Genomics based studies of gastric tumors identify ICOS as potential target for therapeutic intervention

ABSTRACT# 1685

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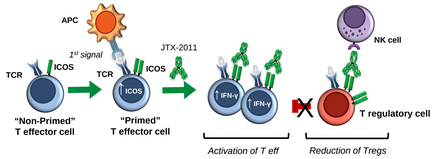
ABSTRACT & BACKGROUND

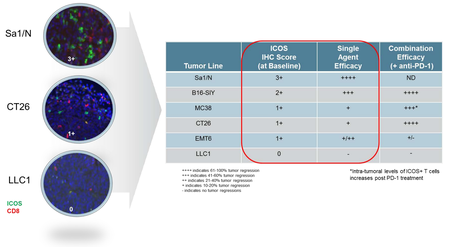
JTX-2011, an ICOS agonist antibody, is the first clinical program to emerge from Jounce's Translational Science Platform, which couples the choice of target mechanism to potential predictive biomarkers of response. ICOS (Inducible T cell CO-Stimulator), a co-stimulatory molecule expressed primarily on T lymphocytes, was prioritized as a target based on preclinical data and clinical data that identified ICOS as a potentially key molecule in providing optimal anti-tumor benefit following anti-CTLA-4 therapy. Data from our preclinical studies shows that tumor reduction in animals occurs only when a certain percentage of ICOS positive immune cells are resident within the tumor or in combination with a PD-1 inhibitor. Thus ICOS expression is a key element of our biomarker-driven approach in the ICONIC clinical trial. Based on this biomarker approach we have identified gastric cancer as a cancer of potential interest for an ICOS-targeted immunotherapy approach.



JTX-2011 Dual Mechanism of Action

Gastric adenocarcinoma was identified as a tumor of interest based on the integrated analysis of RNA, DNA and clinical data from the Cancer Genome Atlas (TCGA). This analysis was performed within stomach adenocarcinoma (STAD) to understand the context in which ICOS is expressed. ICOS levels were correlated to gene signatures of immune infiltrate as well as other clinical attributes and molecular markers. ICOS and PD-L1 levels were assessed by IHC in human tumor samples and in biopsies from ICONIC participants. IHC and RNA analyses reveals a dynamic range of ICOS expression across gastric adenocarcinoma tumors with high prevalence in both EBV+ and MSI-H tumors as well as a subset of EBV-/MSS tumors. There is a correlation between ICOS, ICOS signature, PD-L1 and IFNγ signatures, but RNA analysis indicates that a subpopulation of gastric tumors with lower levels of PD-L1 expression may be ICOS positive. Integrative analysis of tumors identifies gastric cancer as an attractive indication for exploration of JTX-2011 plus a PD-1 inhibitor based on the relatively high frequency of ICOS expression within this tumor type. ICOS expression has a dynamic range of expression within gastric cancer. Thus, an ICOS IHC biomarker is being used to enrich for patients with gastric cancer in the Phase 2 portion of ICONIC, which is designed to assess JTX-2011 alone and in combination with a PD-1 inhibitor.

Figure 1: Monotherapy response is related to percentage of ICOS-expressing immune cells in syngeneic tumor models



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

++++ indicates 81-100% tumor regression
+++ indicates 41-60% tumor regression
++ indicates 21-40% tumor regression
+ indicates 10-20% tumor regression
- indicates no tumor regressions

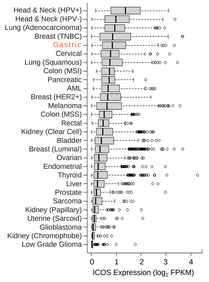
*Intra-tumoral levels of ICOS+ T cells increases post PD-1 treatment

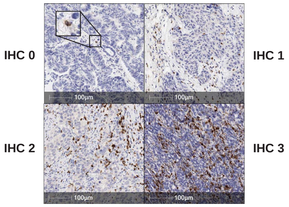
Response of syngeneic tumor models treatment with an ICOS agonist, scored by ICOS expression. Representative images are shown in the top panel.

- Monotherapy response was primarily observed in ICOS high models.
- Combination therapy required immune cell presence, but was not dependent on percentage of ICOS expressing-immune cells at baseline.

