Preclinical Assessment of JTX-2011, An Agonist Antibody Targeting ICOS, Supports Evaluation In ICONIC Clinical Trial

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AACR Annual Meeting
April 2, 2017
Major Symposium
“Emerging Targets in Immunotherapy”
Sustainable immunotherapy pipeline

Comprehensive Interrogation of the TME to Develop a Sustainable Innovative Pipeline

- Comprehensive interrogation of the TME
- Identifying optimal immune cell targets and developing new immunotherapies
- Patient enrichment strategies using predictive biomarkers

Translational Science Platform
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Many Potential Targets: Why Choose ICOS?

- Data from Founders’ labs demonstrated clinical correlate and outcome data that supported activation of ICOS.
- Subsequent laboratory evidence in animal tumor reduction studies.

Jounce Approach

Adapted from Mellman et al. Nature 480, 480-489 (2011)
Many Potential Targets: Why Choose ICOS?

Human clinical and mouse preclinical data support activating ICOS receptor for anti-tumor benefit

Chen et al, PNAS (2009);
Carthon et al, Clin Can Res (2010);
Ng Tang et al, Canc Immunol Res (2013)

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Chi et al. (2010) 71:5445-5454
JTX-2011: ICOS Agonist Antibody

JTX-2011: Key Features

- Specificity for ICOS
- Species cross-reactive
- Agonist activity
- Humanized rodent antibody
- hIgG1 Fc backbone
JTX-2011 Dual Mechanism Shifts Balance of T Cells Towards Anti-Tumor Activity

• Stimulate T effector cells in tumor
• Selectively reduce T regulatory cells in tumor

JTX-2011 is designed to

“Non-Primed” T effector cell

“Primed” T effector cell

TCR

ICOS

APC

1st signal

JTX-2011

TCR

ICOS

IFN-γ

↑

↑

↑

↑

Activation of T eff

Reduction of T regs

T regulatory cell

NK cell
JTX-2011 Stimulates Primed Human T Cells

No Indiscriminate Activation of T cells

Activation of *primed* CD4+ T effector cells

No activation of *unprimed* CD4+ T effector cells

% Proliferation

CD3 in all wells except unstimulated

JTX-2011 (nM)
JTX-2011 Induces Signaling Through AKT Pathway

- ICOS antibody re-capitulates signaling activity of ICOS ligand
  - Induces pAKT signal in CD4+ T cells when cross-linked
JTX-2011 Dual Mechanism Shifts Balance of T Cells Towards Anti-Tumor Activity

“Non-Primed” T effector cell

“Primed” T effector cell

IFN-γ↑

IFN-γ↑

JTX-2011 is designed to

- Stimulate T effector cells in tumor
- Selectively reduce T regulatory cells in tumor

Activiation of T eff

Reduction of T regs
Selective Reduction in Tumor but not Peripheral T Regulatory Cells

Mouse JTX-2011 selectively reduces tumor T regulatory cells \textit{in vivo}

• Reduction in tumor T regulatory but not tumor T effector cells
• No change in T cell subsets in spleen, lymph nodes or periphery
ICOS Expression is Highest on Mouse and Human Intratumoral Tregs

**Multiplexed IF**

- Tumor cells (gold)
- T regulatory cells (red and green)
- CD4(+) T cells expressing ICOS target within human tumors (green)

**Flow cytometry**

- CD11b+/CD14+
- CD8+
- CD4 Teff
- CD4 Treg

![Flow cytometry graph](graph.png)
Selective Reduction of Tregs vs Teffs *in vitro*

- ICOS antibody selectively depletes Tregs from IL-2 activated PMBC
- Under these *in vitro* activation conditions, Tregs and Teffs express similar levels of ICOS
Single Agent Development of JTX-2011
Supported by Long-Lasting Response in Preclinical Tumor Models

Days post-inoculation of tumor cells

Control

ICOS Antibody

Animals cured of tumors are immune to tumor re-challenge

Sa1/N Tumors

Tumor free / animals treated

Tumor volume (mm$^3$)

Days after tumor re-challenge

Animals previously cured by anti-ICOS

No prior treatment

1/10

7/10

1/2

2/2
Fc Effector Function is Required for Optimal Anti-Tumor Activity
Loss of Activity with Fc Deficient Version of Antibody

Control

ICOS Antibody

Fc-Deficient ICOS Antibody

Sa1/N Tumors

Tumor free / animals treated
Combination Development of JTX-2011 with Anti-PD-1
Supported by Enhanced Anti-tumor Activity in Preclinical Models

Control antibody

Anti-PD-1

ICOS Antibody

ICOS Antibody + Anti-PD-1

CT26 Tumors

Tumor free / animals treated

DO NOT POST
Preclinical Safety Features of JTX-2011

**JTX-2011-induced T Cell Activation Requires Initial T Cell Priming**

- No cytokine storm in GLP toxicology studies
- No cytokine induction by JTX-2011 alone or in combination with Opdivo® in human whole blood assays

**Activity of ICOS Antibody is Tumor-centric: No Depletion of Tregs in the Periphery**

- NOAEL = 50 mg/kg; highest dose tested in cynomolgus monkey IND-enabling GLP toxicology study

**Preclinical Toxicity Studies Predict Safety Margin**

- Cytokine Storm Not Predicted from *in vitro* and *in vivo* Studies
  - No cytokine storm in GLP toxicology studies
  - No cytokine induction by JTX-2011 alone or in combination with Opdivo® in human whole blood assays
Pharmacodynamic Biomarker: Target Engagement in Mouse
Efficacy in Syngeneic Mouse Tumor Model Correlates with Duration of ICOS Target Engagement

