Phase 1 Safety Of ICOS Agonist Antibody JTX-2011 Alone and with Nivolumab (Nivo) in Advanced Solid Tumors; Predicted vs. Observed Pharmacokinetics (PK) in ICONIC

ABSTRACT# 192770

Howard A. Burris III[1], Margaret K. Callahan[2], Anthony W. Tolcher[3], Shivaani Kummar[4], Gerald Steven Falchook[5], Russell Kent Pachynski[6], Scott S. Tykodi[7], Geoffrey Thomas Gibney[8], Tanguy Y. Seiwert[9], Justin F. Gainor[10], Patricia LoRusso[11], James Hilbert[12], Josh F Apgar[12], Fei Hua[12], Manny Lazaro[13], Myles Clancy[13], Baoyu Ding[13], Elizabeth G. Trehu[13], Timothy Anthony Yap[14]
[1]Sarah Cannon Research Institute, Nashville, TN; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]START, San Antonio, TX; [4]Stanford University School of Medicine, Stanford, CA; [5]Sarah Cannon Research Institute at HealthONE, Denver, CO; [6]Washington University School of Medicine in St. Louis, St. Louis, MO; [7]University of Washington and Fred Hutchinson Cancer Research Center, Seattle, WA; [8]Georgetown Lombardi Comprehensive Cancer Center; [9]University of Chicago, Chicago, IL; [10]Massachusetts General Hospital, Boston, MA; [11]Yale Cancer Center, New Haven, CT; [12]Applied Biomath, Lincoln, MA; [13]Jounce Therapeutics, Cambridge, MA; [14]MD Anderson Cancer Center, Houston, TX

JTX-2011 Background

ICOS Agonist

JTX-2011 is a humanized IgG1κ agonist monoclonal antibody that specifically binds to the Inducible CO-Stimulator of T cells (ICOS).

Mechanism of Action

Preclinical Pharmacology and Modeling

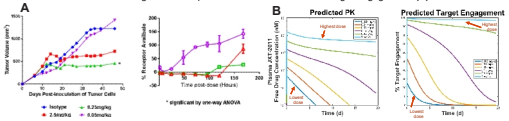
Mouse → Rat → Monkey → Man

Mouse, rat and non-human primate (NHP) are all pharmacologically relevant species
- ICOS expressed at similar levels on similar immune cell subsets across species
- JTX-2011 shows equivalent affinity and potency across species

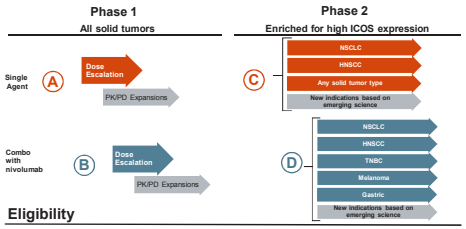
Anti-tumor activity observed in preclinical mouse syngeneic tumor models both as a single agent and in combination with anti-PD-1 antibody
- Single agent efficacy correlates with percentage of ICOS expressing immune cells in murine tumors at baseline
- Maximal efficacy correlates with ICOS target engagement (TE) through ~Day 7 in the mice
  - TE was similar in peripheral and intratumoral T cells in mouse syngeneic tumor models

Quantitative Systems Pharmacology (QSP) Modeling informed first-in-human dose selection based on:
- Rodent and NHP PK data
- In vivo and/or ex vivo data from mouse **(A)**, NHP and human (not shown)

Predictions for human PK and ICOS availability (target engagement)
- First in Human starting dose anticipated to have transient ICOS target engagement **(B)**



ICONIC Phase 1 / 2 Study Design



Eligibility

Major Inclusion Criteria
- Confirmed cancer that is recurrent, metastatic or persistent after at least one line of therapy and with no further standard treatment options
- Male or Female ≥ 18 years of age
- ECOG Performance Status: 0-1
- Predicted life expectancy of ≥ 3 months
- Archival tumor tissue required for all subjects
- Any advanced, non-hematological, extracranial malignancy with disease progression after treatment with all available therapies known to confer clinical benefit
- May have evaluable but non-measurable disease

Major Exclusion Criteria
- Refused standard therapy
- History of intolerance, hypersensitivity, or treatment discontinuation due to severe immune adverse events on prior immunotherapy
- Immunodeficiency
- Active or prior history of autoimmune disease
- Symptomatic or uncontrolled brain metastases, leptomeningeal disease, or spinal cord compression

ICONIC Phase 1 Study Population: All solid tumors, no enrichment for high ICOS expression

