Biomarker Driven Indication Selection in JTX-2011 ICONIC Clinical Trial

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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 responses1,2. JTX-2011 is an ICOS agonist antibody in clinical development for advanced solid tumors (ICONIC trial). JTX-2011 is designed to generate an anti-tumor immune response via stimulation of T effector cells and preferential induction of intra-tumoral T regulatory cells (Tregs). Single agent JTX-2011 administration, or combination with PD-L1 blockade, results in expansion of ICOS expressing tumors 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 histological 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) by ex vivo/histoculture analysis of human HNSCC was treated with JTX-2011 and assessed for anti-ICOS signature induction.

RESULTS

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

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

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

Figure 4: Head and Neck Squamous Cell Carcinoma

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

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

SUMMARY

1. JTX-2011 is proposed to work via a dual mechanism by sending an agonistic signal to T cells and by selective enrichment of intra-tumoral Tregs.
2. ICOS is expressed on both T eff and Treg cells within the tumor microenvironment.
3. JTX-2011 is efficacious in several mouse syngeneic models and responses are correlated with percentage of ICOS expressing intra-tumoral T cells of baseline.
4. ICOS is highly expressed across a wide range of malignancies and has a dynamic range within indications.
5. In vivo functional assays, tumors which an ICOS signature is enriched also treated with JTX-2011 have increased tumor infiltration of effector T cells.
6. Indications with the highest percentage of ICOS expressing T cells have been selected for Phase 2 expansions in the ICONIC trial.


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