American Association for Cancer Research Investor Meeting

Targeting the Tumor Microenvironment
Forward-Looking Statements

All of the statements in this presentation that are not statements of historical facts constitute forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Examples of such statements include future product development and regulatory events and goals, anticipated clinical trial results and strategies, product collaborations, our business intentions and financial estimates and results. These statements are based upon management’s current plans and expectations and are subject to a number of risks and uncertainties which could cause actual results to differ materially from such statements. A discussion of the risks and uncertainties that can affect these statements is set forth in the Company’s annual and quarterly reports filed from time to time with the Securities and Exchange Commission under the heading “Risk Factors.” The Company disclaims any intention or obligation to revise or update any forward-looking statements, whether as a result of new information, future events, or otherwise.
American Association for Cancer Research Investor Meeting

Opening Remarks

Dr. Helen Torley
President and CEO

April 18, 2016
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<thead>
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<th>Presenter</th>
</tr>
</thead>
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President and CEO                                      |
| 10 minutes| Focus on the Tumor Microenvironment              | Dr. Michael LaBarre  
VP, Chief Scientific Officer                               |
| 10 minutes| PEGPH20 Immuno-Oncology                         | Dr. Sanna Rosengren  
Director, Immunology and Cell Biology                         |
| 10 minutes| PEG-ADA2: PEGylated Adenosine Deaminase 2       | Dr. Christopher Thanos  
Senior Director, Biotherapeutics Discovery                     |
| 10 minutes| HTI-1511: Anti-EGFR Antibody-Drug Conjugate     | Dr. Christopher Thanos  
Senior Director, Biotherapeutics Discovery                     |
<p>| 15 minutes| Questions and Answers                           | All                                                |</p>
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Focus on the Tumor Microenvironment

Dr. Michael LaBarre
Vice President, Chief Scientific Officer

April 18, 2016
Our Focus: Developing Therapeutics That Target the Tumor Microenvironment (TME)

Modify the TME Structure

- **PEGylated human recombinant PH20 (PEGPH20)**
  - to deplete hyaluronan (HA) in the TME and increase tumor access

Leverage the TME Biochemistry and Physiology

- **PEGylated adenosine deaminase 2 (PEG-ADA2)**
  - to deplete adenosine (an immune checkpoint) in the TME
- **Anti-EGFR-ADC (HTI-1511)**
  - to bind preferentially to EGFR at low pH in TME and deliver cytotoxic drug conjugate to tumor cells
The Tumor Microenvironment

- Cancer cell
- Vasculature
- HA
- Collagen
- Macrophage
- T cell
- Treg
- MDSC
- Fibroblast
- Adenosine
- Molecular Receptors
The Tumor Microenvironment

- Collagen
- Fibroblast
- Vasculature
- Macrophage
- Treg
- MDSC
- T cell
- Adenosine
- HA
- Molecular Receptors
- HA and Collagen
The Tumor Microenvironment

- Cancer cell
- Vasculature
- HA
- Collagen
- Macrophage
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- MDSC
- Fibroblast
- Adenosine
- Molecular Receptors
The Tumor Microenvironment

Regions of
- Low O₂
- Low pH
The Tumor Microenvironment

Collagen

Fibroblast

Vasculature

Macrophage

T cell

Treg

MDSC

Adenosine

Molecular Receptors

HA and Collagen
Hyaluronan (HA) Can Be a Barrier to Therapeutic and Immune Cell Access to Tumor Cells

- **HA is a Structural Carbohydrate**
  - Hydrophilic, viscous polysaccharide

- **Stabilizes the Tumor Microenvironment**
  - Provides structure for extracellular and cell surface components

---

Hyaluronan (HA) Can Be a Barrier to Therapeutic and Immune Cell Access to Tumor Cells

- **HA is a Structural Carbohydrate**
  - Hydrophilic, viscous polysaccharide

- **Stabilizes the Tumor Microenvironment**
  - Provides structure for extracellular and cell surface components

- **Compromises Access to the Tumor**
  - Increased tumor interstitial pressure
  - Vasculature compression
  - Can decrease therapeutic and immune cell access

---

HA Accumulation Associated With Decreased Survival in Some Tumors in Clinical Trials

Negative correlation with survival also reported in gastric, colorectal, ovarian, non-small cell lung, metastatic breast and prostate cancers.

