Preclinical Assessment of JTX-2011, An Agonist Antibody Targeting ICOS, Supports Evaluation In ICONIC Clinical Trial

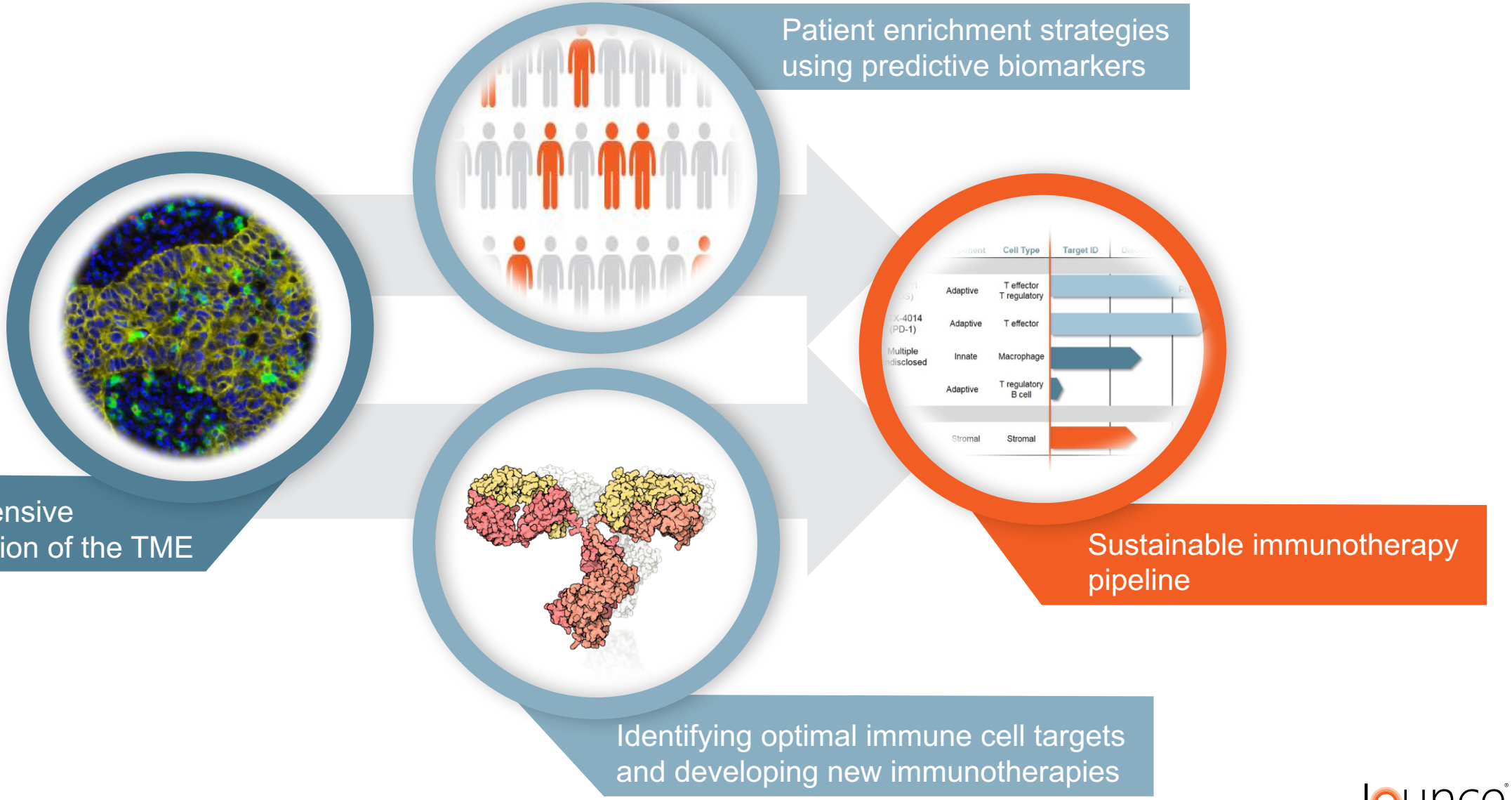
Jennifer Michaelson, Ph.D.

AACR Annual Meeting
April 2, 2017
Major Symposium
"*Emerging Targets in Immunotherapy*"

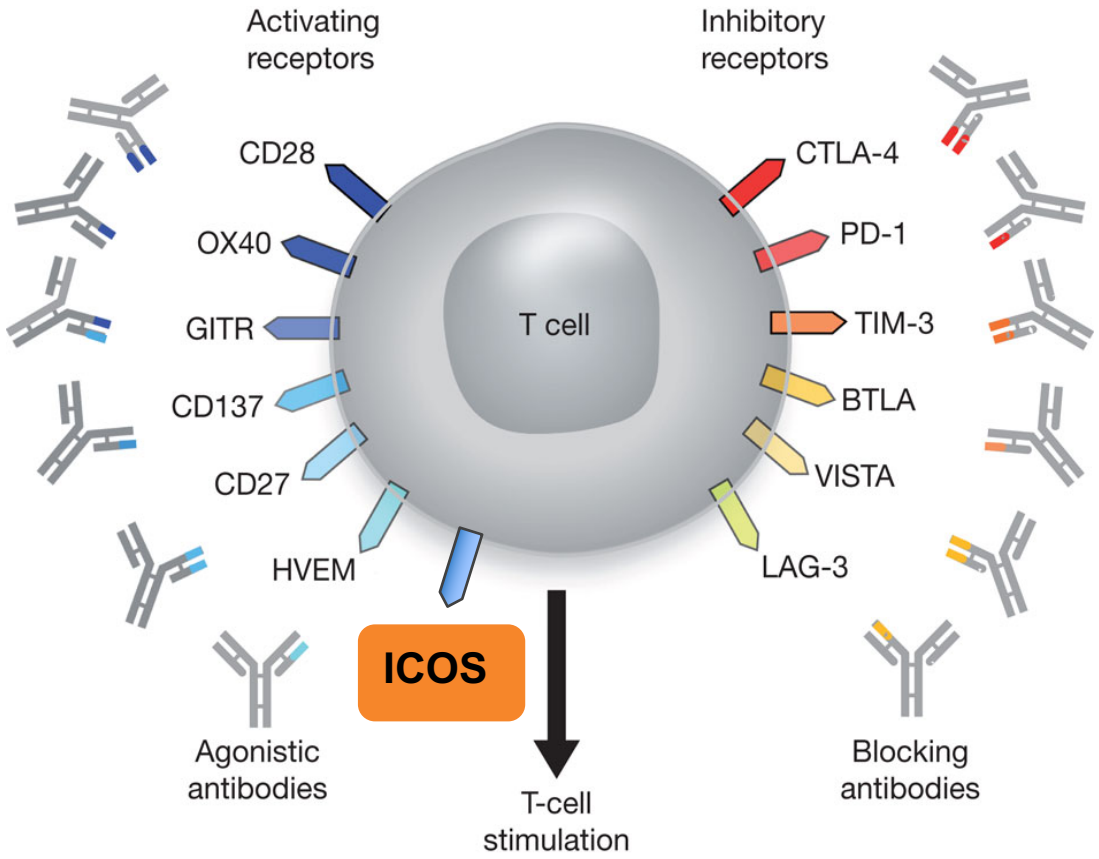
Jounce® THERAPEUTICS

Translational Science Platform

Comprehensive Interrogation of the TME to Develop a Sustainable Innovative Pipeline



Many Potential Targets: Why Choose ICOS?



