A biomarker-driven approach for the development of the ICOS agonist antibody, JTX-2011

Heather A. Hirsch
On behalf of Jounce Therapeutics JTX-2011 team

Immuno-Oncology Biomarkers: Today’s Imperatives for Tomorrow’s Needs
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Presenter Disclosure Information

Heather A. Hirsch

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Rationale for Biomarkers and Complementary and/or Companion Diagnostics in Immunotherapy

- (+) for predictive response biomarkers
- (-) for predictive response biomarkers

All-comers
- No use of biomarkers for patient enrichment
- Minority of patients respond

Enrichment
- Use of biomarkers that may predict response
- Ensures sufficient number of biomarker (+) patients

Selection
- Biomarker expression required for enrollment
- Maximizes for potential responders

For illustrative purposes only, actual numbers may vary. Biomarker positive does not guarantee response to drug.
Translational Science Platform

Patient enrichment strategies using predictive biomarkers

Comprehensive interrogation of the TME

Identifying optimal immune cell targets and developing new immunotherapies

Sustainable immunotherapy pipeline

Transformative, long lasting treatments for patients

ADVANCING CANCER IMMUNOTHERAPY WORLDWIDE
JTX-2011 Shifts Balance of T Cells Towards Anti-Tumor Activity

Activation of T effector cells

Selective reduction of intratumoral T regulatory cells
**Critical Requirements for Preclinical Response to JTX-2011**

1. **Sustained target engagement in vivo: all available ICOS must be bound by JTX-2011**

   ![Graph showing tumor volume over days post-inoculation](image)

   - **Control**: 1/10
   - **Anti-ICOS**: 7/10

   Days post-inoculation of SA1/N tumor cells

   * Upon rechallenge “cured” mice reject tumors

   Efficacy in mouse tumor models observed only at doses resulting in sustained target engagement

   PK/PD model predicted human dose resulting in sustained target engagement

2. **Efficacy in mouse tumor models requires ICOS(+) infiltrating immune cells within the tumor**

   ![Diagram of tumor cells and immune cells](image)

   - **Tumor cells** (gold)
   - **T regulatory cells** (red and green)
   - **CD8(+) T cells** expressing ICOS target within human tumors (green)

   ICOS biomarker scoring system developed to determine threshold to predict response

   Biomarker translated to human tumors for patient enrichment in the clinic

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Phase 2 Indication Selection & Patient Enrichment via Biomarkers

- **ICOS protein levels vary across indications and within individual indications**
- **ICOS RNA levels correlate well with ICOS protein levels via IHC**

**Rank order of tumor indications based on ICOS RNA expression in TCGA**

- **Head & Neck (HPV)**
- **Head & Neck (HPV)**
- **Lung (Adenoc)**
- **Breast (Th)**
- **Stomach**
- **Cervical**
- **Lung (Squ)**
- **Genit (Bladder)**
- **Pancreatic**
- **AML**
- **Breast (HER2)**
- **Melanomas**
- **Colon (MSE)**
- **Rectal (Adenoc)**
- **Kidney (Clear Cell)**
- **Bladder**
- **Breast (Luminal)**
- **Ovarian**
- **Uterine (Endo)**
- **Thyroid**
- **Liver**
- **Prostate**
- **Sarcoma**
- **Kidney (Papillary)**
- **Uterine (Sarcom)**
- **Glialblastomas**
- **Kidney (Chrom)**
- **Low Grade Glioma**

**ICOS Expression, log(FPKM)**

- **Frequency of ICOS+ Tumors by IF**

**IHC and NanoString analysis of HNSCC histoculture samples**
Phase 2 Indication Selection & Patient Enrichment via Biomarkers

1. **Select indication priorities**

   HNSCC, NSCLC, TNBC, melanoma, gastric, plus undisclosed “niche” indications

   Includes IO naïve and IO failures

2. **Prospective enrichment of biomarker high patients into study cohorts**

   10 patients in each cohort ICOS 2/3

   ICOS 2/3 required for preclinical efficacy
Integrated Approach to Understanding ICOS in the Context of Immune Oncology Landscape

Collaborations with premier institutions

1000s of human tumors interrogated

Integrated TCGA and internal data analysis

Enriching patients for our clinical trials

Adaptive immune cells
Innate immune cells
Stromal cells
Integrated Approach to Understanding ICOS in the Context of Immune Oncology Landscape
ICONIC: Adaptive, Biomarker-Driven Clinical Study

