Emergence of an ICOS hi CD4 T cell subset correlates with tumor reductions in subjects treated with the ICOS agonist antibody JTX-2011

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**Abstract**

Background: Inducible T cell Co-stimulator (ICOS) is a costimulatory molecule expressed primarily on T lymphocytes that is upregulated upon cell activation. ICOS was identified as a potential target of interest based on clinical data from studies with anti-CTLA4. Sustained ICOS upregulation was associated with clinical benefit, with preclinical data confirming a role for ICOS signaling in optimal anti-tumor activity. JTX-2011 is a first-in-class ICOS agonist antibody that has been demonstrated preclinically to have a tumor-centric dual mechanism of action through stimulation of CD4 T effector cells and depletion of intra-tumoral T regulatory cells. Clinical and biological activity of JTX-2011 is currently being evaluated in the advanced solid tumor setting in the ongoing Phase III ICONIC trial (NCT02942850).

Methods: Relapsed/refractory cancer patients received escalating doses of JTX-2011 as a monotherapy or in combination with nivolumab (240mg) administered q3w. Serial collection of peripheral blood mononuclear cells (PBMCs) was performed to enable longitudinal assessment of biological activity through flow cytometry-based assays, including target engagement (TE) and immunophenotyping (IP).

Results: At the RP2D, peripheral TE demonstrated sustained (>70%) engagement over the entire dose cycle, and IP data demonstrated no consistent changes in T cell populations following JTX-2011 treatment. Further analysis of peripheral T cell phenotype demonstrated the emergence of an ICOS hi subset of CD4 T cells in select subjects. Interestingly, the emergence of this cell population correlated with tumor reductions in both JTX-2011 monotherapy and combination subjects. Of the evaluable subjects assessed (N=37), emergence of the ICOS hi CD4 T cell subset was detected in 17/37 subjects with a reduction of their target lesion >30%, but not in any subject with best overall response of progressive disease.

Conclusion: Analysis of longitudinal blood samples from subjects treated with JTX-2011 suggests that the emergence of a distinct ICOS hi population of peripheral CD4 T cells correlates with clinical benefit, with preclinical data confirming a role for ICOS in its therapeutic activity.

**JTX-2011 Pre-Clinical Rationale for ICOS Agonist IgG1 Antibody**

Shifting the balance of T cells towards antitumor activity

**ICONIC: Phase III Adaptive Study Design**

Phase 1

All solid tumors, no enrichment for ICOS expression

Phase 2

Pls must have progression of all available therapies. Enrolled for plts with high ICOS expression

**Figure 1: JTX-2011 Treatment Does not Induce Significant Changes in Immune Cell Subsets in Peripheral Blood**

A) JTX-2011 Monotherapy

B) JTX-2011+ Nivolumab Combination Therapy

Changes in peripheral blood CD4 T effector cells, Tregs, CD8 T cells and NK cells were assessed by flow cytometry using PBMCs collected at the indicated time points. Data shown are mean ± SD for JTX-2011 monotherapy at 0.1mg/kg (N=4), JTX-2011 monotherapy at 0.3mg/kg (N=4) (B), JTX-2011 0.1mg/kg + Nivolumab (N=7) (C), or JTX-2011 0.3mg/kg + Nivolumab (N=16) (D).

**Figure 2: JTX-2011 Saturates ICOS on Peripheral T Cells at Doses Above 0.1mg/kg q2w**

**Figure 3: Emergence of an ICOS hi CD4 T Cell Population is a Potential Biomarker of Response**

The emergence of ICOS hi cells was detected using flow cytometry on peripheral blood mononuclear cell samples from subjects in the ICONIC trial, both JTX-2011 monotherapy and in combination with nivolumab. Assessment of target lesion responses was conducted by individual study investigators, with target lesion response plotted against the emergence of the ICOS hi CD4 T cell population. Data are as presented at ASCO 2018 and are from the April 4, 2018 data cutoff.

**Figure 4: Emergence and Persistence of ICOS hi CD4 T Cells is Observed in Subjects Responding to JTX-2011**

Emergence of ICOS hi CD4 T cells was assessed longitudinally in PBMCs from subjects treated with JTX-2011 using flow cytometry. A) Emergence of ICOS hi CD4 T cells is detected in a subject with confirmed PR treated with 0.3mg/kg JTX-2011 in combination with nivolumab. ICOS hi cells expressed T-bet and were not Tregs. B) Emergence of ICOS hi CD4 T cells was detected in a subject with confirmed PR treated with JTX-2011 at 0.3mg/kg. C) ICOS hi CD4 T cells emerged and were subsequently lost in a subject with stable disease treated with 0.3mg/kg JTX-2011 in combination with nivolumab.

**Figure 5: Emergence of ICOS hi CD4 T Cells in ICONIC is due to Activity of JTX-2011 and not PD-1 Inhibition**

**Figure 6: Soluble JTX-2011 Induces a Polyfunctional Cytokine Response in Pre-existing ICOS hi, but not ICOS lo CD4 T Cells**

**References**