Rats

Abstract #3912
Rat chronic toxicology study

- Sprague Dawley Rats
- 10 weeks old males

Groups
- Control
- MM-310 10 mp/kg bw
- MM-310 20 mp/kg bw
- MM-310 40 mp/kg bw
- Docetaxel 10 mp/kg bw (DTX)

RBC  HGB  HCT  RETIC  PLT  WBC  LUC  NEUT  BASO  EOS  LYMPH  MONO

Treatment Phase
Day 18

Recovery
Day 30

% Decrease from control

mg/kg bw treatment

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MM-310: EphA2-Targeted Docetaxel ADN

**Docetaxel prodrug**
[Approximately 30,000 per Ls]
- Broad spectrum activity
- Dose-limiting toxicities

**EphA2 Targeting**
- High prevalence in multiple tumor types
- Expression in stroma: Tumor-associated blood vessels & myofibroblasts

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High Prevalence of EphA2 in Multiple Indications

Abstract #750

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Cancer Cells</th>
<th>Tumor-associated myofibroblasts</th>
<th>Tumor-associated blood vessels</th>
<th>EphA2 Overall Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urothelial (n=20)</td>
<td>95%</td>
<td>0%</td>
<td>80%</td>
<td>95%</td>
</tr>
<tr>
<td>Gastric/GEJ (n=20)</td>
<td>90%</td>
<td>15%</td>
<td>85%</td>
<td>100%</td>
</tr>
<tr>
<td>Head &amp; Neck (n=19)</td>
<td>84%</td>
<td>0%</td>
<td>47%</td>
<td>100%</td>
</tr>
<tr>
<td>Non-Small Cell Lung (n=41)</td>
<td>58%</td>
<td>2.4%</td>
<td>58%</td>
<td>68%</td>
</tr>
<tr>
<td>Ovarian (n=18)</td>
<td>55%</td>
<td>39%</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>Pancreatic (n=19)</td>
<td>79%</td>
<td>0%</td>
<td>58%</td>
<td>89%</td>
</tr>
<tr>
<td>Prostate (n=23)</td>
<td>27%</td>
<td>27%</td>
<td>28%</td>
<td>52%</td>
</tr>
<tr>
<td>Triple Negative Breast (n=77)</td>
<td>7%</td>
<td>0%</td>
<td>44%</td>
<td>48%</td>
</tr>
</tbody>
</table>
MM-310: EphA2-Targeted Docetaxel ADN

EphA2 Targeting
- High prevalence in multiple tumor types
- Expression in stroma: Tumor-associated blood vessels & myofibroblasts

Docetaxel prodrug
[Approximately 30,000 per Ls]
- Broad spectrum activity
- Dose-limiting toxicities

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EphA2 Target Engagement *In vitro* is Highly Specific

\[ \text{pearson } r=0.81 \]
Interplay Between Nanotherapeutic Delivery & EphA2 Targeting

Perfusion
Permeability
Transport
Specific Cell Uptake
Non-Specific Uptake

Normal Endothelium
Tumor Endothelium


IV
Dil5-EphA2-Ls
Dil3-NT-Ls
Co-localization analysis
EphA2 Targeting Mediates Retention of the ADN in Primary Tumors, Not in Normal Tissues
EphA2 Targeting Leads to Retention of the ADN in the Core of the Tumor

EphA2 targeting \textit{in vivo} is predominantly seen in the tumor core
Evidence of Target Engagement *In Vivo* in Lung Metastasis

**Metastatic Breast Cancer Model**
MDA-MB-231 IV

**Control Animal**
- Nuclei
- EphA2-Ls
- NT-Ls

**Metastatic Breast Cancer Model**
MDA-MB-231 Orthotopic

**Nuclei**
**EphA2-Ls**
**NT-Ls**
EphA2 Targeting Contributes to Activity

EphA2 targeting contributes to activity in a context dependent manner.
**Docetaxel Prodrug Nanoliposome**
- Increases circulation time
- Protects against hematologic toxicities in rodent and non-rodent models
- Leads to sustained release at the tumor site

**EphA2 Targeting**
- Targets cancer cells in the core of primary tumors, and metastatic lesions
- Leads to more pronounced and sustained tumor regression *in vivo*
- EphA2 is expressed in tumor-associated blood vessels

**MM-310 Abstracts**

- **Nanoposomal targeting of Ephrin Receptor A2 (EphA2): Clinical translation**
  Targeting the Microenvironment - Abstract #750
  Sunday, April 17, 2016 1:00 PM – 5:00 PM

- **Activity of an EphA2-targeted docetaxel nanoliposome in pancreatic patient-derived models as monotherapy and in combination with Gemcitabine**
  Experimental and Molecular Therapeutics - Abstract #2069
  Monday Apr 18, 2016 1:00 - 5:00 PM

- **MM-310, a novel EphA2-targeted docetaxel nanoliposome**
  Therapeutics - Abstract #3912
  Tuesday Apr 19, 2016 1:00 PM - 5:00 PM