Biomarker Driven Indication Selection in JTX-2011 ICONIC Clinical Trial

ABSTRACT# 11602

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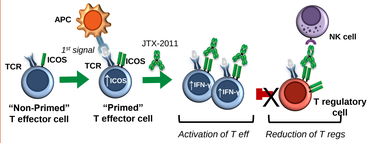
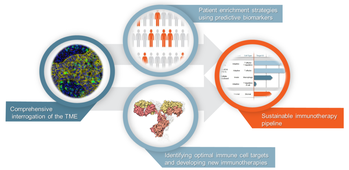
BACKGROUND

ICOS (Inducible T cell CO-Stimulator) is a co-stimulatory molecule expressed primarily on T lymphocytes. Clinical and preclinical data suggest that ICOS mediates anti-CTLA-4 driven anti-tumor responses[1-4]. JTX-2011 is an ICOS agonist antibody in clinical development in advanced solid tumors (ICONIC trial). JTX-2011 is designed to generate an anti-tumor immune response via stimulation of T effector cells and preferential reduction of intra-tumoral T regulatory cells (Tregs). Single agent preclinical efficacy correlates with the percentage of ICOS-expressing T cells within the tumor. We report indication selection and patient enrichment strategy for ICONIC using in silico and IHC analysis and assessment of potential predictive biomarkers for JTX-2011 using ex vivo tumor histoculture system.



METHODS

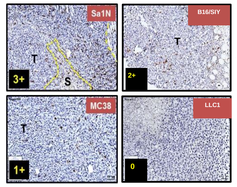
Integrated analysis of RNA, DNA and clinical data was performed from the Cancer Genome Atlas for ICOS expression in histologic and molecularly defined tumors and immune cell signatures. ICOS expression was analyzed by IHC in a subset of indications based on ranking from in silico analysis. ICOS expression on intra-tumoral Tregs and PD-L1 were analyzed in a cohort of 126 head and neck squamous cell carcinomas (HNSCC). *Ex vivo* histoculture assays of human HNSCC was treated with JTX-2011 and assessed for IFNγ gene signature induction.



Translational Science Platform:
Comprehensive interrogation of the TME to develop a sustainable innovative pipeline

RESULTS

Figure 1: Response to ICOS antibody is associated with high ICOS levels on intra-tumoral T cells in mouse syngeneic tumor models



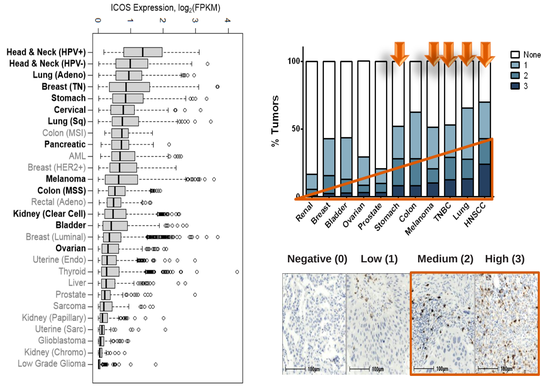
Tumor	ICOS IHC Score	Single Agent Efficacy	Combination Efficacy (+ anti-PD-1)
Sa1/N	3+	++++	ND
B16-SIY	2+	+++	++++
MC38	1+	+	+++*
CT26	1+	+	++++
EMT6	1+	+/++	+/-
LLC1	0	-	-

++++ indicates 61-100% tumor regression
+++ indicates 41-60% tumor regression
++ indicates 21-40% tumor regression
+ indicates 10-20% tumor regression
- indicates no tumor regressions

*Intra-tumoral levels of ICOS+ T cells increases post PD-1 treatment

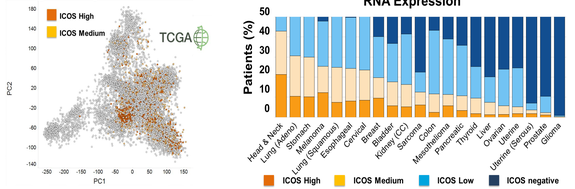
Tumors were harvested from untreated syngeneic mouse models at ~100 mm3, fixed and paraffin embedded, and subjected to ICOS IHC. Tumor models were evaluated for ICOS expression were scored as 0, 1+, 2+, or 3+. Representative images are shown in the top panel. The table in the bottom illustrates the correlation between monotherapy efficacy of ICOS antibody and expression of ICOS in each tumor model

Figure 2: Analysis of ICOS mRNA expression in TCGA by RNAseq and protein expression by indication within human tumors



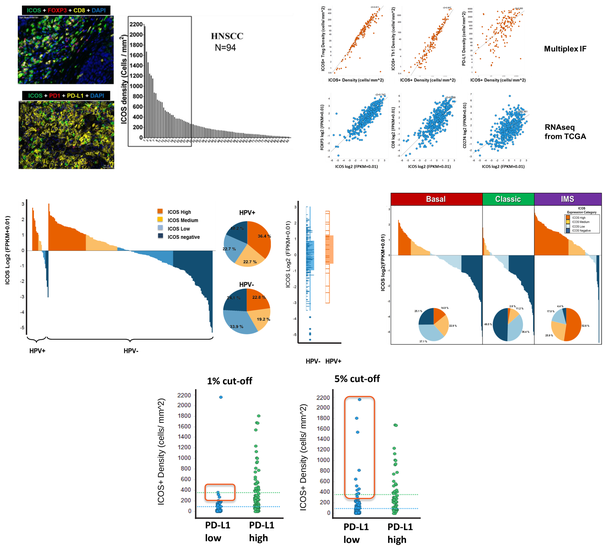
(Left Panel) Ranking of tumor indications in TCGA based on ICOS FPKM (Right Panel) Ranking of indications based on protein expression analysis