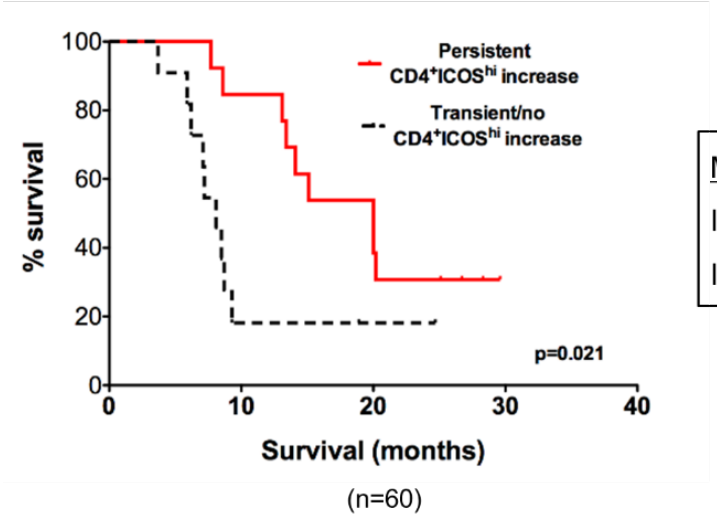
Jounce Approach

- Data from Founders' labs demonstrated clinical correlate and outcome data that supported activation of ICOS
- Subsequent laboratory evidence in animal tumor reduction studies

Many Potential Targets: Why Choose ICOS?

Human clinical and mouse preclinical data support activating ICOS receptor for anti-tumor benefit

Ipi-treated Melanoma Patients



(n=60)

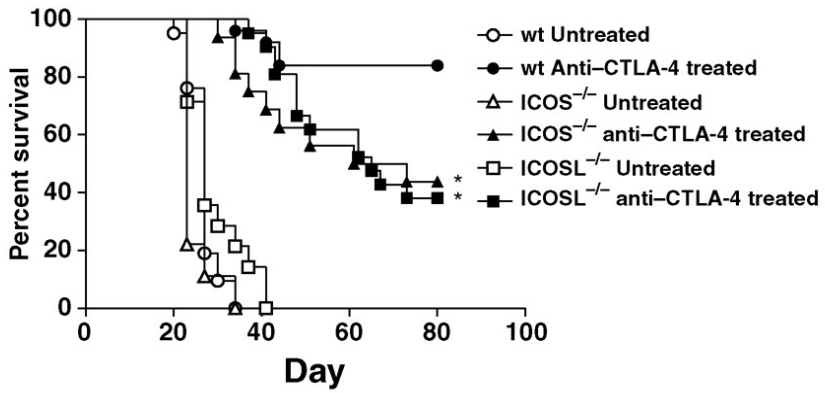
Median survival:

$ICOS^{hi}$ = 20 months

$ICOS^{lo}$ = 8.1 months

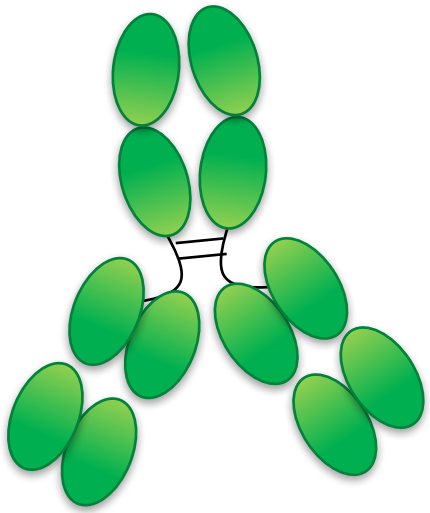
Chen et al, PNAS (2009);
Carthon et al, Clin Can Res (2010);
Ng Tang et al, Canc Immunol Res (2013)

Impaired Tumor Rejection In ICOS−/− and ICOSL−/− Mice Treated with Anti–CTLA-4 Therapy



