ICONIC: Biologic and clinical activity of first in class ICOS agonist antibody JTX-2011 +/- nivolumab (nivo) in patients with advanced cancers

Timothy A. Yap¹, Howard A. Burris², Shivaani Kummar³, Gerald S. Falchook⁴, Russell K. Pachynski⁵, Patricia LoRusso⁶, Scott S. Tykodi⁷, Geoffrey T. Gibney⁸, Justin F. Gainor⁹, Osama E. Rahma¹⁰, Tanguy Y. Seiwert¹¹, Funda Meric-Bernstam¹, Mariela A. Blum Murphy¹, Jennifer K. Litton¹, Ellen Hooper¹², Heather A. Hirsch¹², David Y. Lee¹², Christopher J. Harvey¹², Myles Clancy¹², Ty McClure¹² and Margaret K. Callahan¹³

¹The University of Texas MD Anderson Cancer Center, Houston, TX; ²Sarah Cannon Research Institute, Nashville, TN; ³Stanford University School of Medicine, Stanford, CA; ⁴Sarah Cannon Research Institute at HealthONE, Denver, CO; ⁵Washington University School of Medicine in St. Louis, St. Louis, MO; ⁶Yale Cancer Center, New Haven, CT; ⁷University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA; ⁸Georgetown Lombardi Comprehensive Cancer Center; ⁹Massachusetts General Hospital, Boston, MA; ¹⁰Dana Farber Cancer Institute, Boston, MA; ¹¹University of Chicago, Chicago, IL; ¹²Jounce Therapeutics, Cambridge, MA; ¹³Memorial Sloan Kettering Cancer Center, New York, NY

NCT02904226
Why Choose ICOS as a Target?

- **ICOS**: Inducible CO-Stimulator of T cells
  - Expression on T cells associated with favorable outcome with ipilimumab
  - Preclinical data show functional importance of host ICOS
  - Upregulated by variety of agents - ideal combination target

- ICOS induced on peripheral CD4 (and CD8) T cells post-ipilimumab therapy

- Persistent upregulation on CD4 T cells associated with improved clinical outcomes

- Impaired tumor rejection in ICOS−/− and ICOSL−/− mice treated with anti-CTLA-4 therapy

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Fu et al, Cancer Res (2011)
JTX-2011: Preclinical Rationale for ICOS Agonist IgG1 Antibody

Shifting the balance of T cells towards antitumor activity

- Monotherapy efficacy in mouse tumors with high % ICOS expressing immune cells
- Enhanced efficacy in combination with PD-1 and CTLA-4 inhibitors
- Period of sustained target engagement required for preclinical antitumor efficacy
- Tumor-centric pharmacology with no reduction in peripheral immune cell subsets in mice
ICONIC Phase 1 and 2 Objectives

**Phase 1**

**Primary:** JTX-2011 alone and in combination with nivo
- Safety and tolerability
- MTD and RP2D

**Secondary**
- PK/PD for JTX-2011
- PK for nivo

**Exploratory:** JTX-2011 alone and in combination with nivo
- Preliminary efficacy by RECIST 1.1 (CT scans q9w)*
- Peripheral blood
  - Gene signatures
  - Immune cell subsets
- Paired tumor biopsies (PK/PD cohorts)
  - Gene signatures
  - Immune cell subsets
- Putative predictive biomarkers of response

**Phase 2**

**Primary:** JTX-2011 alone and in combination with nivo
- Preliminary efficacy by RECIST 1.1 (CT scans q9w)*
- Confirm safety and tolerability
- Confirm MTD and RP2D

**Secondary**
- Confirm PK/PD for JTX-2011
- Confirm PK for nivo

**Exploratory:** JTX-2011 alone and in combination with nivo
- Peripheral blood
  - Gene signatures
  - Immune cell subsets
- Putative predictive biomarkers of response
  - Archival and fresh pre-treatment biopsies
    - ICOS expression
    - Gene signatures

* Investigator assessed; to be confirmed by central review

Data cut-off April 4, 2018
**ICONIC Study Design**

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

- **JTX-2011** 0.003-1.0 mg/kg IV q3w
  - **Dose Escalation**
  - **PK/PD Expansions**

- **JTX-2011** 0.01-0.3 mg/kg IV q3w + nivo 240 mg IV q3w
  - **Dose Escalation**
  - **PK/PD Expansions**

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

- **JTX-2011** 0.3 mg/kg IV q3w
  - **Phase 2 Triggered Upon:** Identification of safe dose where PK/PD predicts anticipated clinically effective dose
  - **PK/PD Expansions**