RESULTS

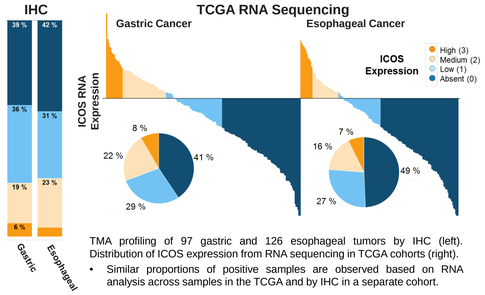
Figure 2: Gastric cancer shows ICOS RNA expression, with a range of expression observed at the protein level





- Across TCGA Indications ICOS RNA was highly expressed in gastric cancer patients (left).
- IHC staining of ICOS within gastric cancer samples shows a dynamic range of samples from low (0) to high (3) percentage of cells staining positive for ICOS (right).

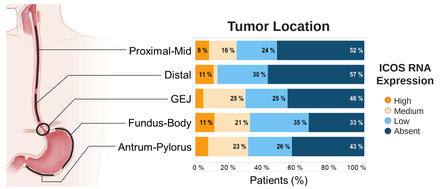
Figure 3: Protein levels of ICOS can be approximated by RNA expression in gastric and esophageal tumors from TCGA



TMA profiling of 97 gastric and 126 esophageal tumors by IHC (left). Distribution of ICOS expression from RNA sequencing in TCGA cohorts (right).

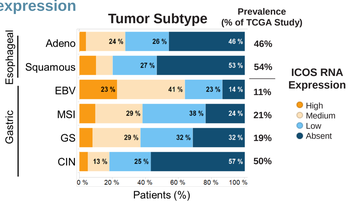
- Similar proportions of positive samples are observed based on RNA analysis across samples in the TCGA and by IHC in a separate cohort.

Figure 4: ICOS RNA expression is independent of gastric or esophageal cancer location



- ICOS RNA expression was not associated with location in the digestive tract.

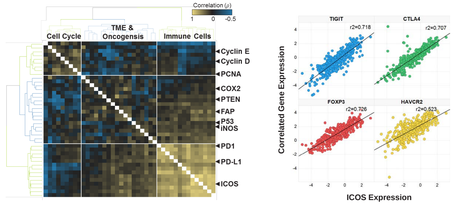
Figure 5: Subtypes of gastric cancer are enriched for higher ICOS RNA expression



Binned ICOS RNA expression analysis of TCGA samples shows that:

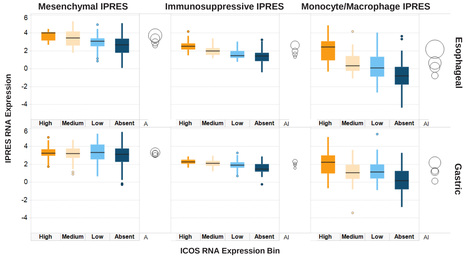
- EBV+ tumors, while rare, have the highest ICOS expression of all subtypes tested.
- Microsatellite instable (MSI) and genomically stable (GS) tumors have intermediate ICOS expression.
- Esophageal and chromosomally instable (CIN) gastric tumors show lower ICOS expression.

Figure 6: Co-expression of ICOS RNA with immunological, microenvironment, and tumor-intrinsic markers



Co-expression analysis between cell cycle, oncogenic, tumor micro-environment, and immune infiltrate genes identified:

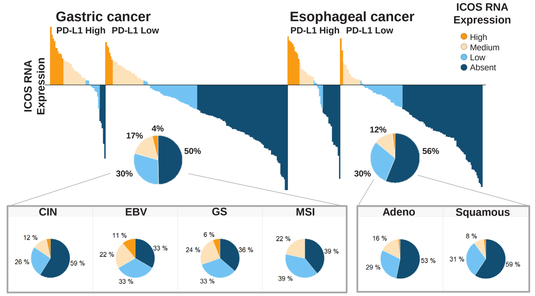
- ICOS is most highly correlated with other immune infiltration genes.
- Immune genes most highly correlated with ICOS include known markers of Tregs such as FOXP3, and CTLA4 and co-inhibitory signals such as TIGIT, and TIM3 (HAVCR2).