Fu et al. Cancer Res 2011;71:5445-5454

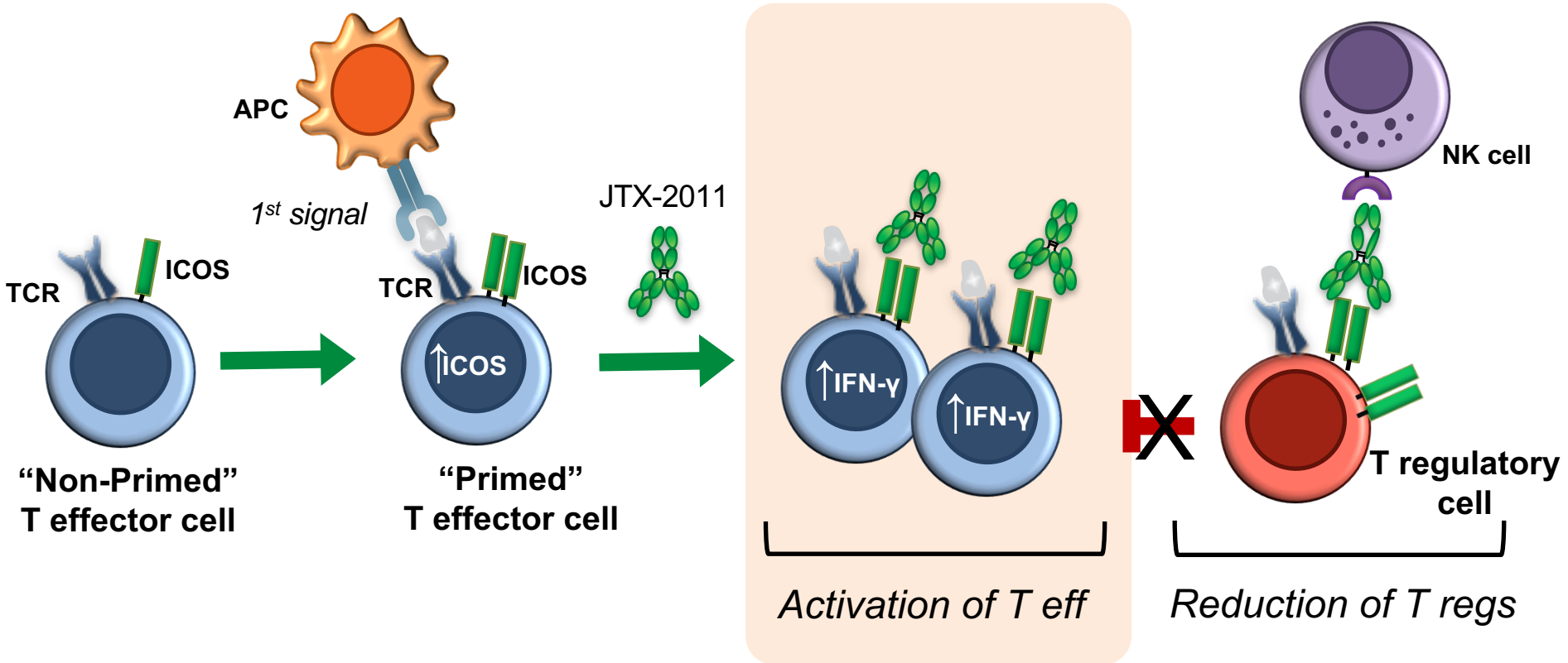
JTX-2011: ICOS Agonist Antibody



JTX-2011: Key Features

- Specificity for ICOS
- Species cross-reactive
- Agonist activity
- Humanized rodent antibody
- hIgG1 Fc backbone

JTX-2011 Dual Mechanism Shifts Balance of T Cells Towards Anti-Tumor Activity



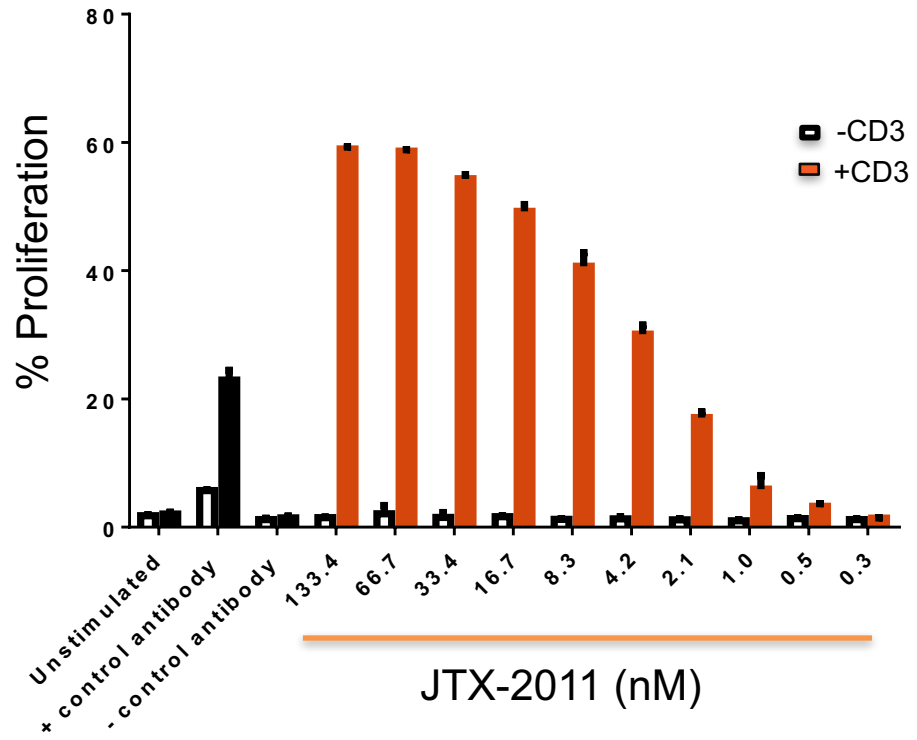
JTX-2011 is designed to

- Stimulate T effector cells in tumor
- Selectively reduce T regulatory cells in tumor