- **JTX-2011** 0.3 mg/kg IV q3w + nivo 240 mg IV q3w
  - **Any solid tumor type**
  - **NSCLC***
  - **HNSCC***
  - **Gastric***
  - **Additional tumor types based on emerging science**

*Required to have failed PD-1 inhibitor in FDA-approved indications

*NSCLC***
*HNSCC***
*TNBC*
*Melanoma***
*Gastric***
*Additional tumor types based on emerging science*

**Data cut-off April 4, 2018**
## ICONIC Patient Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>JTX-2011</th>
<th></th>
<th>JTX-2011 + nivo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase 1</td>
<td>Phase 2</td>
<td>Phase 1</td>
<td>Phase 2</td>
</tr>
<tr>
<td>n</td>
<td>40</td>
<td>29</td>
<td>31</td>
<td>87</td>
</tr>
<tr>
<td>Median age, yrs (Range)</td>
<td>63 (24, 78)</td>
<td>67 (31, 81)</td>
<td>56 (29, 80)</td>
<td>62 (37, 85)</td>
</tr>
<tr>
<td>ECOG 0/1, n (%) / n (%)</td>
<td>8 (20%) / 32 (80%)</td>
<td>2 (7%) / 27 (93%)</td>
<td>8 (26%) / 22 (71%)*</td>
<td>25 (29%) / 60 (71%)*</td>
</tr>
<tr>
<td>Tumor types</td>
<td>8-TNBC, 4-Colon, 3-Melanoma, 3-Oropharynx, 2-Sarcoma, 2-Prostate, 2-Renal, 2-Endometrial, 2-Unknown Origin, 12-Other Solid Tumors</td>
<td>8-Gastric, 5-NSCLC, 4-HNSCC, 12-Other Solid Tumors (TNBC, Ovarian, Pancreatic, Neuroendocrine, Rectal, Melanoma, Endometrial, Bladder, Unknown, Sublingual)</td>
<td>5-TNBC, 4-Colon, 3-Gastric, 2-Sarcoma, 2-Endometrial, 2-Breast, other, 2-Rectal, 2-Cervix, 2-Eosophageal (squam), 7- Other Solid Tumors</td>
<td>29-Gastric, 23-HNSCC, 19-TNBC, 13-NSCLC, 2-Melanoma, 1-Endometrial</td>
</tr>
<tr>
<td>≥3 Prior therapy for metastatic disease, n (%)</td>
<td>32 (80%)</td>
<td>21 (72%)</td>
<td>23 (74%)</td>
<td>46 (54%)*</td>
</tr>
</tbody>
</table>

Safety population: all subjects who received at least one dose of JTX-2011; *ECOG status not available on all subjects; #Prior therapy data not available on all subjects

Data cut-off April 4, 2018
## ICONIC Phase 2 Characteristics

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>HNSCC</th>
<th>NSCLC</th>
<th>TNBC</th>
<th>Gastric</th>
<th>Other Solid Tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>4</td>
<td>23</td>
<td>5</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Prior therapy for metastatic disease, n*(%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1</td>
<td>n=4</td>
<td>n=22</td>
<td>n=5</td>
<td>n=12</td>
<td>n=19</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>2 (9%)</td>
<td>0</td>
<td>1 (8%)</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>3</td>
<td>7 (32%)</td>
<td>2 (40%)</td>
<td>3 (25%)</td>
<td>5 (26%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>≥4</td>
<td>0</td>
<td>1 (25%)</td>
<td>0</td>
<td>3 (16%)</td>
<td>5 (63%)</td>
</tr>
<tr>
<td></td>
<td>3 (75%)</td>
<td>6 (27%)</td>
<td>5 (42%)</td>
<td>8 (42%)</td>
<td>0</td>
</tr>
<tr>
<td>Prior IO, n* (%)</td>
<td>4 (100%)</td>
<td>22 (100%)</td>
<td>5 (100%)</td>
<td>12 (100%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Prior IO Refractory, n (%)</td>
<td>2 (50%)</td>
<td>12 (55%)</td>
<td>2 (40%)</td>
<td>1 (8%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Brain mets, n* (%)</td>
<td>1 (25%)</td>
<td>2 (9%)</td>
<td>0</td>
<td>3 (23%)</td>
<td>3 (16%)</td>
</tr>
<tr>
<td>Liver mets, n* (%)</td>
<td>1 (25%)</td>
<td>5 (22%)</td>
<td>1 (20%)</td>
<td>4 (31%)</td>
<td>10 (53%)</td>
</tr>
</tbody>
</table>

*Safety population: all subjects who received at least one dose of JTX-2011

*Patients for whom prior therapy information is available

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JTX-2011 is Well Tolerated Alone and Combined with nivo