Table 1: Disposition as of May 12, 2017

JTX-2011 Monotherapy (Part A)							
mg/kg	0.003	0.01	0.03*	0.1	0.3	1.0	Total
Dosed	3	3	5	11	7	5	34
Treatment discontinuation	3 (100.0)	3 (100.0)	4 (80.0)	5 (45.5)	2 (28.6)	1 (20.0)	18 (52.9)
Disease progression	3 (100.0)	3 (100.0)	3 (60.0)	3 (27.3)	2 (28.6)	1 (20.0)	15 (44.1)
Adverse event	-	-	-	1 (9.1)	-	-	1 (2.9)
Subject declined further participation	-	-	-	1 (9.1)	-	-	1 (2.9)
Clinical deterioration			1 (20.0)				1 (2.9)
Weeks on Study mean (SD)	9 (0.50)	9 (0.87)	9(6.53)	9(4.12)	8 (4.08)	4 (1.86)	8 (4.06)

JTX-2011 + Nivolumab (Part B)					
mg/kg	0.01	0.03	0.1	0.3	Total
Dosed	3	3	3	3	12
Treatment discontinuation	-	2 (66.7)	-	-	2 (16.7)
Disease progression	-	2 (66.7)	-	-	2 (16.7)
Weeks on Study mean (SD)	22 (0.93)	10 (5.79)	11 (0.60)	6 (1.05)	12 (6.58)

* 1 subject was assigned to 0.03 mg/kg, but received 0.3 mg/kg for 45 minutes (equivalent to 0.225 mg/kg) on Cycle 1 day 1 and continued on 0.03 mg/kg afterwards. For safety purposes, this subject was grouped to 0.3 mg/kg

Table 2: Demographics and Prior Therapies

	JTX-2011 (N=34)	JTX-2011 + Nivolumab (N=12)	All Phase 1 Subjects (N=46)
Sex, n (%)			
Male	15 (44.1)	2 (16.7)	17 (37.0)
Female	19 (55.9)	10 (83.3)	29 (63.0)
Age			
Mean (SD)	60.5 (11.34)	59.4 (10.90)	60.2 (11.12)
Race, n (%)			
Black or African American	4 (11.8)	1 (8.3)	5 (10.9)
White	25 (73.5)	11 (91.7)	36 (78.3)
Other	3 (8.8)	-	3 (6.5)
Not Reported	2 (5.9)	-	2 (4.3)
Prior Systemic Therapy			
Cytotoxic Chemotherapy	34 (100.0)	11 (91.7)	45 (97.8)
Immunotherapy	9 (26.5)	7 (58.3)	16 (34.8)
PD-1 or PD-L1	8 (23.5)	6 (50.0)	14 (30.4)
Other therapies	24 (70.6)	8 (66.7)	32 (69.6)
Line of Prior Therapies			
Median (min, max)	4.0 (1, 12)	5.0 (3, 8)	4.0 (1, 12)

ICONIC Phase 1 PK/PD Results (Interim)

Table 3: Summary of JTX-2011 PK Parameters† for JTX-2011 Monotherapy

	JTX-2011 Dose (mg/kg)						
	0.003 (n=3)	0.01 (n=3)	0.03 (n=4)	0.10 (n=10)	0.23 (n=1)*	0.30 (n=5)	1.0 (n=4)
$AUC_{0-\infty}$ (μg·h/mL)	1.75 (139%)	7.90 (17%)	45.6 (127%)	309 (34%)	911	1020 (78%)	3110 (42%)
$AUC_{0\text{-}tz}$ (μg·h/mL)	1.50 (177%)	7.68 (17%)	44.2 (124%)	293 (33%)	784	592 (158%)	2340 (35%)
C_{max} (μg/mL)	0.06 (61%)	0.18 (15%)	0.50 (57%)	1.99 (28%)	5.79	5.70 (22%)	14.50 (21%)
CL (mL/h)	1.71 (139%)	1.27 (17%)	0.66 (127%)	0.32 (34%)	0.25	0.29 (78%)	0.32 (42%)
$t_{½}$ (h)†	30.1 (58%)	30.8 (16%)	83.4 (40%)	106 (32%)	196	227 (73%)	175 (48%)
Vss (mL/kg)	65.1 (46%)	56.0 (30%)	72.4 (65%)	53.0 (28%)	60.0	70.3 (44%)	74.3 (29%)

