ICONIC: Phase 1/2 Trial of ICOS Agonist JTX-2011 Alone and in Combination with Nivolumab (nivo)

Olivia Sears[1], Howard A. Burris III[2], Margaret K. Callahan[3], Anthony W. Tolcher[4], Shivaani Kummar[5], Gerald Steven Falchook[6], Russell Kent Pachynski[7], Scott S. Tykodi[8], Geoffrey Thomas Gibney[9], Tanguy Y. Seiwert[10], Justin F. Gainor[11], Patricia LoRusso[12], Manny Lazaro[1], Myles Clancy[1], Ella Li[1], Baoyu Ding[1], Elizabeth G. Trehu[1], Timothy Anthony Yap[13]

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

Abstract

Background: JTX-2011 is an agonist monoclonal antibody that targets ICOS, Inducible CO-Stimulator of T cells. A dual mechanism of action is intended to induce proliferation and stimulation of CD4 T effector cells and selectively deplete intratumoral T regulatory cells. JTX-2011 has shown preclinical anti-tumor effects both as a single agent and in combination with anti-PD-1 antibodies, with single agent efficacy correlated with % of ICOS expressing T cells in tumors. An ICOS IHC assay was used to identify human tumor types with the highest levels of ICOS expressing T cells.

Methods: ICONIC is a first-in-human Phase 1/2, open label, adaptive clinical study of JTX-2011 alone or in combination with a fixed dose of nivo in subjects with advanced solid tumors. It is designed to assess safety and tolerability, determine the maximal tolerated dose (MTD) and recommended Phase 2 dose, and evaluate preliminary efficacy.

- **Part A:** 3+3 dose escalation of JTX-2011, with Safety/PK/PD expansion cohorts at 2 or more dose levels.
- **Part B:** 3+3 dose escalation of JTX-2011 in combination with nivo, with Safety/PK/PD expansion cohorts at two or more dose levels.
- **Part C:** ≥3 JTX-2011 cohorts in tumors expected to have higher levels of ICOS expressing T cells (non small cell lung cancer [NSCLC], head and neck squamous cell cancer [HNSCC], and others), with ICOS enrichment by IHC.
- **Part D:** ≥ 5 JTX-2011 + nivo cohorts in tumors expected to have higher levels of ICOS expressing T cells (NSCLC, HNSCC, triple negative breast cancer (TNBC), melanoma, gastric, and others), with ICOS enrichment by IHC.

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
- Part A&B: available and consent to provide archival tumor tissue
- Part C&D: available and consent to provide archival tumor tissue, have a lesion that can be biopsied at acceptable clinical risk (as judged by the investigator), and agree to a fresh biopsy

Major Exclusion Criteria:

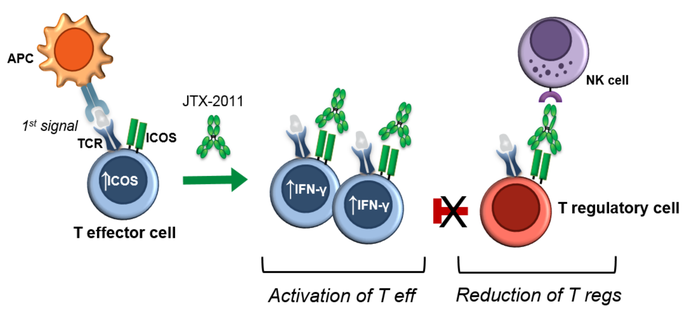
- Refused standard therapy
- History of intolerance, hypersensitivity, or treatment discontinuation due to severe immune adverse events on prior immunotherapy
- Immunodeficiency
- Active or prior history of autoimmune disease
- Symptomatic or uncontrolled brain metastases, leptomeningeal disease, or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

Endpoints

- Safety and tolerability
- Pharmacokinetics, target engagement, and other Pharmacodynamic markers
- Efficacy by RECIST 1.1 and irRC; Overall response rate (ORR), Duration of Response, Disease Control Rate, Progression Free Survival (PFS), Landmark PFS, Overall Survival (OS)