PEGPH20 Targets Hyaluronan in the TME

Removal of HA by PEGPH20 demonstrated in HA-high tumor animal models to:

- Decrease intratumoral pressure
- Decompress vasculature
- Increase perfusion
- Increase access for therapeutics
- Increase access for immune cells
PEGPH20 Decreased HA in an HA-high Wilms’ Tumor Animal Model

WT-CLS1/HAS3 HA-high peritibial Wilms’ tumor model

Vehicle

PEGPH20 37.5 µg/kg (HED)

HA (brown) staining with HTI-601 (HA-specific binding probe developed at Halozyme)

Tumors harvested 6h after 2 doses of Vehicle or PEGPH20 on days 0 and 3

Cowell et al. (2016). AACR Annual Meeting, Poster #2463
PEGPH20 Reduced Tumor Interstitial Fluid Pressure in HA-high Prostate Cancer Animal Model

PC3 peritibial prostate tumor model

Time after Treatment (min)

IV dose

Normalized Tumor IFP

PEGPH20 Dose (mg/kg)

Vehicle ~40 mmHg

0.015

0.15

1.5

4.5

15

Thompson et al. Mol Cancer Ther. 9:3052 (2010)
Hyperechoic microbubbles imaged to visualize vasculature “space” or vascular area of peritibial PC3 tumors ± PEGPH20 (15 mg/kg, IV). Blue tracing is tumor area.

Thompson et al. Mol Cancer Ther. 9:3052 (2010)
Vascular Decompression Increased Drug Delivery in HA-high Prostate Cancer Animal Model

**PC3 peritibial prostate tumor model**

Increased tumor DOXIL (measured as doxorubicin)

Increased drug accumulation not observed in normal tissues tested

Thompson et al. Mol Cancer Ther. 9:3052 (2010)
PEG PH20 Increased Activity of Vincristine and Dactinomycin in HA-high Wilms’ Tumor Animal Model

WF-CLS1/HAS3 HA-high peritibial tumor model

PEGPH20 37.5 µg/kg (HED), vincristine 0.415 mg/kg, dactinomycin 0.125 mg/kg 2x weekly

Cowell et al. (2016). AACR Annual Meeting, Poster #2463
PEG PH20 Increased Activity of Vincristine and Dactinomycin in HA-high Wilms’ Tumor Animal Model

**WF-CLS1/HAS3 HA-high peritibial tumor model**

PEGPH20 37.5 µg/kg (HED), vincristine 0.415 mg/kg, dactinomycin 0.125 mg/kg 2x weekly

Cowell et al. (2016). AACR Annual Meeting, Poster #2463
PEG PH20 Increased Tumor Growth Inhibition of shIDO-ST in HA-high Pancreatic Cancer Animal Model

PEGPH20 2.25 mg/kg on day 13
shIDO-ST 5 x 10^6/dose on day 14, 15 and 16 (n=3/group)

PEGPH20 With shIDO-ST Increased Immune Cell Influx in HA-high Pancreatic Cancer Animal Model

PEGPH20 2.25 mg/kg on day 13
shIDO-ST 5 x 10^6/dose on day 14, 15 and 16
Tumors extracted 96 hours post-ST treatment

KPC-derived pancreatic cancer model

PEG PH20 + Control-ST

PEG PH20 + shIDO-ST

Epi-fluorescence

Counts

Neutrophil accumulation

Manuel et al. Cancer Immunol Res. 3:1096, Figure S8 (2015)
### Leukocytes (e.g., NK cells\(^1\), T cells\(^2\), neutrophils\(^3\))

### shIDO-ST cellular immunotherapy\(^3\)

### Liposomes/nanoparticles (e.g., ABRAXANE®\(^4\), DOXIL®\(^5\))

### Monoclonal antibodies (e.g., cetuximab\(^6\), trastuzumab\(^1\))

### Small molecules (e.g., gemcitabine\(^7\))

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American Association for Cancer Research
Investor Meeting

