Utilizing Probody® Technology to Develop Therapeutics to Undruggable Targets

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This presentation concerns products that have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). No representation is made as to their safety or effectiveness for the purposes for which they are being investigated.
Overview of Probody® technology

CX-2029: A Probody Drug Conjugate (PDC) Targeting Transferrin Receptor (CD71)
• Target rationale (rapid internalization, ubiquitous tumor expression)
• Preclinical efficacy and nonclinical safety

CX-2043: A PDC targeting EpCAM (CD326)
• Target rationale (high tumor expression)
• Preclinical efficacy and nonclinical safety
Probody Therapeutics are Designed to be Activated in the Tumor Microenvironment (TME)

ON TARGET TOXICITY LIMITS THE DEVELOPMENT OF POTENTIALLY ATTRACTIVE ANTIBODY THERAPEUTICS

• “Masked” to limit binding to normal tissue
• “Un-masked” by tumor-associated proteases
• Linkers cleaved by multiple proteases for utility across tumor types

CYTOMX PROBODY PLATFORM IS DESIGNED TO LOCALIZE TARGET BINDING TO TUMOR

• Maintaining potency
• Reducing side effects
• Enabling new target opportunities

PROBODY PLATFORM IS APPLICABLE ACROSS MULTIPLE TARGETS AND MODALITIES

• Improve therapeutic window for validated targets
• Create therapeutic window for undruggable targets
• Applicable to multiple binding modalities
Activated Proteases are Prevalent in Tumors but Not in Healthy Tissue

Upregulated protease activity is a hallmark of all cancers. 


Protease activity is tightly controlled in healthy tissues.

Primary Tumor
- Angiogenesis
- Inflammation
- Invasion
- Proliferation and survival
- Extravasation
- Colonization and outgrowth

Metastasis

Imaging of active protease

Primary Colon Cancer
Metastatic Colon Cancer
Normal Colon
Probody Platform is Applicable Across Multiple Modalities

IMMUNE MODULATORS/ CHECKPOINT INHIBITORS
- PD-L1 (CX-072)
- PD-1 (CX-188)
- CTLA-4 (BMS-986249, 986288)

ANTIBODY DRUG CONJUGATES
- CD166 (CX-2009)
- CD71 (CX-2029)
- EpCAM (CX-2043)
- Multiple undisclosed programs

T-CELL BISPECIFICS
- EGFR-CD3 (CX-904)
- Multiple undisclosed programs

CYTOKINES
- Multiple undisclosed programs

DISCOVERY STAGE

Probody Platform is Applicable Across Multiple Modalities
Probody Platform Expands Target Landscape; Converting Undruggable to Druggable

Efficiently Internalizing  
High Membrane Expression  
Uniform Tumor Expression  
Majority of Patients Express at High Level  
Highly Expressed in Multiple Common Cancers

These targets are typically expressed highly in normal tissues → not suitable for traditional ADC
CX-2029:
A Probody Drug Conjugate (PDC)
Targeting CD71, Transferrin Receptor

Clinical Presentation: Dr. Alison Hannah, CMO
12:10pm Sept. 16th, Clinical Stream
CD71 (TfR1) Transferrin Receptor

- Transmembrane glycoprotein that efficiently internalizes iron-bound transferrin
- Ubiquitously expressed on malignant cells, i.e. NSCLC-SCC, CRC, esophageal
- ‘Professional’ internalizing antigen
- Also expressed in healthy tissues with high iron requirement, notably
  - Dividing cells
  - Erythrocyte precursors
- Considered ‘undruggable’ with traditional ADC technology
- CX-2029 is a masked form of a proprietary anti-CD71 antibody conjugated to MMAE (DAR = 2)
  - Partnership with AbbVie

CX-2029 is Active in CDX and PDX Tumor Models in Mice

- Parental anti-CD71 antibody binds equivalently to human and monkey CD71 (ELISA)
- Intact Probody therapeutic shows reduced binding to CD71
- Protease activation of PDC restores binding activity
- Broad, potent activity in mouse tumor models

### Model Type

<table>
<thead>
<tr>
<th>Model Type</th>
<th>CDX (unselected)</th>
<th>PDX (high expressing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regressions or Stasis</td>
<td>15/21 (71%)</td>
<td>30/36 (83%)</td>
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</table>

### EFFICACY IN PDX MODELS

- **CDX** - cell line derived xenograft
- **PDX** - patient derived xenograft
CX-2029 Was Tolerated at a Higher Dose Than CD71 ADC in *Cynomolgus* monkeys, DAR = 2

<table>
<thead>
<tr>
<th>Test Article</th>
<th>Dose (mg/kg)</th>
<th>Outcome</th>
<th>Hemoglobin*</th>
<th>Neutrophil count*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>NA</td>
<td>--</td>
<td>13.1</td>
<td>4,693</td>
</tr>
<tr>
<td>CX-2029 (PDC)</td>
<td>6</td>
<td>Tolerated</td>
<td>10.1</td>
<td>347</td>
</tr>
<tr>
<td>CX-2029 (PDC)</td>
<td>12</td>
<td>Not tolerated</td>
<td>9.0</td>
<td>87</td>
</tr>
<tr>
<td>CX-2030 (ADC)</td>
<td>6</td>
<td>Not tolerated</td>
<td>6.6 (d10)</td>
<td>20 (d10)</td>
</tr>
<tr>
<td>CX-2030 (ADC)</td>
<td>2</td>
<td>Not tolerated</td>
<td>9.3 (d7)</td>
<td>70 (d7)</td>
</tr>
<tr>
<td>CX-2030 (ADC)</td>
<td>0.6</td>
<td>Tolerated</td>
<td>12.2</td>
<td>280</td>
</tr>
</tbody>
</table>