<table>
<thead>
<tr>
<th>Related AEs*</th>
<th>JTX-2011</th>
<th>JTX-2011 + nivo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase 1: all doses (n=40) n (%)</td>
<td>Phase 2 (n=29) n (%)</td>
</tr>
<tr>
<td>Any related TEAE</td>
<td>All TEAEs Grade 3/4 All TEAEs Grade 3/4</td>
<td>All TEAEs Grade 3/4 All TEAEs Grade 3/4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23 (58) 7 (18)</td>
<td>19 (66) 0</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (8) 0</td>
<td>6 (21) 0</td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>5 (13) 0</td>
<td>1 (3) 0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>4 (10) 0</td>
<td>2 (7) 0</td>
</tr>
<tr>
<td>Chills</td>
<td>4 (10) 0</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (10) 0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (10) 3 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>4 (10) 0</td>
<td>1 (3) 0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (3) 0</td>
<td>0</td>
</tr>
<tr>
<td>AST increased</td>
<td>2 (5) 1 (3)</td>
<td>1 (3) 1 (3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (8) 3 (8)</td>
<td>2 (7) 0</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- DLTs on mechanism at 1.0 mg/kg JTX-2011 alone (Grade 3 AST/ALT, Grade 3 pleural effusion)
- 2 possibly related Grade 5 AEs with JTX-2011 + nivo: increased bilirubin, encephalopathy

*all related TEAEs experienced by ≥ 5% of pts or Gr 3/4 events experienced by > 1 pt listed in order of decreasing frequency of Total related AEs

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JTX-2011 Pharmacokinetics and Pharmacodynamics

**Phase 1**
- RP2D 0.3 mg/kg mono and combo based on:
  - Safety
  - Sustained Target Engagement in peripheral blood through Cycle 1
  - Dose dependent increase in IFN-gamma with JTX-2011 at 1-6 hours after first dose
  - No significant impact on peripheral immune cell subsets for JTX-2011 or JTX-2011 + nivo
  - No impact of nivo on JTX-2011 PK

**Phase 2**
- RP2D 0.3 mg/kg mono and combo confirmed:
  - Sustained Target Engagement beyond Cycle 1
  - No significant change in IFN-gamma after first dose with JTX-2011 or JTX-2011 + nivo
  - No significant impact on peripheral immune cell subsets for JTX-2011 or JTX-2011 + nivo
  - No impact of nivo on JTX-2011 PK
  - Nivo PK: Cmin (mean)
    - C1D15 = 18.3 mcg/mL
    - C1D22/C2D1 = 14.6 mcg/mL
    - C5D1 = 30.1 mcg/mL

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JTX-2011 Monotherapy: Clinical Activity

**Phase 1 (n=40*)**
- Durable SD
  - Endometrial 7+ mths, CRPC 6+ mths
- Disease Control Rate = 25% (10)
- 75% discontinuation ≤ C3, 15% in C1

**Phase 2 (n=27*)**
- Ongoing RECIST PR in 1/8 gastric
  - Gastric 8.5+ mths
- Disease Control Rate = 19% (5)
- 78% discontinuation ≤ C3, 19% in C1

*Evaluable: Dosed and ≥ 1 scan or discontinued treatment, Disease Control Rate= confirmed PR + SD ≥ 9 wks

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**JTX-2011 + nivo: Clinical Activity**

**Phase 1 (n=31*)**
- Ongoing RECIST PR in 1/4 gastric
  - Gastric 11+ mths (JTX-2011 0.1 mg/kg)
  - Disease Control Rate = 29% (9)
  - 58% discontinuation ≤ C3, 10% in C1

**Phase 2 (n=75*)**
- Ongoing RECIST PRs and/or SD
  - Gastric, TNBC, NSCLC
  - Disease Control Rate = 32% (24)
  - 69% discontinuation ≤ C3, 17% in C1

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*Evaluable= Dosed and ≥ 1 scan or discontinued treatment, Disease Control Rate= confirmed PR + SD ≥ 9 wks

**Data cut-off April 4, 2018**

**Timothy A. Yap MD, PhD**

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**Graphs:**

- **Change from baseline (%):**
  - Y-axis: 0 to 100
  - X-axis: Weeks Since Treatment Initiation
  - Key:
    - Ongoing
    - PD-1 inhibitor naive
    - PD-1 inhibitor failure
    - Off-treatment
JTX-2011 + nivo: Ongoing Disease Control in Gastric, TNBC and NSCLC

Tumor reductions = 33% (4)
ORR = 0
DCR = 58% (7)

67% D/C ≤ C3, 0 in C1

Tumor reductions = 29% (8)
ORR = 4% (1)
DCR = 36% (10)