PEG PH20 Immuno-Oncology

Dr. Sanna Rosengren
Director, Immunology and Cell Biology

April 18, 2016
The Tumor Microenvironment

- Cancer cell
- Vasculature
- HA
- Collagen
- Macrophage
- T cell
- Treg
- MDSC
- Fibroblast
- Adenosine
- Molecular Receptors
The Tumor Microenvironment

Immune Cell Involvement

- Cancer cell
- Vasculature
- HA
- Collagen
- Macrophage
- T cell
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- Molecular Receptors
Anti-Tumor T Cells Face Immunosuppressive Barriers in the TME
Anti-Tumor T Cells Face Immunosuppressive Barriers in the TME
Anti-Tumor T Cells Face Immunosuppressive Barriers in the TME

**Immuno-suppressive cells**
- Regulatory T cell
- Myeloid suppressor cell
- M2 macrophage

**Legend**
- Blocking interaction

**Immune checkpoints**
- PD-L1
- PD-1
- CTLA4

**Blocking interaction**
- PD-L1
- PD-1
- CTLA4
Anti-Tumor T Cells Face Immunosuppressive Barriers in the TME

Immunosuppressive cells

- Regulatory T cell
- Myeloid suppressor cell
- M2 macrophage

Legend

- Blocking interaction
- High Levels
  Immunosuppressive cytokines and growth factors

Immune checkpoints
- Tumor cell
- PD-1
- PD-L1
- Anti-tumor T cell
- Antigen-presenting dendritic cell
- CTLA4
Some Biomarkers of Immunosuppression Increased in HA-high Colon Cancer Animal Model

CT26/HAS3 HA-high syngeneic colon tumor model

IL10
(immunosuppressive cytokine)

p = 0.009

FoxP3
(regulatory T cell marker)

p = 0.002

CTLA4
(immune checkpoint)

p = 0.008

Other immunosuppressive genes, including PD-L1 and IDO, were not significantly different in this model

Rosengren et al. (2016). AACR Annual Meeting, Poster #4886
Does PEG PH20 Increase Activity of Anti-CTLA4 Antibodies in HA-high Tumors?

- CTLA4 engagement blocks co-stimulation of activated T cells
- Anti-CTLA4 antibodies can lower tumor immunosuppression
- PEG PH20 might enhance their efficacy in HA-high tumors
PEGPH20 37.5 µg/kg (HED) biweekly, 24h prior to anti-CTLA4 or IgG2b isotype control (4 mg/kg)

Rosengren et al. (2016). AACR Annual Meeting, Poster #4886
PEGPH20 Effect on Anti-CTLA4 Activity in HA-high and HA-low Colon Cancer Animal Models

CT26/HAS3 HA-high model

- Isotype control
- PEGPH20
- Anti-CTLA4
- PEGPH20 + anti-CTLA4

CT26 HA-low model

- Isotype control
- PEGPH20
- Anti-CTLA4
- PEGPH20 + anti-CTLA4

PEGPH20 37.5 µg/kg (HED) biweekly, 24h prior to anti-CTLA4 or IgG2b isotype control (4 mg/kg)

Rosengren et al. (2016). AACR Annual Meeting, Poster #4886
Does PEG PH20 Increase the Activity of Anti-PD-1/PD-L1 Antibodies in HA-high Tumors?

- PD-1/PD-L1 interaction sends signal of exhaustion to T cell
- Anti-PD-1/PD-L1 antibodies can lower tumor immunosuppression
- PEG PH20 might enhance their efficacy in HA-high tumors
PEGPH20 Increased Activity of Anti-PD-1 in HA-high Pancreatic Cancer Animal Model

PEGPH20 37.5 µg/kg (HED) 2x weekly, 24h prior to anti-PD-1 (0.5 mg/kg)

KPC-derived HA-high pancreatic tumor model

PEGPH20 37.5 µg/kg (HED) 2x weekly, 24h prior to anti-PD-1 (0.5 mg/kg) Rosengren et al. (2016). AACR Annual Meeting, Poster #4886
PEGPH20 Increased Activity of Anti-PD-L1 in HA-high Pancreatic Cancer Animal Model