Table 4: Summary of JTX-2011 PK Parameters† for JTX-2011 + Nivolumab

	JTX-2011 + Nivolumab			
	JTX-2011 Dose (mg/kg)			
	0.010 (n=3)	0.030 (n=2)	0.100 (n=3)	0.300 (n=3)
$AUC_{0-\infty}$ (μg·h/mL)	11 (56%)	26 (95%)	236 (44%)	1070 (36%)
$AUC_{0\text{-}tz}$ (μg·h/mL)	11 (56%)	26 (95%)	150 (160%)	832 (21%)
C_{max} (μg/mL)	0.25 (26%)	0.49 (19%)	1.98 (19%)	5.94 (12%)
CL (mL/h)	0.90 (55%)	1.15 (95%)	0.42 (45%)	0.28 (36%)
$t_{½}$ (h)†	31.8 (22%)	37.6 (86%)	88.6 (43%)	175 (46%)
Vss (mL/kg)	41.6 (30%)	51.2 (6%)	52.5 (16%)	64.3 (27%)

* One patient was accidentally dosed with this dose. This patient's safety data was included with the 0.3 mg/kg dose group
† Geometric mean (geometric CV%) was reported for all the parameters except for t_{max} and $t_{½}$, mean and (CV%) was reported

ICONIC Phase 1 Safety Results (Interim)

Safety Results:

- JTX-2011 was dosed to the highest planned level (1 mg/kg for JTX-2011 as a single agent and 0.3 mg/kg in combination with nivolumab).
- The maximum tolerated dose for JTX-2011 is 0.3 mg/kg.
- 2 DLTs (out of 6 subjects) occurred at 1 mg/kg JTX-2011 monotherapy:
  - 1 participant developed a worsening pleural effusion ~10 days after the first dose of JTX-2011
  - 1 participant developed AST/ALT 5x ULN ~23 days after the first dose of JTX-2011. ALT/AST returned to baseline within 72 hours after receiving prednisone 0.5 mg/kg, leading to a diagnosis of immune related hepatitis.
- Treatment emergent serious adverse events† were reported in 11 participants:
  - 10 on JTX-2011 monotherapy at 0.003 mg/kg (1); 0.1 mg/kg (4); 0.3 mg/kg (3); and 1 mg/kg (2)†.
  - 1 on JTX-2011 0.03 mg/kg in combination with nivolumab.
- Grade 3 or 4 related adverse events were reported in 6 participants on JTX-2011 monotherapy and no participants on JTX-2011 in combination with nivolumab.
- Adverse events considered by investigators to be infusion related were reported in 10 participants at doses 0.003 mg/kg through 0.3 mg/kg: 6 on JTX-2011 monotherapy and 4 in combination with nivolumab: chills, pyrexia, diarrhea, hypertension, neck pain, tachycardia, nausea, vomiting, and other infusion related reactions.
- Adverse events considered by investigators to be immune related but not infusion related were reported in 6 participants at doses of 0.03 mg/kg or above: 5 on JTX-2011 monotherapy and 1 in combination with nivolumab: alanine aminotransferase increased, blood alkaline phosphatase increased, lymphocyte count decreased*, neutrophil count decreased*, white blood cell count decreased*, night sweats, pneumonitis, pruritus, rash, tumor pain, diarrhea.
- 1 death was reported due to progressive disease after withdrawal from the study.

* were observed in single participant who received steroids for immune related adverse events.
† SAEs were imported from the safety database. 1 of these subjects was not reported in the clinical database on May 12,2017

Table 5: Summary of Most Frequent Related Adverse Events (≥5% in any column)

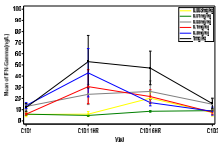
	JTX-2011 Monotherapy (N=34)		JTX-2011 + Nivolumab (N=12)		Total (N=46)	
	All AEs	Grade 3/4	All AEs	Grade 3/4	All AEs	Grade 3/4
# TEAEs*	153	17	40	-	193	17
# Participants w. TEAEs, n (%)	24 (70.6)	11 (32.4)	9 (75.0)	-	33 (71.7)	11 (23.9)
# Participants w. Related TEAEs, n (%)	15 (44.1)	6 (17.6)	6 (50.0)	-	21 (45.7)	6 (13.0)
Subjects w. Related TEAEs, n (%)						
Chills	3 (8.8)	-	2 (16.7)	-	5 (10.9)	-
Nausea	4 (11.8)	-	1 (8.3)	-	5 (10.9)	-
Decreased appetite	3 (8.8)	-	1 (8.3)	-	4 (8.7)	-
Pyrexia	4 (11.8)	-	-	-	4 (8.7)	-
Alanine aminotransferase increased	3 (8.8)	1 (2.9)	-	-	3 (6.5)	1 (2.2)
Diarrhoea	3 (8.8)	3 (8.8)	-	-	3 (6.5)	3 (6.5)
Fatigue	2 (5.9)	-	1 (8.3)	-	3 (6.5)	-
Infusion related reaction	1 (2.9)	-	2 (16.7)	-	3 (6.5)	-
Pruritus	3 (8.8)	-	-	-	3 (6.5)	-
Aspartate aminotransferase increased	2 (5.9)	1 (2.9)	-	-	2 (4.3)	1 (2.2)
Dizziness	2 (5.9)	-	-	-	2 (4.3)	-
Hypokalaemia	1 (2.9)	1 (2.9)	1 (8.3)	-	2 (4.3)	1 (2.2)
Hypomagnesaemia	2 (5.9)	-	-	-	2 (4.3)	-
Vomiting	1 (2.9)	-	1 (8.3)	-	2 (4.3)	-
Back pain	-	-	1 (8.3)	-	1 (2.2)	-
Hypothyroidism	-	-	1 (8.3)	-	1 (2.2)	-

