Lessons Learned from a Clinical Trial Targeting ICOS

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Lessons Learned from a Clinical Trial Targeting ICOS

- Predictions Based on Preclinical Data
- Clinical Trial Design Based on Preclinical Data
- Clinical Data
- Clinical Biomarker Data and Reverse Translational Analyses
- New Hypotheses
- New Clinical Trial Designs
Predictions Based on Preclinical Data
Vopratelimab (JTX-2011): IgG1 Agonist Monoclonal Ab Targets ICOS

Predictions from Preclinical Data

- **Dual MOA**
  - Activation and proliferation of CD4 T effector cells
    - Requires T cell priming
  - Selective reduction of intra-tumoral T regulatory cells
    - No effect on peripheral T regs

- **Requirements for Monotherapy Efficacy**
  - Functional Fc
  - Sustained Target Engagement
  - High ICOS IHC score
Vopratelimab Preclinical Data: Activation and Proliferation of CD4 T effector Cells Requires Initial Priming

Activation of *primed* human CD4+ T effector cells

No activation of *unprimed* CD4+ T effector cells

**Vopratelimab**

**No activation of unprimed CD4+ T effector cells**
Vopratelimab Preclinical Data: Selective Reduction of Intra-tumoral T regs in Mice
No Reduction of T effectors or Peripheral T regs

Selective reduction of human CD4+ Tregs

Mouse JTX-2011 selectively reduces tumor T regulatory cells in vivo

Mouse JTX-2011 does not reduce spleen T regulatory cells in vivo

ICOS expression highest on intratumoral Tregs

% Change in population

-10  -9  -8  -7  -6  -5  -4  -3  -2  -1  0  1  2  3  4  5

CD4+ T effector cells
CD4+ T regulatory cells

Implant Tumor  Treatment (0.2mg/kg)  TIL analysis
Day: 0  7  10  12

% Subset in CD3+

Control Antibody  Parent mJTX-2011

0  20  40  60  80  100

Control Antibody  "JTX-2011"

0  20  40  60  80  100
Vopratelimab Preclinical Data: Fc Effector Function is Required for Optimal Anti-Tumor Activity
Loss of Activity with Fc Deficient Version of Antibody

Control Antibody

ICOS Antibody

Fc-Deficient ICOS Antibody

Days post-inoculation of Sa1/N tumor cells
Vopratelimab Preclinical Data:
Sustained Target Engagement Required for Optimal Efficacy

*In vivo* monotherapy efficacy corresponded to doses at which a period of target engagement was maintained.
Vopratelimab Preclinical Data: High ICOS IHC Score Required for Optimal Efficacy
Better Single-Agent Efficacy in Tumors Expressing Higher Levels of Intra-Tumoral ICOS

<table>
<thead>
<tr>
<th>Tumor Line</th>
<th>ICOS IHC Score (at Baseline)</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
Clinical Trial Design Based on Preclinical Data
Vopratelimab: Phase 2 Indication Selection & Patient Enrichment Based on Intra-tumoral ICOS RNA and IHC Data
**ICONIC: Adaptive Study Design**

**Phase 1**
*All solid tumors, no enrichment for ICOS expression*

- **Dose Escalation**
  - Vopratelimab 0.003-1.0 mg/kg IV q3w

- **PK/PD Expansions**
  - Vopratelimab 0.01-0.3 mg/kg IV q3w + nivo 240 mg IV q3w

**Phase 2**
*Enriched for pts with high ICOS expression*

- **Dose Escalation**
  - Vopratelimab 0.3 mg/kg IV q3w

- **PK/PD Expansions**
  - Vopratelimab 0.3 mg/kg IV q3w + nivo 240 mg IV q3w

**Phase 2 Triggered Upon:**
Identification of safe dose with ≥ 70% TE

- **Phase 2 Enrichment**
  - Any solid tumor type
  - HNSCC*
  - NSCLC*
  - TNBC
  - Melanoma*
  - Gastric*
  - Additional tumor types based on emerging science