PEGPH20 37.5 µg/kg (HED) 2x weekly, 24h prior to anti-PD-L1 or IgG2b isotype control (2 mg/kg)

Rosengren et al. (2016). AACR Annual Meeting, Poster #4886
PEG PH20 Combined With Anti-PD-L1 Induced Regressions in HA-high Pancreatic Cancer Animal Model

KPC-derived HA-high pancreatic tumor model

PEG PH20 3.75 µg/kg (HED) 2x weekly, 24h prior to anti-PD-L1 or IgG2b isotype control (2 mg/kg)

Rosengren et al. (2016). AACR Annual Meeting, Poster #4886
Human Equivalent Dose of PEG PH20 Reduced HA in HA-high Pancreatic Cancer Animal Model

KPC-derived HA-high pancreatic tumor model

Pre-treatment

24 hours after PEG PH20 (37.5 µg/kg)

HA (brown) staining with HTI-601 (HA-specific binding probe developed at Halozyme)

PEG PH20 37.5 µg/kg (HED) 2x weekly, 24h prior to anti-PD-L1 or IgG2b isotype control (2 mg/kg)

Rosengren et al. (2016). AACR Annual Meeting, Poster #4886
PEGPH20 Enhanced Anti-PD-L1 Accumulation in HA-high Ovarian Cancer Animal Model

SKOV3/HAS2 ovarian tumor model with anti-human-PD-L1-AlexaFluor 488

Individual Tumors

Anti-PD-L1-AlexaFluor 488 Fluorescence

Rosengren et al. (2016). AACR Annual Meeting, Poster #4886
HA-high tumor status may lead to a more immunosuppressive TME

In HA-high syngeneic mouse tumors, PEGPH20 enhanced the effect of immune checkpoint inhibitors

In HA-low mouse tumors, a combinatorial effect was not observed

PEGPH20 treatment increased anti-PDL1 antibody accumulation in ovarian tumor xenograft model with elevated HA
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PEG-ADA2: PEGylated Adenosine Deaminase 2

Dr. Christopher Thanos
Senior Director, Biotherapeutics Discovery

April 18, 2016
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- Cancer cell
- Vasculature
- HA
- Collagen
- Macrophage
- T cell
- Treg
- MDSC
- Fibroblast
- Adenosine
- Molecular Receptors
The Tumor Microenvironment - Adenosine
The Adenosine Pathway: A Recognized Immune Checkpoint Interaction

Adenosine: A Key Suppressor of Immune Cells in Tumor Microenvironment

>100x Increase
Tumor Microenvironment Adenosine
~0.1 µM → ~50 µM

Adapted from Stagg & Smyth, Oncogene, 2010
Adenosine: A Key Suppressor of Immune Cells in Tumor Microenvironment

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Tumor Microenvironment Adenosine

~0.1 μM → ~50 μM

Saturation of Adenosine Receptor Checkpoints on Immune Cells

Adapted from Stagg & Smyth, Oncogene, 2010
ADA2: An Approach to Deplete Adenosine in the TME

- Catalyzes the deamination of adenosine to inosine\textsuperscript{1,2}
- Human, extracellular glycoprotein, \( \sim 120,000 \text{ MW} \textsuperscript{1,2} \)
- Highly resistant to inactivation in plasma\textsuperscript{3}
- Produced in standard CHO cells\textsuperscript{3}

\textsuperscript{1}Zavialov AV, Biochem J. 391, p51-7 (2005)
\textsuperscript{3}Wang et al. (2016). AACR Annual Meeting, Poster #1217
PEGylated ADA2: Improved Pharmacokinetics Profile in Animal Model

PEG-ADA2\textsuperscript{K374D} extended PK profile in mice*:

- $t_{1/2} = 37.6$ hours
- Less frequent dosing
- Systemic dosing

*Dosed at 3 mg/kg, n=9 mice/group

Wang et al. (2016). AACR Annual Meeting, Poster #1217
Tumor Growth Inhibition With PEG-ADA2 in Colon Cancer Animal Model