JTX-2011 Stimulates Primed Human T Cells

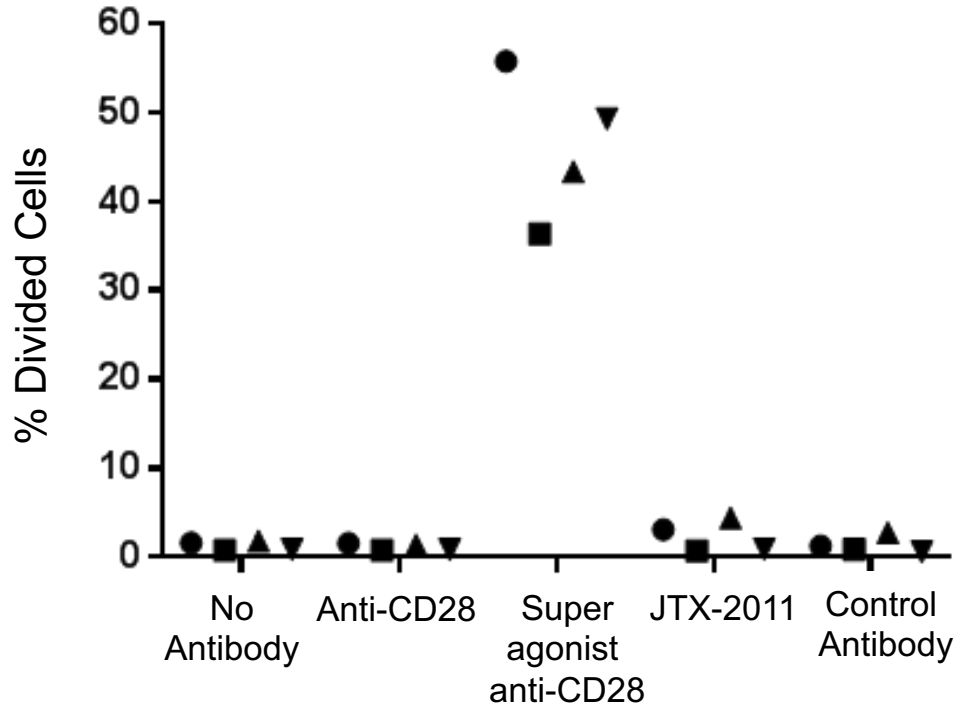
No Indiscriminate Activation of T cells

Activation of *primed* CD4+ T effector cells

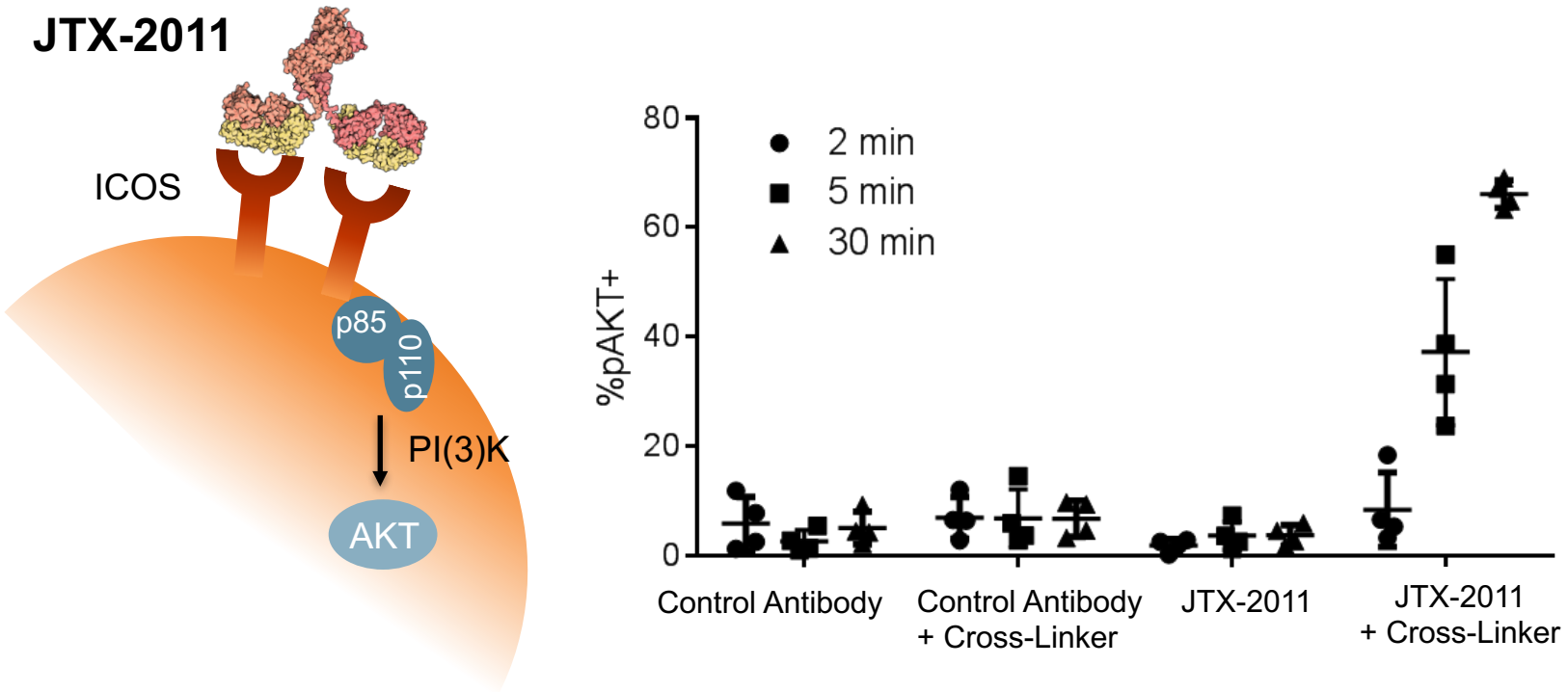


CD3 in all wells
except unstimulated

No activation of *unprimed* CD4+ T effector cells

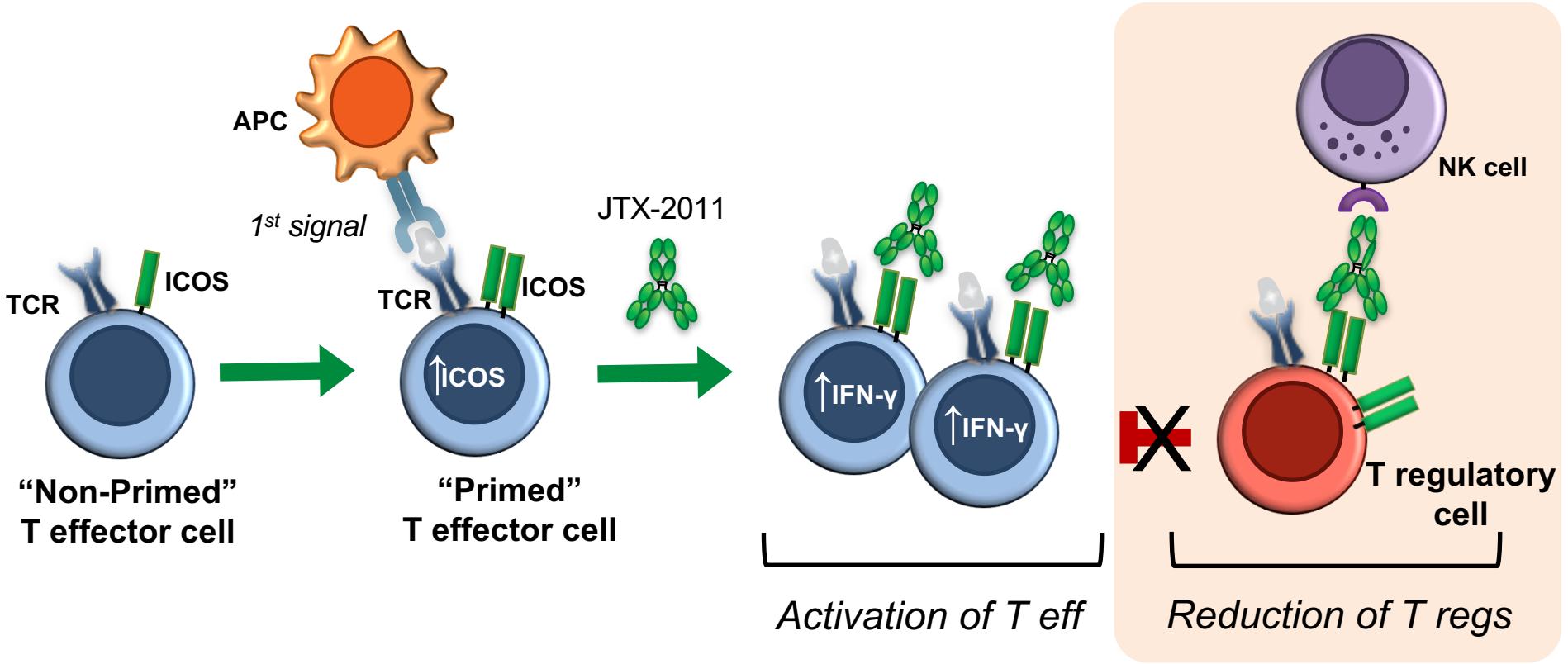


JTX-2011 Induces Signaling Through AKT Pathway



- ICOS antibody re-capitulates signaling activity of ICOS ligand
  - Induces pAKT signal in CD4+ T cells when cross-linked

