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

ABSTRACT# P52

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Abstract

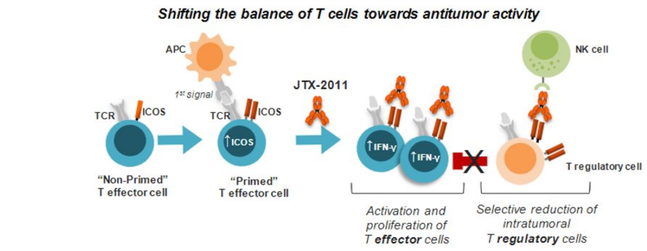
Background: Inducible T cell Co-stimulator (ICOS) is a costimulatory molecule expressed primarily on T lymphocytes that is upregulated upon cell activation. ICOS was identified as a potential target of interest based on clinical data from studies with anti-CTLA-4. Sustained ICOS upregulation was associated 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 I/II ICONIC trial (NCT02904226).

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 consistently significant 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 7/7 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 a radiographic response to JTX-2011 treatment. The emergence of this population may serve as a surrogate biomarker of response and may be useful in guiding future clinical development.

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



ICONIC: Phase I/II Adaptive Study Design

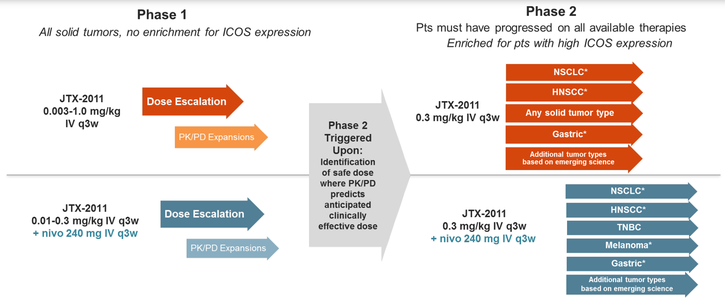
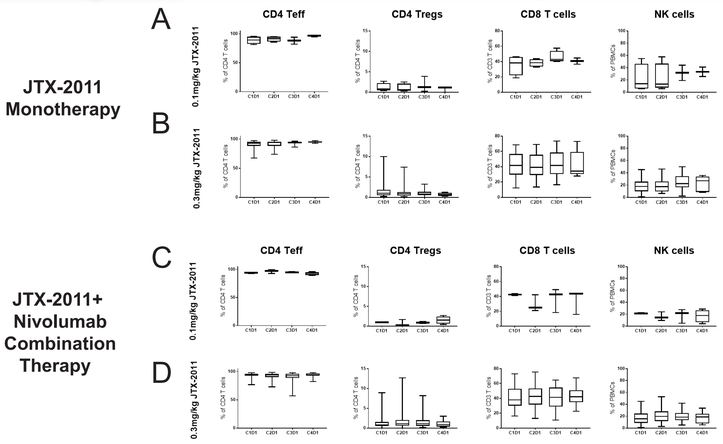
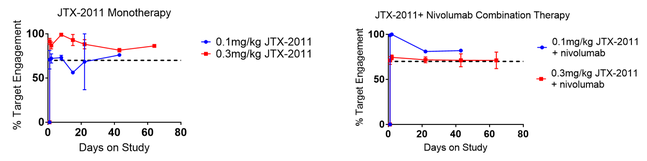


Figure 1: JTX-2011 Treatment Does not Induce Significant Changes in Immune Cell Subsets in Peripheral Blood