Murine CT26 colon tumor model

PEGADA2-K374D, 0.3 mg/kg 2X weekly, IV (N=8)

Wang et al. (2016). AACR Annual Meeting, Poster #1217
PEG-ADA2 Increased T-cell Infiltration in CT26 Colon Cancer Animal Models

Histological Assessment of T-cell infiltration

PEGADA2-K374D, 0.3 mg/kg
2X weekly, IV(N=8)

Wang et al. (2016). AACR Annual Meeting, Poster #1217
CD73 May Be a Useful Biomarker for Identifying Tumor Types That Could Respond to PEG-ADA2

Wang et al. (2016). AACR Annual Meeting, Poster #1217
CD73 May Be a Useful Biomarker for Identifying Tumor Types That Could Respond to PEG-ADA2

\[ \text{ATP} \xrightarrow{\text{CD39}} \text{AMP} \xrightarrow{\text{CD73}} \text{Adenosine} \]

**CD39 Expression in Various Tumors***

**CD73 Expression in Various Tumors***

*Syngeneic mouse tumors

Wang et al. (2016). AACR Annual Meeting, Poster #1217

Various solid tumor types tested
PEG-ADA2 Mediated Tumor Growth Inhibition in CD73-Positive Animal Models

**KLN-205 lung model**

- **Vehicle**
- **PEG-ADA2-K374D**

**KPC-derived pancreatic model**

- **Vehicle**
- **PEG-ADA2-K374D**

* p < 0.0001

PEGADA2-K374D, 0.3 mg/kg
2X weekly, IV(N=8)

Wang et al. (2016). AACR Annual Meeting, Poster #1217
Engineering ADA2 Yielded a Variant With a 16-fold Improvement in Enzymatic Activity

2Wang et al. (2016). AACR Annual Meeting, Poster #1217
Engineering ADA2 Yielded a Variant With a 16-fold Improvement in Enzymatic Activity

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<th>$k_{cat}/K_M \ (1/\text{Ms})$</th>
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<tbody>
<tr>
<td>Wild-Type</td>
<td>10,312</td>
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<td>R222Q/S265N$^2$</td>
<td><strong>165,411</strong></td>
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16x improved

2Wang et al. (2016). AACR Annual Meeting, Poster #1217
PEG-ADA2\textsuperscript{R222Q/S265N} Inhibited Lung Metastasis in Breast Cancer Animal Model

Study day 18, histological assessment
n=6 mice (vehicle), n=8 mice (treatment)
2x weekly dosing, 0.3 mg/kg

\textsuperscript{1}Wang et al. (2016). AACR Annual Meeting, Poster #1217
Treatment With PEG-ADA2 Decreased TME Adenosine Levels in Pancreatic Cancer Animal Model

KPC-derived mouse tumors
10 mm probe (55 kDa MWCO)
Microdialysis perfusates analyzed by LC-MS

Wang et al. (2016). AACR Annual Meeting, Poster #1217
PEG-ADA2 Program Highlights

**Adenosine:** Attractive immune checkpoint target

- Abnormally high levels accumulate in the TME
- Binds to receptor checkpoints on immune cells
- Contributes to an immunosuppressive TME

**PEG-ADA2:** An engineered human enzyme that targets adenosine

- Improved pharmacokinetics and enzyme activity
- Anti-tumor responses observed in several animal models
  - Increase in T-cell infiltration
  - Decrease in high TME adenosine levels
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HTI-1511: Anti-EGFR Antibody-Drug Conjugate

Dr. Christopher Thanos
Senior Director, Biotherapeutics Discovery

April 18, 2016
The Tumor Microenvironment - Molecular Receptors

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Molecular Receptors
Two Limitations With Anti-EGFR Therapeutics

1. Treatment can lead to skin rash
   - May limit dosing
     - ~90% cutaneous side effects\(^1-3\)

2. Downstream, activating mutations
   - KRAS mutations present in over 50% of mCRC\(^4\)
   - BRAF mutations in ~10% of mCRC\(^5\)
   - EGFR mutations in ~3-19% of NSCLC in west\(^6-7\)