*Average HGB (g/dL), d15 or as indicated; average neutrophil count (per ul) on Day 11 or as indicated

- Primary toxicities are hematologic: Neutropenia and anemia
  - Consistent with either on-target (CD71-mediated) and/or off-target toxicity of MMAE
- Mortality at non-tolerated dose levels was attributed to bacterial infection

In clinical trial, phase I/II: NCT03543813 in collaboration with AbbVie
CX-2043: A Probody Drug Conjugate (PDC) Targeting EpCAM
### EpCAM Target Biology and Opportunity for Probody Technology

<table>
<thead>
<tr>
<th>TARGET BACKGROUND</th>
<th>PDC OPPORTUNITY</th>
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<tbody>
<tr>
<td>• Discovered via immunization of cancers in mice in 1979</td>
<td>• Alleviate ON-target/OFF-tumor toxicity (pancreatitis, GI tox)</td>
</tr>
<tr>
<td>• Epithelial cell marker</td>
<td>• Retain potent efficacy</td>
</tr>
<tr>
<td>– Widely used for delivery of toxins and immune stimulatory agents for epithelial cancers</td>
<td>• Improve exposure by reducing target mediated clearance (TMDD)</td>
</tr>
<tr>
<td>• Target with previously approved therapy (Catumaxomab: EpCAM-CD3 TCB)</td>
<td>• Expanded therapeutic index</td>
</tr>
<tr>
<td>– Usage limited to local injection due to toxicity, discontinued in 2017</td>
<td></td>
</tr>
<tr>
<td>• Development of EpCAM-targeting therapeutics hindered by ON-target/OFF-tumor toxicity</td>
<td></td>
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<tr>
<td>– Pancreatitis with α-EpCAM Ab</td>
<td></td>
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<tr>
<td>– GI tox with EpCAM-CD3 BiTE</td>
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</table>

- **Probody therapeutic**
- **Proteases**
- **Substrate linker**
- **Masking peptide**
EpCAM expression is also present in corresponding normal tissues, and high in colon and GI tissues.
CX-2043: A Probody Drug Conjugate (PDC) Targeting EpCAM

- Stochastic lysine conjugation, DAR 3.5 – 4
- Optimized stability with tripeptide linker, cleavable by intracellular lysosomal proteases
- Provides improved bystander activity
Single Dose of CX-2043 is Efficacious, Particularly in High Target Expression Models

NCI-H441 (NSCLC); high expression

HCT116 (CRC) high expression

Calu-3 (NSCLC); high expression

Detroit562 (H&NSCC); med expression

NCI-H292 (NSCLC); low expression

BxPC3 (Pancreatic); low expression

Single dose or fractionated
- CX-2043 low (0.9-2.5 mpk)
- CX-2043 high (3-5 mpk)
- CX-2043 fractionate (QWX3)
- IgG-DM21 high (3-5 mpk)
- Vehicle
CX-2043 is Well Tolerated in Cyno up to 9 mg/kg; Q2WX2 Dosing

<table>
<thead>
<tr>
<th>Dosing (Q2WX2)</th>
<th>ADC</th>
<th>PDC</th>
<th>Isotype</th>
</tr>
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<tbody>
<tr>
<td>3 mpk</td>
<td>Not tolerated</td>
<td>Tolerated</td>
<td>Tolerated</td>
</tr>
<tr>
<td>6 mpk</td>
<td>Not tolerated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9 mpk</td>
<td></td>
<td>Tolerated</td>
<td></td>
</tr>
<tr>
<td>12 mpk</td>
<td></td>
<td>Tolerated</td>
<td></td>
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**TOXICITY**
- **Isotype-DM21-L-G ADC** at 12 mg/kg:
  - Dry, discolored skin; abrasion
  - Liquid feces, mild dehydration
  - ↓ albumin, electrolytes (Na⁺, Cl⁻), RBC
- **EpCAM-DM21-L-G PDC** at 9 mg/kg:
  - Dry skin, slight abrasion
  - Mild dehydration
- **EpCAM-DM21-L-G ADC** at 3 and/or 6 mg/kg:
  - > 10% weight loss, liquid feces
  - Early euthanasia required
  - ↓ albumin, Na⁺, Cl⁻, RBC; ↑ AST, BUN, CRN

**PHARMACOKINETICS**
- Increased PDC exposure relative to ADC suggests mitigation of target mediated clearance (TMDD) and effective masking
## Summary: Utilizing Probody Technology for PDC Development

<table>
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<tr>
<th>Probody Technology</th>
<th>• Designed to be minimally active systemically, until activated in the protease-enriched diseased microenvironment</th>
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</table>
| Probody Advantages | • Mitigation of ON-target/OFF-tumor toxicity  
                        • Allows expansion of target landscape and development of therapeutics to traditionally undruggable targets, i.e. CD71 and EpCAM |
| PDC Opportunities  | • Probody technology combined with next generation of linker-payloads for CX-2043 (EpCAM-PDC) has the potential to realize a therapeutic index |
| Advancing Clinical PDC Programs | • CytomX PDC programs, CX-2009 (CD166) and CX-2029 (CD71), demonstrated promising results and are proceeding to phase II clinical trials. CX-2043 (EpCAM) is in IND enabling studies |