ICOS RNA expression compared to innate PD-1 resistance (IPRES) expression signatures from melanoma[1].

- All signatures increase with higher ICOS in esophageal cancers (top panels).
- Only the chemotaxis IPRES for monocytes and macrophages increases with ICOS RNA expression in gastric cancers (bottom panels).

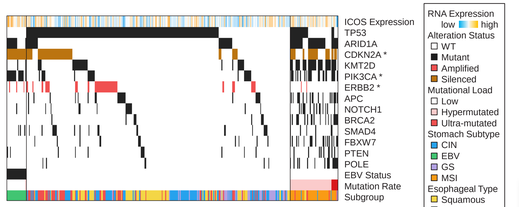
Figure 7: Identification of PD-L1 low, ICOS high patients



Distribution of ICOS RNA expression grouped into high (Q1) or low (Q2-4) PD-L1 RNA expression by indication (top). Distribution of binned ICOS RNA expression across subtypes within an indication (bottom).

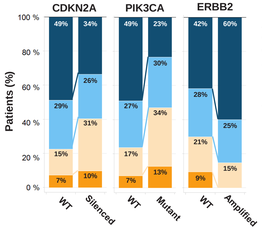
- Within gastric cancer, ICOS is still frequently expressed in PD-L1 low tumors, though the proportion of highly expressing tumors varies by subtype.
- ICOS expression in esophageal tumors is more correlated with PD-L1 expression.

Figure 8: Integrative analysis reveals genomic alternations associated with ICOS RNA expression



Mutational landscape of gastric and esophageal tumors.

- Significant associations (*) were observed between ICOS RNA expression and CDKN2A, ERBB2, and PIK3CA alterations.



Alterations associated with differential RNA expression of ICOS across gastric and esophageal tumors.

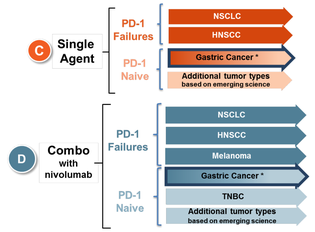
- CDKN2A silencing and PIK3CA mutations were both associated with higher ICOS RNA expression.
- HER2 (ERBB2) amplification was associated with lower ICOS RNA expression.

ICOS RNA Expression: High, Medium, Low, Absent

JTX-2011 ICONIC Trial

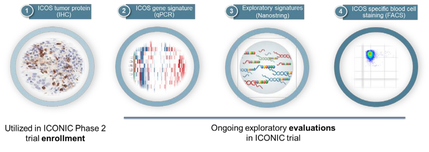
Gastric cancer cohorts are included in the JTX-2011 ICONIC clinical trial

- The Ph I/II ICONIC trial is an adaptive trial design testing JTX-2011 as a single agent or in combination with nivolumab.
- Cohorts for gastric cancer have been initiated as part of both the single agent and combination arms of the trial.



* Due to the September 2017 approval of Keytruda for treatment of gastric cancer, these cohorts in ICONIC include PD-1 inhibitor failure as well as PD-1 inhibitor naive patients.

Exploratory biomarker assessment in ICONIC



- Multiple modes of exploratory biomarkers are being used during the ICONIC trial.

SUMMARY

- ICOS is highly expressed in gastric and esophageal cancers, supporting these indications for inclusion into the ICONIC trial studying the ICOS agonist antibody JTX-2011.
- Expression of ICOS is unrelated to tumor location within the digestive tract, but is related to tumor subtype and genomic alterations intrinsic to gastric and esophageal tumors.
- ICOS is expressed in PD-L1 low tumors, and shows context dependent associations with previously reported innate PD-1 resistance signatures.
- In gastric and esophageal tumors, capturing the interaction between etiology, genomic alterations, and tumor microenvironment is necessary to understand the context of ICOS expression.

References:

1. Hugo W, Zaretsky JM, *et al.* Genomic and Transcriptomic Features of Response to Anti-PD-1 Therapy in Metastatic Melanoma. Cell, 2016 Mar 24;165(1):35-44 DOI: https://doi.org/10.1016/j.cell.2016.02.065

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