\(^1\)Cunningham, NEJM 2004, \(^2\)Van Cutsem, JCO 2012, \(^3\)Amado, JCO 2008
\(^4\)Misale, Cancer Discovery 2014, \(^5\)Barras, Biomarkers in Cancer, 2015
\(^6\)Deerden, Annals in Oncology, \(^7\)Lee, JNCI 2013
Physicochemical Properties Offer Opportunities for TME-Specific Therapeutics

- **Tumor microenvironment**
  - ↓ pH vs. Healthy Tissue
  - ↑ Lactate
  - ↑ Albumin

- **Solid tumor example**
  - **Acidic pH**
  - Blood vessel (immunofluorescent)
  - Proliferation (iododeoxyuridine)
  - Hypoxia (pimonidazole)

Adapted from Lancet Oncol 2010; 11: 661–69
Halozyme mAb has Attenuated In Vitro Binding to EGFR at Skin pH

Huang, L. et al. (2016). AACR Annual Meeting, Poster #1472
Halozyme mAb Attenuated Human Skin Binding vs. Human Tumor Binding in Xenograft Models

Cetuximab Control
Comparable, strong binding between tumor and skin

Day 1  Day 2  Day 3
Tumor  Tumor  Tumor
Skin    Skin    Skin

Huang, L. et al. (2016). AACR Annual Meeting, Poster #1472
Halozyme mAb Attenuated Human Skin Binding vs. Human Tumor Binding in Xenograft Models

Cetuximab Control
Comparable, strong binding between tumor and skin

HALO Anti-EGFR mAb
Strong tumor, attenuated skin binding

Huang, L. et al. (2016). AACR Annual Meeting, Poster #1472
ADCs May Treat EGFR+ Mutation-Resistant Tumors

EGFR mediated signaling promotes cell growth

Adapted from Pao, Nature Reviews Cancer 10, 760-774 (2010)
ADCs May Treat EGFR+ Mutation-Resistant Tumors

**EGFR mediated signaling promotes cell growth**

- EGF
- EGFR
- KRAS
- BRAF
- MEK
- ERK/MAPK

**Naked anti-EGFR mAb inhibits signaling pathway**

- Naked mAb

No signaling

Proliferation
Angiogenesis
Migration
Survival

Adapted from Pao, Nature Reviews Cancer 10, 760-774 (2010)
ADCs May Treat EGFR+ Mutation-Resistant Tumors

EGFR mediated signaling promotes cell growth

Naked anti-EGFR mAb inhibits signaling pathway

Mutation promotes cell growth and is resistant to mAb therapy

Adapted from Pao, Nature Reviews Cancer 10, 760-774 (2010)
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<th>Mutation promotes cell growth and is resistant to mAb therapy</th>
<th>ADC overcomes mutation resistance and selectively kills tumor cell</th>
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EGF mediated signaling promotes cell growth

Naked mAb inhibits signaling pathway

Mutation promotes cell growth and is resistant to mAb therapy

ADC overcomes mutation resistance and selectively kills tumor cell

Adapted from Pao, Nature Reviews Cancer 10, 760-774 (2010)
Tumor Regressions in KRAS- and BRAF-Mutated Tumor Animal Models

**Human TNBC Tumor Xenografts**

MDA-MB-231M (KRAS$^{G13D}$)

- Vehicle
- Cetuximab (30 mg/kg)
- HALO Variant 1 - MMAE (1 mg/kg)
- HALO Variant 1 - MMAE (3 mg/kg)
- HALO Variant 1 - MMAE (10 mg/kg)
- HALO Variant 1 - MMAE (30 mg/kg)

6/6 Regressions, no evidence of tumors

Time (Days)

**Human CRC Tumor Xenografts**

HT29 (BRAF$^{V600E}$)

- Vehicle
- Cetuximab (30 mg/kg)
- HALO Variant 1 - MMAE (1 mg/kg)
- HALO Variant 1 - MMAE (3 mg/kg)
- HALO Variant 1 - MMAE (10 mg/kg)
- HALO Variant 1 - MMAE (30 mg/kg)