*Required to have failed PD-1 inhibitor in FDA-approved indications*
Clinical Data
ICONIC: Demographics and Safety

- Heavily pre-treated patients in Phase 1 and Phase 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 1</th>
<th>Phase 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>40</td>
<td>30</td>
<td>31</td>
<td>100</td>
</tr>
<tr>
<td>ECOG 0/1, n (%)</td>
<td>8 (20%) / 32 (80%)</td>
<td>2 (7%) / 28 (93%)</td>
<td>8 (26%) / 22 (71%)*</td>
<td>30 (31%) / 68 (70%)*</td>
</tr>
<tr>
<td>≥3 Prior therapy for metastatic disease, n (%)</td>
<td>32 (80%)</td>
<td>24 (80%)</td>
<td>23 (74%)</td>
<td>60 (60%)</td>
</tr>
</tbody>
</table>

- vopratelimab is safe and well-tolerated alone and in combination with nivo
  - Related Grade 3/4 AEs in Phase 2 12% with vopratelimab or vopratelimab + nivo
  - Phase 1: DLTs on mechanism at 1.0 mg/kg vopratelimab alone
    - Grade 3 AST/ALT, Grade 3 pleural effusion
  - Phase 2: Two possibly related Grade 5 AEs with vopratelimab + nivo
    - Increased bilirubin, encephalopathy

Safety population: all subjects who received at least one dose of vopratelimab
*ECOG status not available on all subjects
#Prior therapy data not available on all subjects

Data cut-off Jan 17, 2019
ICONIC Efficacy

Vopratelimab monotherapy

CR=0
PR=0
SD=15 (21.4%)

Vopratelimab + nivo

CR=1 (0.8%)
PR=3 (2.3%)
SD=20 (15.4%)

n= Dosed and ≥ 1 scan or discontinued treatment; Spider plot= Investigator measurements; CR, PR, SD= Central Radiology review; data cut-off March 4, 2019
Vopratelimab + nivo Phase 2: Durable Responses and Stable disease

Gastric (n=30)
CR= 0
PR= 1 (3.3%)
SD= 6 (20%)

TNBC (n=23)
CR= 1 (4.3%)
PR= 0
SD= 2 (8.7%)

NSCLC (n=17)
CR= 0
PR= 1 (5.9%)
SD= 4 (23.5%)

HNSCC (n=26)
CR= 0
PR= 0
SD= 3 (11.5%)

n= Dosed and ≥ 1 scan or discontinued treatment; Durable= > 6 months; Spider plot= Investigator measurements; CR, PR, SD= Central Radiology Review; data cut-off March 4 2019
Clinical Biomarker Data and Reverse Translational Analyses
ICOS and PD-L1 IHC are not Correlated with Tumor Reductions

- Concordance between PD-L1 and ICOS scores in archival and fresh tumor tissue
- Neither ICOS score nor PD-L1 score are correlated with response

- ICOS IHC score is based on total tumor infiltrate ICOS positive immune cells
  - does not discriminate between Teff, Treg, and NK cells
  - does not measure ICOS density per immune cell
Emergence and Persistence of ICOS hi CD4 Teff is Observed in Responding* Subjects

*A based on investigator assessments

vopratelimab monotherapy cPR with emergence of ICOS hi CD4 population

Combination therapy cPR. Emerging ICOS hi CD4 T cells are FoxP3+ with a subset T-bet+.