* TEAEs includes all treatment emergent adverse events with start date on or after the first dose of the study drug and on or before 28 days after the last dose of the study drug.

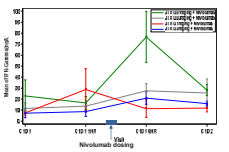
ICONIC Phase 1 Safety/PK/PD Results (Interim)

Interferon-γ

Mean Level of IFN-γ by Dose, JTX-2011



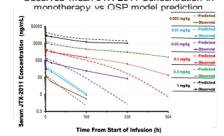
Mean Level of IFN-γ by Dose, JTX-2011 + Nivolumab



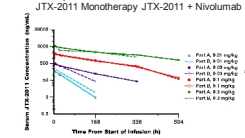
- Mean increase in IFN-γ was observed at 1-6 hours at all dose levels, and may be dose related.
- Increases in TNF-α and IL-6 were also observed.

PK

Observed mean JTX-2011 Concentration in monotherapy vs QSP model prediction



Comparison of Mean JTX-2011 PK between JTX-2011 Monotherapy JTX-2011 + Nivolumab



a. ADA was detected in a participant in Part B 0.03 mg/kg and PK appeared to be impacted.

- The QSP model, based on nonclinical data, predicted human non-linear PK at doses ≤0.01mg/kg and ≥0.3mg/kg
  - The QSP model underestimated exposure at later timepoints for the middle 0.1mg/kg and 0.3mg/kg doses, suggesting that TMDD was saturated at a lower exposure than predicted
  - At lower doses (≤0.1mg/kg) the dose-non-linear PK suggests target-mediated drug disposition (TMDD)
  - At the higher doses, PK is close to dose-linear, suggesting that ≥ 0.3mg/kg saturates TMDD
- The PK of JTX-2011 does not appear to be impacted by co-administration of nivolumab
- Target engagement was >90% through day 21 in 2 evaluable participants in the 0.3 mg/kg monotherapy dose escalation cohort
  - No significant changes from baseline in CD4+ T cells, CD4+ T effector cells, CD4+ T regulatory cells, CD19+ B Cells, CD56+ NK Cells or CD8+ T cells were observed in these participants
- Treatment-emergent Anti-drug antibodies (ADA) were detected in 2/20 evaluable monotherapy participants and 3/10 evaluable combination therapy participants. ADA were transient except in 1 participant, where ADA was detected through 6 weeks. In 1 participant, PK appears to have been impacted.

Summary

- JTX-2011 was well tolerated at doses up to 0.3 mg/kg IV q 21 days as monotherapy and in combination with nivolumab 240 mg IV q 21 days in participants with advanced solid tumors
- Immune related adverse events not related to drug infusion were reported at doses at or above 0.03 mg/kg, including 2 dose limiting toxicities at 1 mg/kg monotherapy.
- JTX-2011 0.3 mg/kg was selected as the recommended Phase 2 dose (RP2D) for monotherapy based on:
  - Safety and tolerability
  - > 90% peripheral target engagement through Day 21 to increase the likelihood of sufficient intratumoral TE
  - PK consistent with the preclinical model and predicted target engagement
  - Lack of peripheral T cell depletion
- Most monotherapy participants at the RP2D remain on study with limited duration of follow-up:
  - 5/7 at 0.3 mg/kg; mean (±SD) duration of 8 (±4.73) weeks
  - 4/5 who started at 1.0 mg/kg and switched to 0.3 mg/kg ; mean (±SD) duration of 4.8 (±1.67) weeks
- 10/12 combination therapy participants remain on study treatment at doses from 0.01-0.3 mg/kg with mean (±SD) duration of 13.1 (±6.70) weeks
- Phase 2 monotherapy cohorts are currently enrolling with enrichment for tumors with high ICOS expression.