Phase 2 Patient Enrichment

**Phase 2 Preliminary Efficacy**

- **Preliminary Efficacy readout expected 1H 2018**

**Enriched for pts with high ICOS expression**

- **NSCLC**
- **HNSCC**
- **Any solid tumor type**
- **New indications based on emerging science**

**Indication Selection**

**Patient Screening / Enrichment**

**The right immunotherapy for the right patients**

- **Single agent**
- **Combo with nivolumab**

- **NSCLC**
- **HNSCC**
- **TNBC**
- **Melanoma**
- **Gastric**

**New indications based on emerging science**
Developing predictive biomarker assays for the ICONIC trial

Potential predictive biomarkers to be correlated with efficacy:

1. ICOS by IHC
2. ICOS gene signature by qPCR
3. Exploration of alternative gene signatures (NanoString analysis)

Correlate with clinical activity
Developing predictive biomarker assays for the ICONIC trial

Potential predictive biomarkers to be correlated with efficacy:

1. ICOS by IHC
2. ICOS gene signature by qPCR
3. Exploration of alternative gene signatures (NanoString analysis)

ICOS IHC  ICOS gene signature qPCR  New gene signature (NanoString)

Correlate with clinical activity
Development of an ICOS IHC assay for ICONIC enrollment

ICOS Scoring Criteria

<table>
<thead>
<tr>
<th>Percent Positive</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1%</td>
<td>0</td>
</tr>
<tr>
<td>≥ 1% but &lt; 5%</td>
<td>1</td>
</tr>
<tr>
<td>≥ 5% but &lt; 15%</td>
<td>2</td>
</tr>
<tr>
<td>≥ 15%</td>
<td>3</td>
</tr>
</tbody>
</table>

*In carcinoma region only

- Chromogenic IHC assay developed in house with proprietary anti-ICOS antibody
- Developed for the Leica Bond III platform
- Assay transferred to and validated at CLIA lab
- Currently in use for ICONIC clinical trial patient stratification

Percent positive ICOS correlates to ICOS RNA expression in HNSCC and NSCLC

Total ICOS IHC score correlates to ICOS RNA expression in HNSCC and NSCLC
Frequency of ICOS positivity in tissue microarrays and ICONIC patient samples

- Immunofluorescence
- Chromogenic IHC assay
- Patient samples screened by IHC

Frequency of ICOS+ Tumors by IHC
Frequency of ICOS+ Tumors by IF
Frequency of ICOS+ Tumors in ICONIC

Chromogenic IHC assay
Patient samples screened by IHC
Developing predictive biomarker assays for the ICONIC trial

Potential predictive biomarkers to be correlated with efficacy:

1. ICOS by IHC
2. ICOS gene signature by qPCR
3. Exploration of alternative gene signatures (NanoString analysis)

Correlate with clinical activity
Developing an ICOS RNA gene signature

Criteria for gene selection:

- Frequently found
  - Must be in the top 300 genes in at least 10 indications
- Highly ranked on average
  - Within the top 75 genes identified on average across indications

The 11 gene ICOS signature is coherent across all solid tumors in TCGA.

ICOS signature is highly correlated to ICOS gene expression across tumors types.
Developing an ICOS RNA gene Signature

- Transferred 11 gene signature to CLIA lab
- Developed with 4 housekeeping controls in FFPE tumor material in multiple indications
- Is currently in use for retrospective testing in the ICONIC trial

The 11 gene ICOS signature is coherent in the PCR assay

ICOS RNA signature by both PCR and NanoString correlates with ICOS IHC

ICOS expression and ICOS signature are highly correlated between PCR and NanoString platforms

Spearman’s ρ: -0.95
P-value: 1.37E-018

Spearman’s ρ: -0.85
P-value: 1.22E-010
Biomarker-Driven Enrichment Strategy
Potential for Establishing Complementary and/or Companion Diagnostics

Biomarker-Driven Enrichment Strategy

Patient Enrollment

Study Enrollment

Patient Enrichment

Indication Selection

All Tumors

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Thank You

As always, Jounce is exceptionally thankful to all of the patients and families participating in the ICONIC clinical trial.