54% D/C ≤ C3, 14% in C1

Tumor reductions = 6% (1)
ORR = 0
DCR = 13% (2)

82% D/C ≤ C3, 35% in C1

Tumor reductions = 12%
ORR = 6% (1)
DCR = 18% (3)

88% D/C ≤ C3, 19% in C1

n= Dosed and ≥ 1 scan or discontinued treatment; Disease Control Rate= confirmed PR + SD ≥ 9 wks; D/C= discontinued

Presented by: Timothy A. Yap MD, PhD

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ICOS Expression in ICONIC Patient Tumor Samples

- Preliminary data suggests relationship between archival and fresh pre-Tx biopsy ICOS scores may vary:
  - May reflect the inducible nature of ICOS
  - May reflect differences in ICOS expression between primary tumor, nodal, and visceral metastases

- Preliminary analysis of evaluable fresh pre-treatment biopsies:
  - Rates of disease control and tumor reductions appear higher in patients with high ICOS score

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<table>
<thead>
<tr>
<th>All evaluable matched archival and fresh tumor biopsies (Phase 1 and Phase 2)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td># matched pairs archival and fresh</td>
<td>58</td>
</tr>
<tr>
<td># of samples that do not change</td>
<td>33 (57%)</td>
</tr>
<tr>
<td># of archival ICOS low to fresh ICOS high</td>
<td>16 (28%)</td>
</tr>
<tr>
<td># of archival ICOS high to fresh ICOS low</td>
<td>9 (15%)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Preliminary efficacy measure</th>
<th>All evaluable subjects with fresh tumor biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
</tr>
<tr>
<td>n</td>
<td>67</td>
</tr>
<tr>
<td>Response (n)</td>
<td>1</td>
</tr>
<tr>
<td>Disease control (n)</td>
<td>14</td>
</tr>
<tr>
<td>Tumor reductions (n)</td>
<td>9</td>
</tr>
</tbody>
</table>

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Timothy A. Yap MD, PhD
ICOS Expression in ICONIC Patient Peripheral Blood Samples

Tumor Reductions Associated with Emergence of ICOS\textsuperscript{hi} CD4\textsuperscript{+} T cell Population

Emergence of ICOS\textsuperscript{hi} CD4\textsuperscript{+} T cell population
- Observed in 7/7 subjects with target PR\textsuperscript{*}
- Not observed in 10/10 subjects with PD\textsuperscript{*}

N = 37 including subjects from mono and combo cohorts

Limited longitudinal samples for some subjects

\textsuperscript{*}Best response observed for target lesion

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JTX-2011 Monotherapy RECIST PR in Gastric Cancer

Tumor reduction associated with emergence of ICOS\textsuperscript{hi} T cell population

- 51yo female diagnosed with advanced gastric cancer June 2016
- 3 prior lines of therapy, IO naïve
- JTX-2011 therapy began May 2017; Durable RECIST PR 8.5+ mths (ongoing)

Emergence of peripheral ICOS\textsuperscript{hi} CD4 T cell population

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JTX-2011+ nivo RECIST PR in Gastric Cancer

Tumor reduction associated with emergence of ICOS$^{hi}$ T cell population

- 43yo female diagnosed with MSS gastric adenocarcinoma in Dec 2013
- 6 prior lines of therapy, IO naive
- JTX-2011 therapy (0.1mg/kg) + nivo (240mg q3w) began May 2017; Durable RECIST PR 11+ mths (ongoing)
- ICOS target saturation sustained over 21-day dosing cycle

**Baseline (12.6cm)**
5/18/2017

**On-treatment (4.1cm)**
4/2/2018 (15 cycles)

**Emergence of peripheral ICOS$^{hi}$ CD4+ T cell population**

- Cycle 7
- Cycle 9 vs Cycle 7
- Cycle 10 vs Cycle 7
- Cycle 12 vs Cycle 7

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Timothy A. Yap MD, PhD
Conclusions

• Safety and tolerability demonstrated in heavily pre-treated patients
  - JTX-2011 0.3 mg/kg well tolerated as monotherapy and with nivo 240 mg q3w

• RECIST partial responses and stable disease in advanced cancers
  - Gastric cancer- mono and combo PRs
  - TNBC- combo PR
  - NSCLC- combo stable disease and tumor reductions in PD-1 inhibitor failures

• Potential on-mechanism ICOS biomarker identified
  - Emergence of ICOS hi CD4 T-cell population, which appears to associate with antitumor activity

• Ongoing clinical trial includes a planned combination with ipilimumab
The ICONIC investigators would like to thank:

All patients and their families

The clinical study teams and participating centers

Jounce Therapeutics