JTX-2011 Dual Mechanism Shifts Balance of T Cells Towards Anti-Tumor Activity

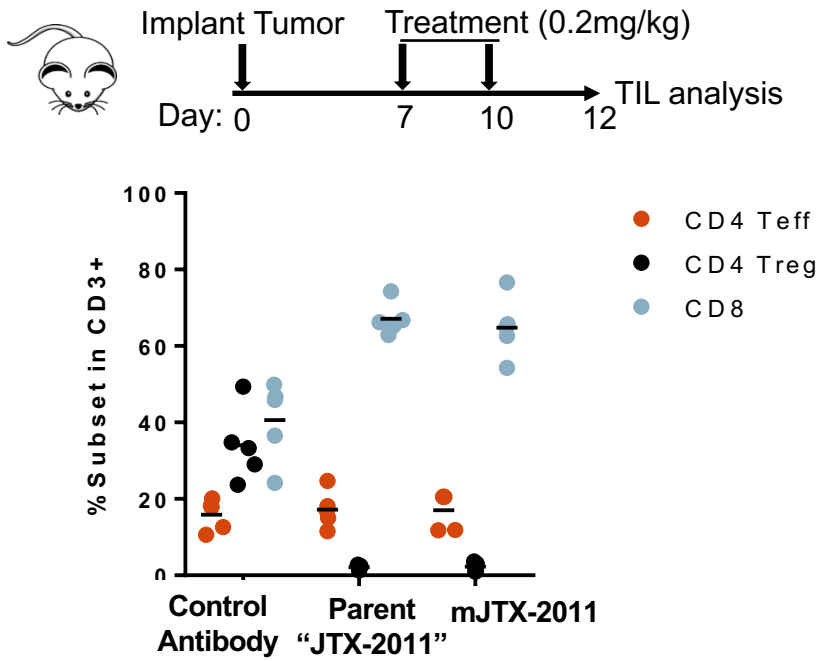


JTX-2011 is designed to

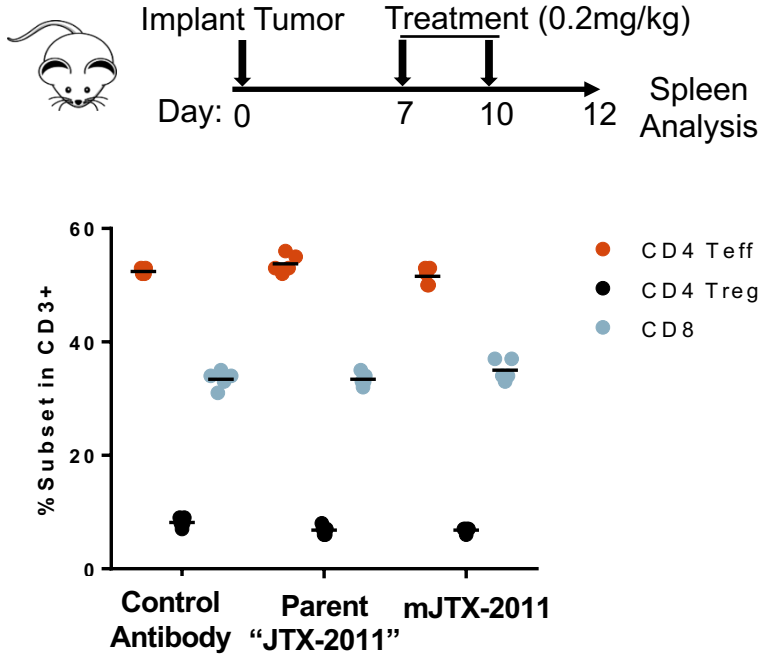
- Stimulate T effector cells in tumor
- Selectively reduce T regulatory cells in tumor

Selective Reduction in Tumor but Not Peripheral T Regulatory Cells

Mouse JTX-2011 selectively reduces tumor T regulatory cells *in vivo*



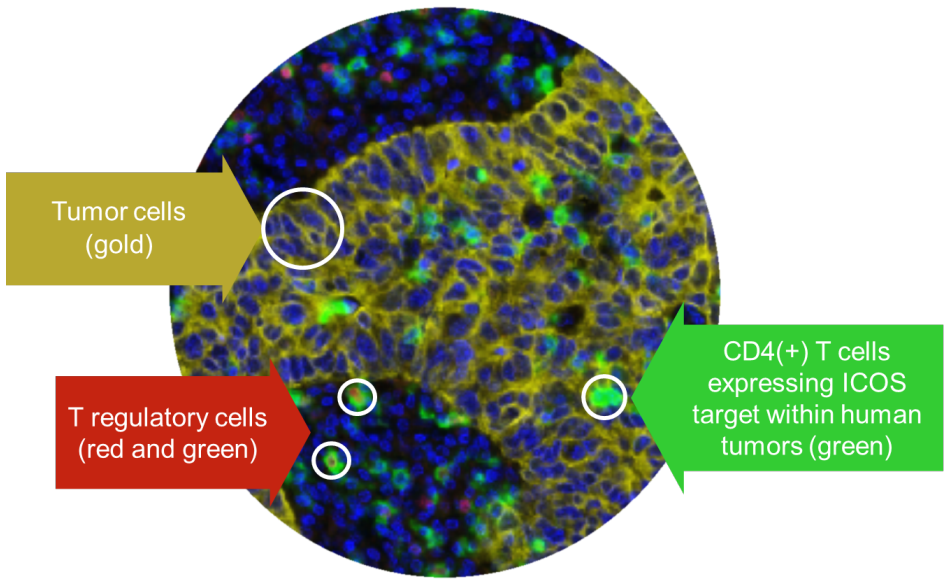
Mouse JTX-2011 does not reduce spleen T regulatory cells *in vivo*