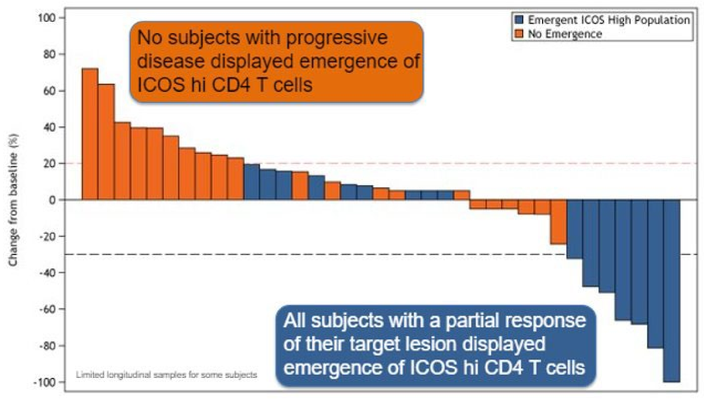
Changes in peripheral blood CD4 Teffector cells, Tregs, CD8 T cells and NK cells were assessed by flow cytometry using PBMCs collected at the indicated time points. Data shown are mean ± SD for JTX-2011 monotherapy at 0.1mg/kg (N=7) (A), JTX-2011 monotherapy at 0.3mg/kg (N=8) (B), JTX-2011 0.1mg/kg + Nivolumab (N=7) (C), or JTX-2011 0.3mg/kg + nivolumab (N=11) (D).

Figure 2: JTX-2011 Saturates ICOS on Peripheral T Cells at Doses Above 0.1mg/kg q3w



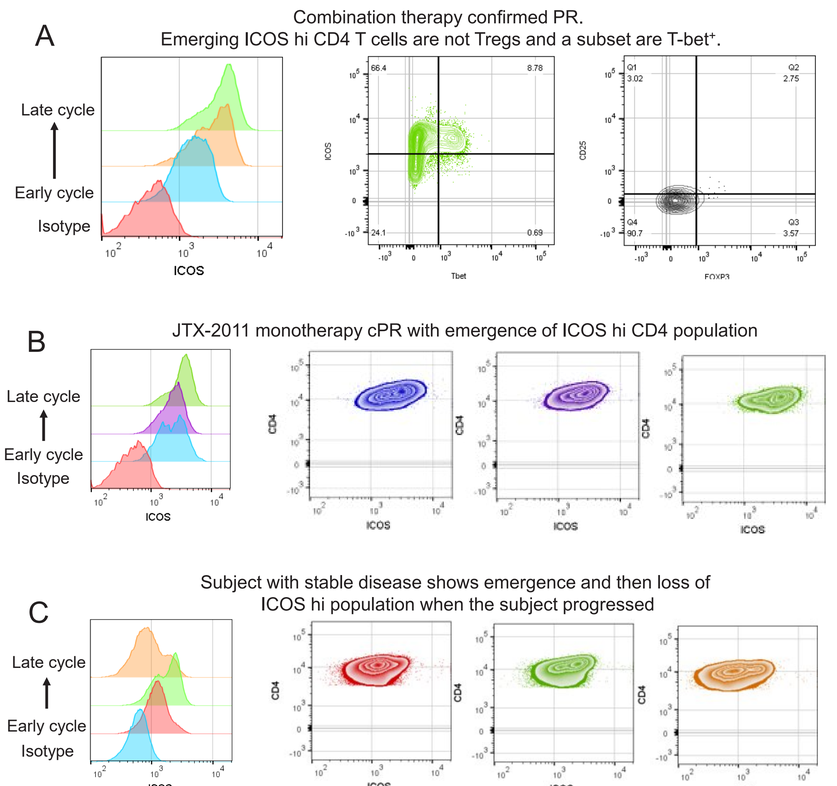
Target engagement by JTX-2011 was assessed on peripheral blood CD4 T cells following dosing with JTX-2011. A Target engagement score of ≥ 70% was deemed saturating in our assay. Data are population level analysis and are plotted as mean ± SD. Data from 15 monotherapy and 28 combination therapy subjects are shown.