Time (Days)

*Dosing stopped at Day 38* 

*Dosing stopped at Day 39*

n=6 mice group

2X weekly dosing

Huang, L. et al. (2016). AACR Annual Meeting, Poster #1472
Next Generation ADC Technology

1st Generation Chemistries

Random Lysine Conjugation Cysteine Conjugation

Heterogeneous

ThioBridge™
Cysteine Conjugation

More homogeneous

Thanos, 2016 in press
HTI-1511: Anti-EGFR mAb Conjugated With Thiobridge-MMAE Highly Homogeneous

4 Drug Conjugates per mAb (98.2%)

HALO anti-EGFR mAb

4 Thiobridge MMAE’s

Analytical Hydrophobic Interaction Chromatography

Chromatography Peak = HTI-1511
- HALO anti-EGFR mAb
- Thiobridge MMAE Chemistry
- Drug: Antibody Ratio = 4

Huang, L. et al. (2016). AACR Annual Meeting, Poster #1472
Improved ADC Stability Observed in Primate Model

Exposure Ratio (ER) =

\[
\frac{\text{Group Mean AUC of ADC}}{\text{Group Mean AUC of Total}} \times 100
\]

Huang, L. et al. (2016). AACR Annual Meeting, Poster #1472
Pilot Toxicology: Safety Profile Tested in Primate Model

1 Cycle, 2 Dose Study Design, N=3 animals per group

- **Parameters**
  - Clinical observations and food consumption
  - Body weight
  - Dermal scoring
  - Clinical pathology
  - ECG and blood pressure
  - Veterinary physical examinations and ophthalmology
  - Histology
  - Pharmacokinetics

- Limited dermal scoring findings comparable with vehicle control group
- No unexpected findings observed at either dose (2.5 mg/kg and 8 mg/kg)
- Safety profile met criteria for candidate nomination and further investment

Huang, L. et al. (2016). AACR Annual Meeting, Poster #1472
Complete Tumor Regressions Observed in Patient Derived (PDx) Tumor Models in Mice

**NSCLC (EGFR⁺, KRAS^{pG12C}) PDx**

![Graph showing tumor volume over study days for NSCLC PDx models treated with Vehicle and HTI-1511.]

**Cholangiocarcinoma (EGFR⁺, KRAS^{pG12A}) PDx**

![Graph showing tumor volume over study days for Cholangiocarcinoma PDx models treated with Vehicle and HTI-1511.]

N=8 mice / group
2.5 mg/kg (weekly dosing)

Huang, L. et al. (2016). AACR Annual Meeting, Poster #1472
Engineered mAb with attenuated binding to human skin grafts

ADC mechanism targets KRAS- or BRAF-mutated tumors in mice

Utilization of next generation, Thiobridge chemistry
  • More homogeneous, stable

Safety profile met criteria for candidate nomination

Complete tumor responses observed in PDx tumor models

IND enabling studies underway
<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 minutes</td>
<td>Opening Remarks</td>
<td>Dr. Helen Torley, President and CEO</td>
</tr>
<tr>
<td>10 minutes</td>
<td>Focus on the Tumor Microenvironment</td>
<td>Dr. Michael LaBarre, VP, Chief Scientific Officer</td>
</tr>
<tr>
<td>10 minutes</td>
<td>PEGPH20Immuno-Oncology</td>
<td>Dr. Sanna Rosengren, Director, Immunology and Cell Biology</td>
</tr>
<tr>
<td>10 minutes</td>
<td>PEG-ADA2: PEGylated Adenosine Deaminase 2</td>
<td>Dr. Christopher Thanos, Senior Director, Biotherapeutics Discovery</td>
</tr>
<tr>
<td>10 minutes</td>
<td>HTI-1511: Anti-EGFR Antibody-Drug Conjugate</td>
<td>Dr. Christopher Thanos, Senior Director, Biotherapeutics Discovery</td>
</tr>
<tr>
<td>15 minutes</td>
<td>Questions and Answers</td>
<td>All</td>
</tr>
</tbody>
</table>
American Association for Cancer Research Investor Meeting

Q&A