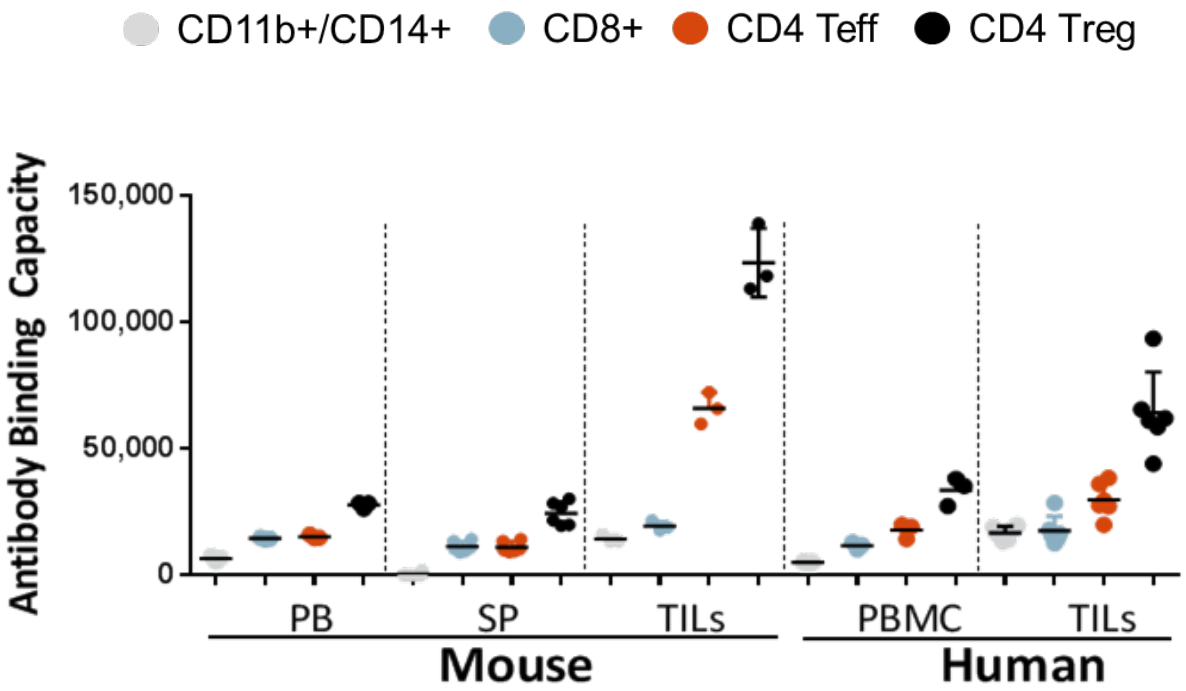
- Reduction in tumor T regulatory but not tumor T effector cells
- No change in T cell subsets in spleen, lymph nodes or periphery