**Average Tumor Growth Curves**

- Days Post-inoculation of Tumor Cells vs. Tumor Volume (mm$^3$)
  - Isotype
  - 0.25 mg/kg
  - 2.5 mg/kg
  - 0.05 mg/kg

**ICOS Engagement on Peripheral Blood CD4 T Cells**

- Time post-dose (Hours) vs. % Receptor Available
  - 2.5 mg/kg
  - 0.25 mg/kg
  - 0.05 mg/kg

**Induction of JTXP**

- Time post-dose (Hours) vs. JTXP MFI
  - Isotype
  - 0.25 mg/kg
  - 2.5 mg/kg
  - 0.05 mg/kg

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Tumor Free Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>1/10</td>
</tr>
<tr>
<td>0.25</td>
<td>5/10</td>
</tr>
<tr>
<td>2.5</td>
<td>5/10</td>
</tr>
</tbody>
</table>
Preclinical Pharmacokinetics and Pharmacodynamics
PK and PD in Cynomolgus Monkey Preclinical Studies

• Pharmacokinetics:
  – T1/2 = 5-12 days in ADA-negative monkeys

• Pharmacodynamic readouts
  – Target engagement: ICOS is fully engaged for the duration of the dosing interval at all doses
  – JTXP induction: JTXP is induced on monkey cells in peripheral blood

Non-GLP tox study dosed up to 75 mg/kg with no toxicity observed
Preclinical QSP Modeling of JTX-2011
Predictions for PK and Target Engagement in First-in-Human Study

A. Plasma JTX-2011 Free Drug Concentration

B. Peripheral Blood Free Receptor on CD4+ T cells (%)

starting dose

highest dose
Patient Selection Strategy Supported by Mouse Models
Better Single-Agent Efficacy in Tumors Expressing Higher Levels of Intra-Tumoral ICOS

**ICOS IHC Score**

<table>
<thead>
<tr>
<th>Tumor</th>
<th>ICOS IHC Score</th>
<th>Single Agent Efficacy</th>
<th>Combination Efficacy (+ anti-PD-1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sa1/N</td>
<td>3+</td>
<td>+++</td>
<td>ND</td>
</tr>
<tr>
<td>B16-SIY</td>
<td>2+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>MC38</td>
<td>1+</td>
<td>+</td>
<td>+++*</td>
</tr>
<tr>
<td>CT26</td>
<td>1+</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>EMT6</td>
<td>1+</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>LLC1</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**** indicates 61-100% tumor regression
*** indicates 41-60% tumor regression
** indicates 21-40% tumor regression
* indicates 10-20% tumor regression
- indicates no tumor regressions

*Intra-tumoral levels of ICOS+ T cells increases post PD-1 treatment
Indication Selection & Patient Enrichment
ICOS Immunohistochemistry (IHC)

1. ICOS protein levels vary across indications

![ICOS protein levels across indications](image1)

2. ICOS protein levels within high ICOS indications vary across individual patients

![ICOS protein levels within high ICOS indications](image2)

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ICOS protein levels vary across indications:
- None
- Low (1+)
- Medium (2+)
- High (3+)

ICOS protein levels within high ICOS indications:
- HNSCC (n=94)
- NSCLC (n=204)
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

Patient enrichment for our clinical trials
Translational Science Platform Informs Biomarker Strategy
Example from NSCLC

ICOS expression levels across subtypes of NSCLC tumors

ICOS levels are not associated with smoker status

A subset of PD-L1 low tumors have high levels of ICOS expression
Biomarker-Driven Strategy for Patient Enrichment

Potential for Establishing Complementary and/or Companion Diagnostics
ICONIC: Adaptive, Biomarker-Driven Clinical Study
Phase 1/2 Preliminary Efficacy Proof-of-Concept

Phase 1
Safety, PK and PD

- All-comers, no enrichment for ICOS expression
- Dose escalate to anticipated clinically effective dose

A  Single Agent

B  Combo with nivolumab

Phase 2
Preliminary Efficacy

- Enriched for patients with high ICOS expression

C  Single Agent

D  Combo with Nivolumab

- New indications based on emerging science*

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

- NSCLC
- HNSCC
- TNBC
- Melanoma
- Gastric
- New indications based on emerging science*

* Additional indications, including niche indications, identified through Jounce Translational Science Platform
JTX-2011: Agonist Monoclonal Antibody that Targets ICOS

ICOS: T cell Surface Protein Receptor with Strong Target Rationale

- Member of family of immune modulators that includes PD-1 and CTLA-4
- Potential importance of ICOS supported by key clinical observations
- Pharmacological activity is focused in the tumor

JTX-2011: Agonist Antibody Targeting ICOS

- Significant anti-tumor activity seen in preclinical studies
- Preclinical data supports use as both a single agent and in combination
- Safety, PK, and pharmacodynamic features in the monkey inform human FIH study
- Potential predictive biomarkers identified for patient enrichment strategies

ICONIC: JTX-2011 Phase 1/2 Clinical Trial

- JTX-2011 being evaluated as monotherapy and in combination with nivolumab
- Phase 1 to assess safety, PK and PD – ongoing
- Phase 2 will incorporate patient enrichment strategy
Thank You

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