Subject with stable disease shows emergence and then loss of ICOS hi population when the subject progressed

*based on investigator assessments
Anti-Tumor Activity Correlates with Vopratelimab Mechanistic Biomarker

ICOS hi CD4 Cells Emerge in Patients with Target Lesion Reductions*

- Observed in 7/7 subjects with target lesion PR
- Not observed in 12/12 subjects with progressive disease

PD-1i Does Not Induce ICOS hi CD4 Cells

- 77 patients treated with PD-1/L1i monotherapy
- 6 confirmed responders
- 0 patients with ICOS hi CD4 cells

Limited longitudinal samples for some subjects
N=45 subjects from mono and combo cohorts with evaluable samples

*Best response observed for target lesion, based on investigator assessments
Soluble vopratelimab Induces *ex vivo* Cytokine Responses only in ICOS hi CD4 T Cells

*Consistent with vopratelimab need for primed CD4 T effectors*
No Significant Changes in Peripheral Blood Immune Cell Subsets over 3 Cycles

A. Vopratelimab Monotherapy

B. Vopratelimab + Nivolumab Combination Therapy
No Significant Change in Cycle 2 in Intra-tumoral Immune Cell Subsets, Including Tregs

ICOS staining is significantly reduced on intra-tumoral Treg, CD4eff, and CD8 cells with sustained exposure

- Loss of ICOS observed in 5/8 monotherapy and combination subjects, including 1 confirmed PR*
- All had trough concentrations ≥200 ng/mL (200-1400)
- Sustained target saturation in all with available data

- Persistent ICOS observed in 3/8 subjects (no responders*)
- All had trough concentrations < 100 ng/mL (<20-<100)
- Target engagement data unavailable

Is on treatment loss of ICOS staining due to down-regulation of the receptor due to sustained signaling and internalization (negative feedback)?
ICOS on Peripheral T cells Saturated at Doses above 0.1mg/kg q3w

- % available ICOS in whole blood at different concentrations of vopratelimab
- Incubated at 37 degrees for 1hr, 4hrs, or 18hrs

ICOS is internalized over time when bound by vopratelimab
Target Saturation: How Long is Too Long?

Preliminary PK/PD modeling predicts prolonged saturation in both blood and tumor at 0.3 mg/kg q3w. Is a lower, less frequent dose advisable?

- Dotted/Shaded is a model based on clinical TE data
- Solid line is a model based on TE, vopra affinity, PK, and target distribution

*Saturated signaling* based on primary CD4+ cells

*Based on primary CD4+ cells*
What have we learned from the clinic?

Preclinical Predictions

Dual MOA
- Activation and proliferation of CD4 T effector cells
  - Requires T cell priming
- Selection reduction of intra-tumoral Tregs
  - No effect on peripheral Tregs

Requirements for Efficacy
- Sustained Target Engagement
- High ICOS IHC score

Clinical Observations

MOA
- Activation and proliferation of primed CD4 T effector cells
  - Requires Priming/presence of ICOS hi CD4 T cells
- No apparent reduction of intra-tumoral Tregs to date
  - No effect on peripheral immune cell subsets
- Continuous Target Engagement may be too much stimulation
- ICOS IHC score not predictive of efficacy
  - High ICOS score may reflect high numbers of Tregs
  - ICOS IHC does not discriminate between ICOS lo and ICOS hi cells
- A better predictive biomarker is needed
Evolving Vopratelimab MoA Based on Reverse Translational Analyses of Clinical Data

Sustained Activation & Proliferation of CD4 T effector cells; Production of cytokines

Cancer Antigen “Priming”

ICOS hi primed CD4 T effector cell

Vopratelimab

IFN-γ

No Activation, Proliferation, or Production of Cytokines Observed

No “Priming”

ICOS

Vopratelimab
Vopratelimab: Reverse Translational Work Leads to Two Development Paths

New hypothesis: vopra will result in expansion, activation, and proliferation of primed ICOS hi CD4 T effectors

**CTLA-4i Combination**
Prioritize combination agents that induce ICOS hi CD4 cells

**Predictive Biomarker**
Identify baseline characteristics to predict which patients have pre-existing ICOS hi CD4 cells

**Induction of ICOS by Ipilimumab**

Data cut-off as of December 18, 2018

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