ICOS Expression is Highest on Mouse and Human Intratumoral Tregs

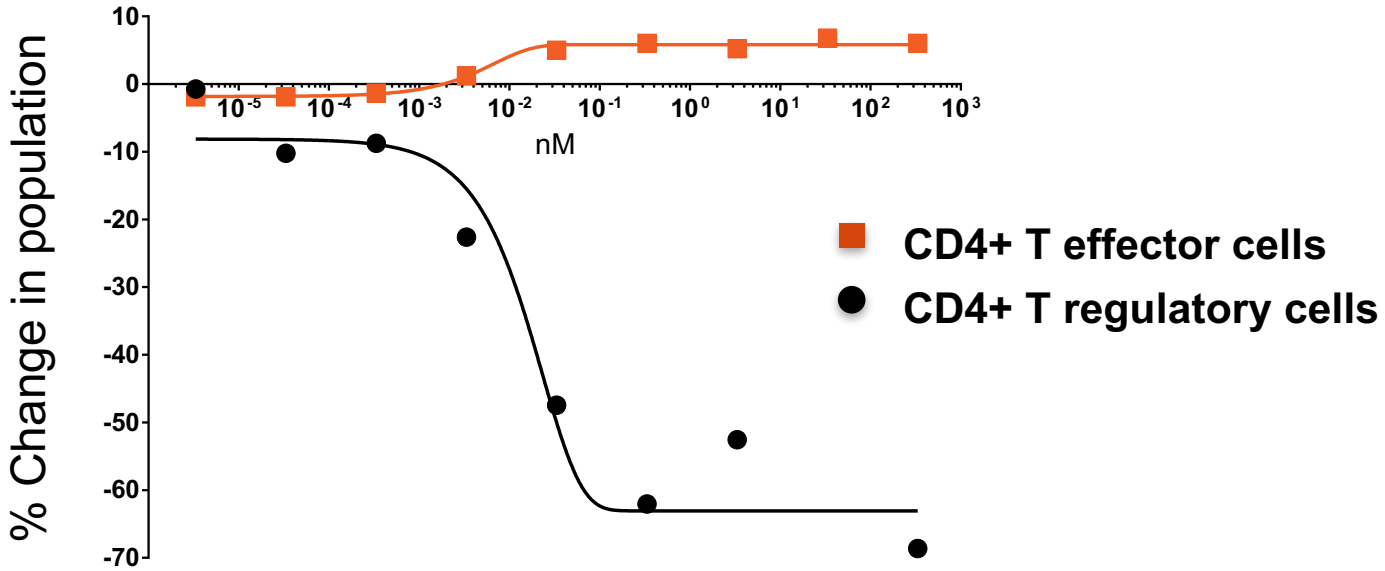
Multiplexed IF

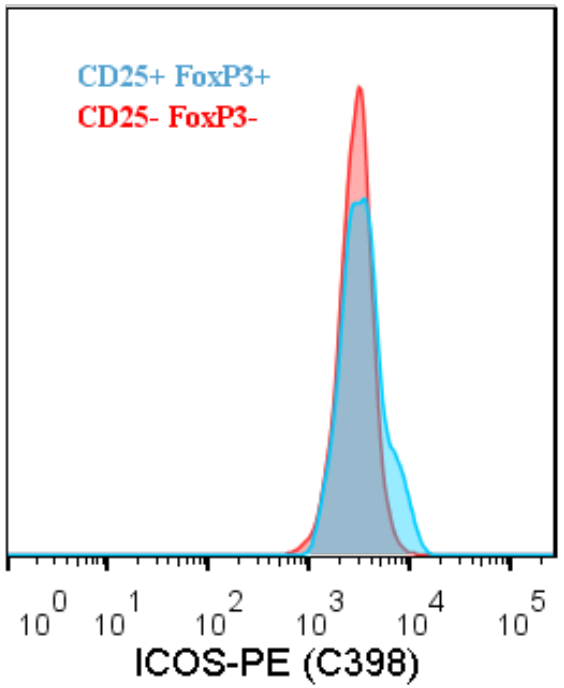


Flow cytometry



Selective Reduction of Tregs vs Teffs *in vitro*



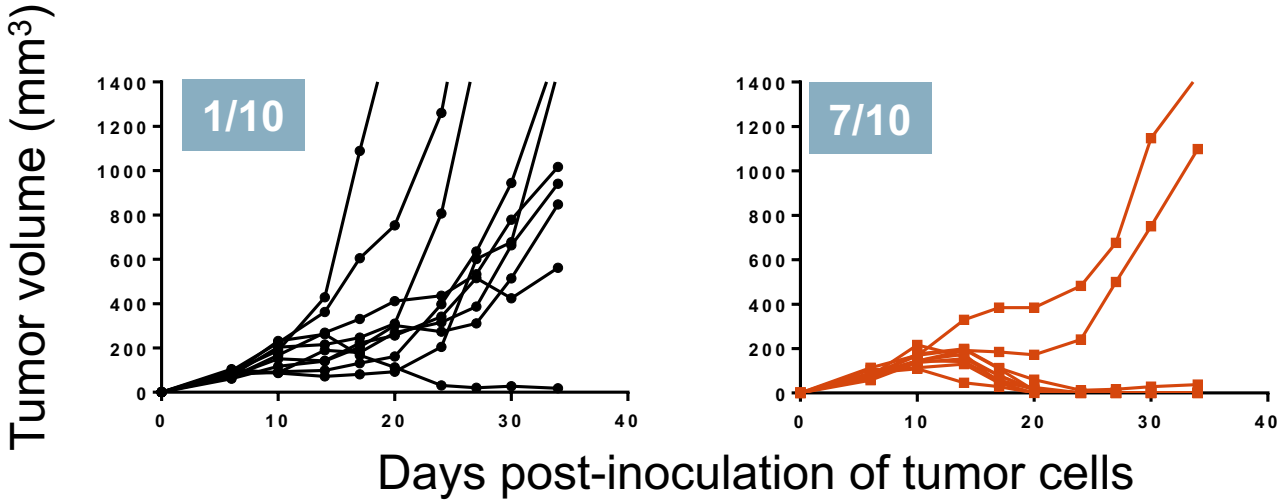


- ICOS antibody selectively depletes Tregs from IL-2 activated PMBC
- Under these *in vitro* activation conditions, Tregs and Teffs express similar levels of ICOS