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

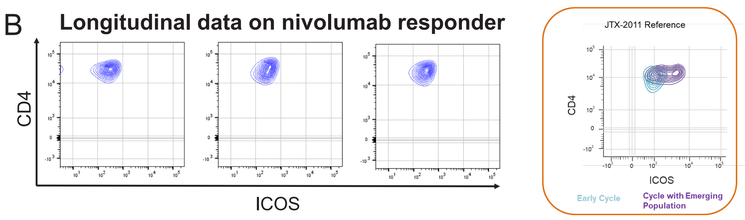


Emergence of ICOS hi CD4 T cells was assessed longitudinally in PBMCs from subjects treated with JTX-2011 using flow cytometry. A) Emergence of ICOS hi CD4 T cells is detected in a subject with confirmed PR treated with 0.1mg/kg JTX-2011 in combination with nivolumab. ICOS hi cells expressed T-bet and were not Tregs. B) Emergence of ICOS hi CD4 T cells was detected in a subject with confirmed PR treated with JTX-2011 as a monotherapy 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

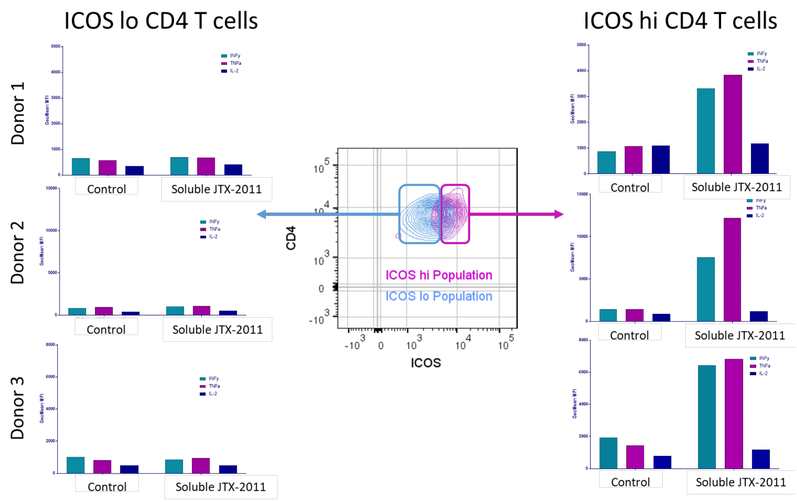
A

Indication Type	# of Subjects Profiled	# of Known Responders to PD-1i Treatment	% of ICOS hi Cells Observed
Melanoma	12	1	0
Lung	64	5	0
Other	1	0	0



Samples from subjects receiving standard of care PD-1 inhibitor treatment were obtained from a commercial biorepository. In total, PBMCs from 77 subjects were assessed and compromised primarily lung cancer and melanoma. A summary of samples tested in shown in table A. B) Longitudinal flow profile of a NSCLC subject who responded to nivolumab shows no induction of ICOS hi CD4 T cells. C) Longitudinal flow profile of a NSCLC subject who responded to pembrolizumab shows no induction of ICOS hi CD4 T cells. Contour plots are arranged in chronological order, starting with baseline profiles for each responder.

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



PBMCs from healthy donors were stimulated to induce an ICOS hi CD4 population (representative plot in inset). Following removal of stimulus and resting of the CD4 T cells, soluble JTX-2011 was added, and intracellular cytokine production was assessed by flow cytometry.

Induction of ICOS hi T cells has been demonstrated to occur in response to anti-CTLA4 treatment.

Conclusions

- JTX-2011 treatment results in no significant change in peripheral T cell subsets, consistent with preclinical observations, and JTX-2011 maintains target saturation at the RP2D of 0.3 mg/kg administered q3w as well as 0.1mg/kg administered q3w
- Strong pharmacodynamic evidence of JTX-2011 activity has been observed:
  - Emergence of an ICOS hi CD4 T cell population was detected in a subset of subjects being treated with JTX-2011 as a monotherapy or in combination with Nivolumab
  - The presence of ICOS hi CD4 T cells tracked with clinical response
  - Analysis of PBMCs from subjects treated with a PD-1 inhibitor demonstrated no emergence of ICOS hi CD4 T cells, demonstrating emergence of this population in ICONIC was due to activity of JTX-2011
- Stimulation of a pre-existing ICOS hi CD4 population by JTX-2011 induces a polyfunctional cytokine response, which may suggest combining with agents that induce ICOS hi may achieve greater clinical benefit. JTX-2011 is currently in clinical development with ipilimumab.

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