Figure 3: Setting thresholds based on IHC extrapolation to assess frequency of expression in each indication



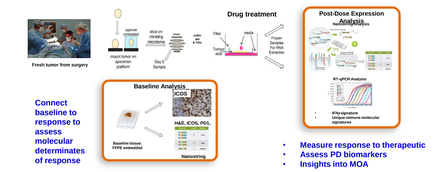
(Left Panel) Principal component analysis of solid tumors in TCGA overlaid with ICOS expression based on thresh holds set by IHC frequency. (Right Panel) Frequency of ICOS expression groups within indications in TCGA.

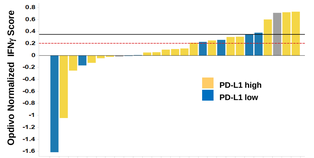
Figure 4: Head and Neck Squamous Cell Carcinoma

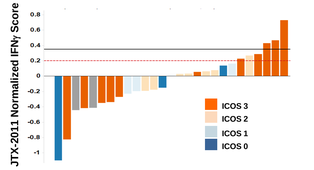


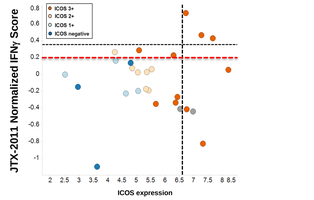
(A) ICOS is expressed over a dynamic range within HNSCC and is tightly associated with Tregs as demonstrated by IF and RNAseq from the TCGA database. (B) Distribution of ICOS Expression Across HPV subtypes molecularly defined HNSCC Subgroups. Samples from the HNSC TCGA RNAseq dataset were subgrouped based on the maximum spearman correlation with the published centroids from each subgroup (Keck *et al*, 2015). RNAseq samples were binned into high, medium, low, and absent ICOS using thresholds based on proportions observed in across multiple indications using IHC (Figure 3). Distributions of ICOS expression are shown based on RNA-Seq expression. (C) High ICOS density is observed in PD-L1 positive patients. Co-staining of ICOS and PDL1 was performed by multiplex IF on HNSCC tumor samples. There is a subset (7-17%) of patients that are PD-L1 low with high ICOS (>200 cell/mm2) infiltration.

Figure 5: Functional Testing of Biomarker Hypotheses using *ex vivo* histoculture



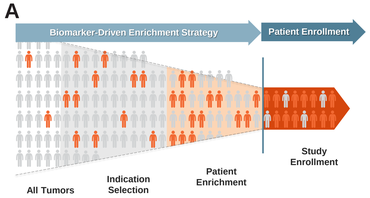


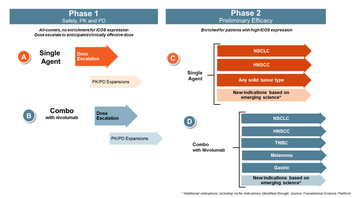




(A) Human histoculture is used as a functional assay to test both indication selection biomarkers as well discovery of potential PD biomarkers. Schematic of the process by which histoculture is performed. (B) *Ex vivo* histoculture analysis of anti-PD1 treatment of HNSCC tumors. Induction of IFNγ signature is used as a proxy for tumor response to anti-PD1 therapy. The dashed black line shows strong IFNγ response and red lines shows moderate IFNγ response (C) *Ex vivo* histoculture analysis of JTX-2011 treatment of HNSCC tumors. (D) Tumors with both strong and moderate induction of IFNγ signature are ICOS high. Additionally, tumors that have strong response to JTX-2011 also have high levels of ICOS RNA.

Figure 6: Indications selected for JTX-2011 ICONIC clinical trial





SUMMARY

- JTX-2011 is proposed to work via a dual mechanism by sending an agonistic signal to Teff cells and by selective depletion of intratumoral Tregs
- ICOS is expressed on both Teff and Treg cells within the tumor microenvironment
- JTX-2011 is efficacious in several mouse syngeneic models and response is correlated to with percentage of ICOS expressing intra-tumoral T cells at baseline
- ICOS is highly expressed across a wide range of malignancies and has a dynamic range within indications.
- In ex vivo functional assays, tumors in which an IFNγ signature is induced after treatment with JTX-2011 have higher levels of ICOS both by IHC and RNA.
- Indications with the highest percentage of ICOS expressing T cells have been selected for Phase 2 expansions in the ICONIC trial

References:

1. Chen et al. *Anti-CTLA-4 therapy results in higher CD4+ICOShi T cell frequency and IFN-gamma levels in both nonmalignant and malignant prostate tissues.* PNAS, 2009. **106(8)** p.2729-2734.
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3. Ng Tang et al. *Increased frequency of ICOS+ CD4 T cells as a pharmacodynamic biomarker for anti-CTLA-4 therapy* Cancer Immunology Research, 2013. **1(4)** p.229-234.
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5. M. Keck *et al*. *Integrative Analysis of Head and Neck Cancer Identifies Two Biologically Distinct HPV and Three Non-HPV Subtypes.* Clinical Cancer Research, 2015. **21**(4) p.870-881
6. The RNA expression results shown here were based upon data generated by the TCGA Research Network: http://cancergenome.nih.gov/.