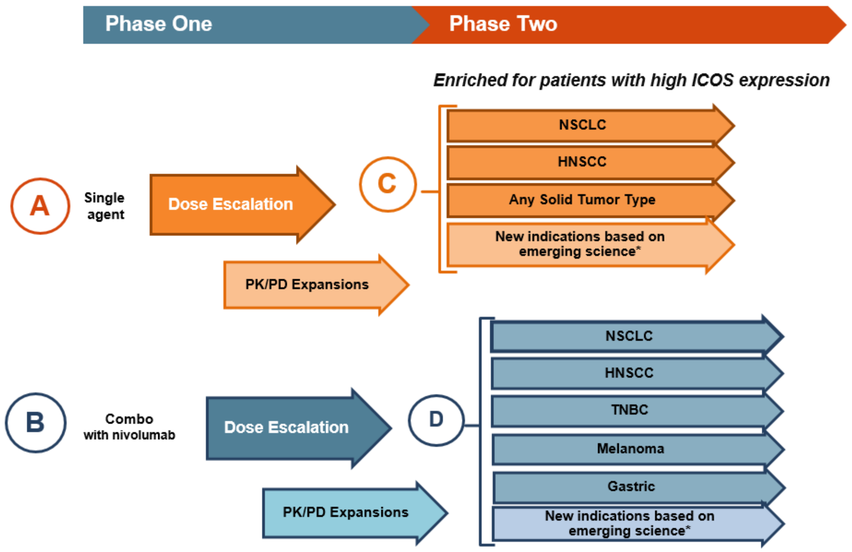
ICOS Agonist JTX-2011 Background

- JTX-2011 is a humanized IgG1κ agonist monoclonal antibody that specifically binds to the Inducible CO-Stimulator of T cells (ICOS) and is designed to generate an anti-tumor immune response through stimulation of T effector cells and selective reduction of T regulatory cells within tumors.
- JTX-2011 has shown preclinical anti-tumor effects both as a single agent and in combination with anti-PD-1 antibodies.
- In preclinical models, single agent efficacy correlated with percent of ICOS expressing T cells in tumors.
- JTX-2011 is being developed in patients with advanced solid tumors who have no standard therapeutic options.
- An ICOS IHC assay was used to identify human tumor types with the highest levels of ICOS expressing T cells.



Dual mechanism of action

ICONIC: Adaptive, Biomarker-Driven, Clinical Study



* Additional indications, including niche indications, identified through our Translational Science Platform

Inclusion and Exclusion Criteria

General Inclusion Criteria:

- Willing and able to participate and comply with all trial requirements and provide informed consent
- Have 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

Part A/B Dose Escalation Criteria:

- 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

Parts A and B PK/PD Expansion Criteria:

- Must have a tumor lesion that can be biopsied at acceptable risk and must agree to both a fresh biopsy between screening and C1D1 and a second biopsy after completion of two cycles of study treatment

Part C and D Criteria:

- All subjects must have a tumor lesion that can be biopsied at acceptable risk and must agree to a fresh biopsy between screening and C1D1

Major Exclusion Criteria:

- Refused standard therapy
- Hx 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

Study Objectives

Phase 1 Part A and B: ***Assessing Safety and Tolerability of JTX-2011 as a monotherapy and as a combination therapy with nivolumab***

Primary:
- Assess safety and tolerability of JTX-2011 monotherapy and in combination with nivolumab in subjects after single and multiple ascending doses
- Determine maximum tolerated dose (MTD) and recommended Phase II dose (RP2D)

Secondary:
- PK and PD of JTX-2011 when in administered as a monotherapy and in combination with nivolumab
- PK of nivolumab when administered in combination with JTX-2011

Exploratory:
- Effect on peripheral blood immune cell markers and gene signatures
- Efficacy as a combination therapy (ORR, Duration of Response, Disease Control Rate, PFS, OS)
- Correlation between predictive biomarkers and efficacy

Phase 2 Part C and D: ***JTX-2011 monotherapy and combination therapy expansions with selected cohorts stratified for ICOS expression***

Primary:
- Preliminary Efficacy (ORR, Duration of Response, Disease Control Rate, PFS, OS) as a monotherapy and in combination with nivolumab in expansion groups with enrichment for ICOS expression
- Confirm safety and tolerability as a monotherapy and combination therapy
- Confirm MTD and RP2D

Secondary: Confirm PK and PD of JTX-2011

Exploratory:
- Examine correlation between potential predictive biomarkers of response and efficacy
- Evaluate effect on peripheral blood immune cell markers and gene signatures

Clinical Sites

1. Stanford University School of Medicine
2. Sarah Cannon Research Institute at HealthONE
3. Yale New Haven Hospital
4. The University of Chicago Medicine Comprehensive Cancer Center
5. Massachusetts General Hospital Cancer Center
6. Washington University School of Medicine
7. Georgetown Lombardi Comprehensive Cancer Center
8. University of Washington
9. Sarah Cannon Research Institute at TriStar Health
10. South Texas Accelerated Research Therapeutics, LLC
11. The University of Texas- MD Anderson Cancer Center
12. Memorial Sloan Kettering Cancer Center

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