Single Agent Development of JTX-2011

Supported by Long-Lasting Response in Preclinical Tumor Models

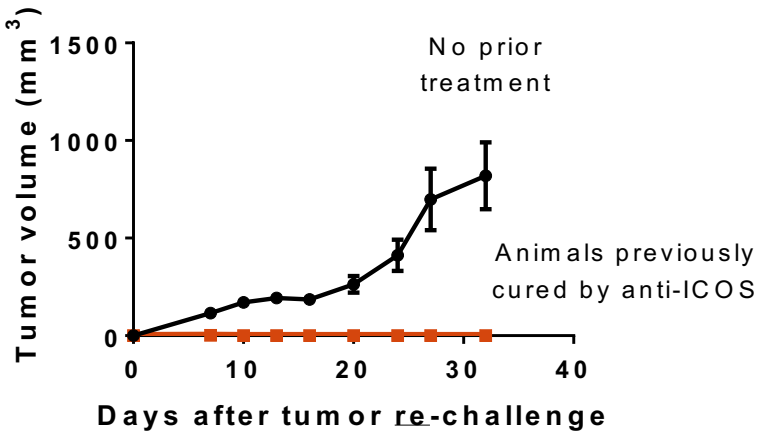
Control | **ICOS Antibody**



Sa1/N Tumors

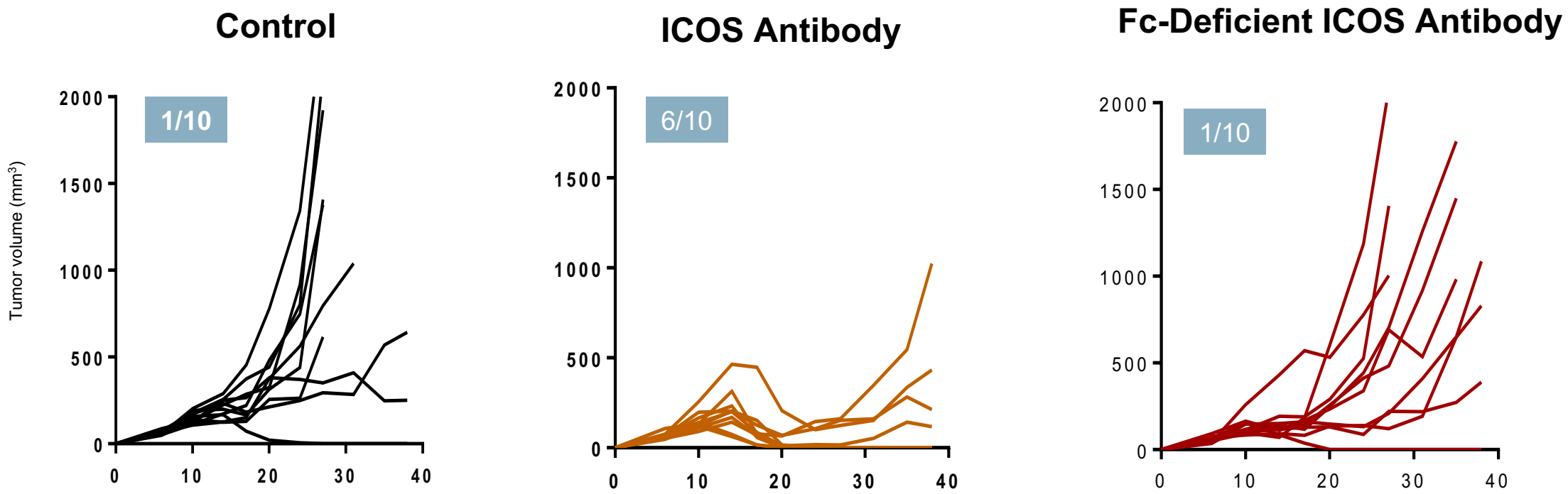
Tumor free / animals treated

Animals cured of tumors are immune to tumor re-challenge



Fc Effector Function is Required for Optimal Anti-Tumor Activity

Loss of Activity with Fc Deficient Version of Antibody

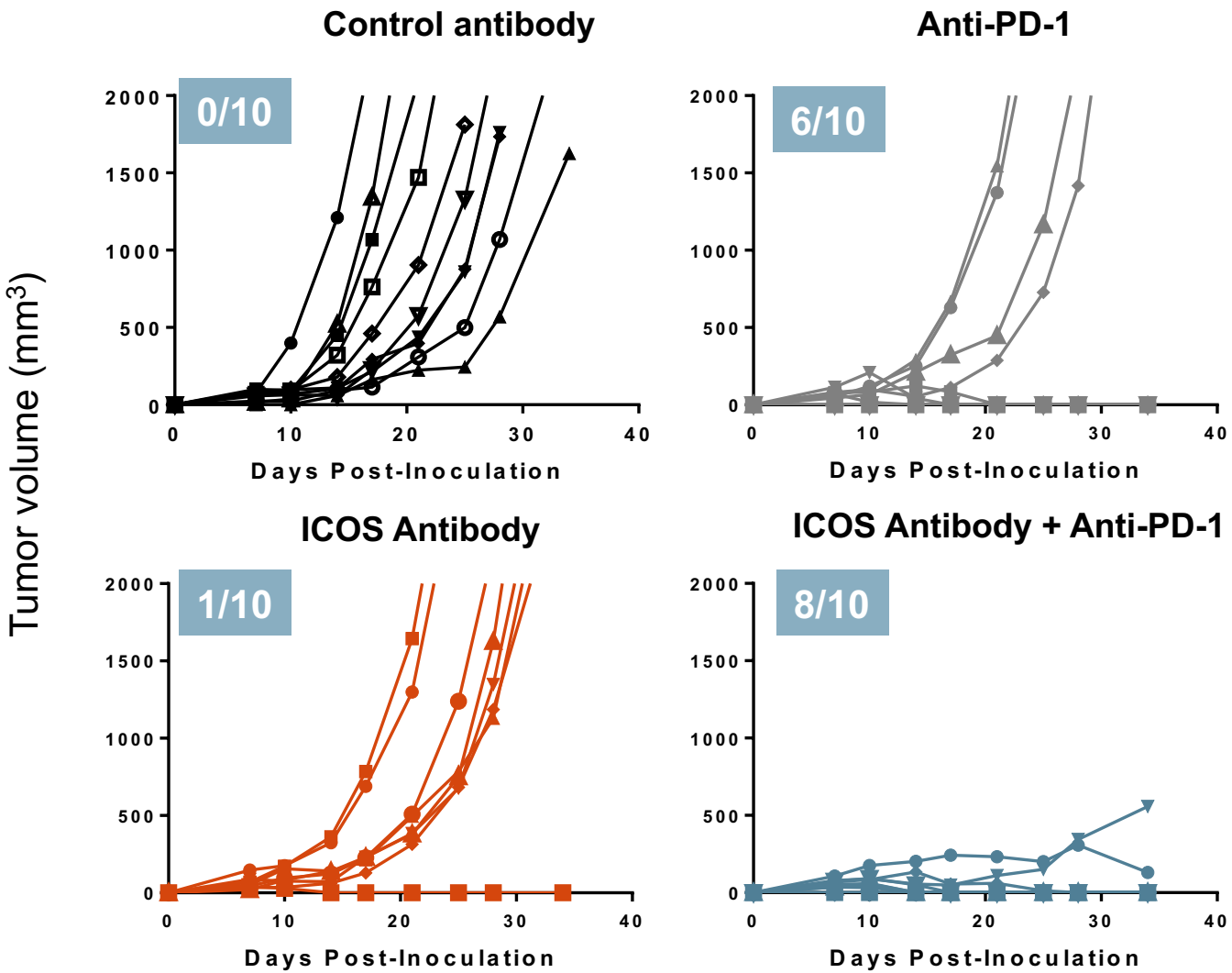


Sa1/N Tumors

Tumor free / animals treated

Combination Development of JTX-2011 with Anti-PD-1

Supported by Enhanced Anti-tumor Activity in Preclinical Models

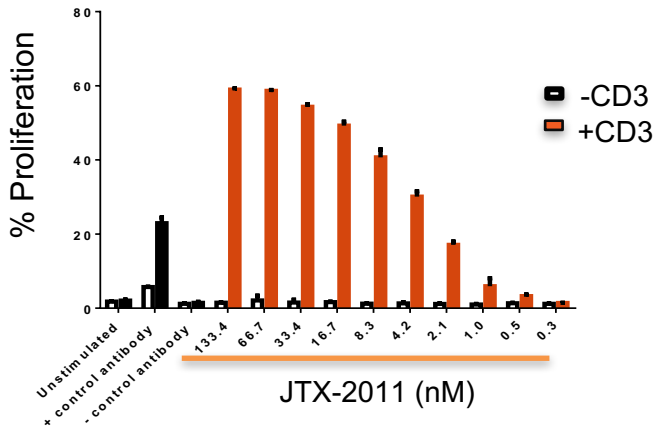


CT26 Tumors

Tumor free / animals treated

Preclinical Safety Features of JTX-2011

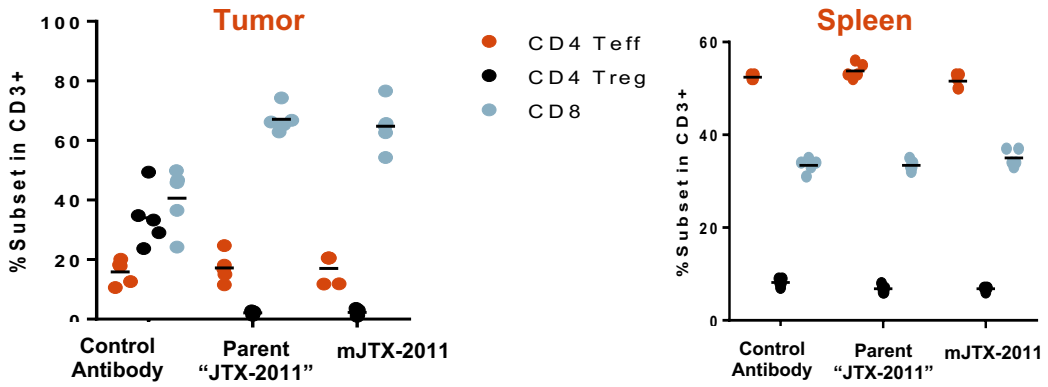
JTX-2011-induced T Cell Activation Requires Initial T Cell Priming



Preclinical Toxicity Studies Predict Safety Margin

- NOAEL = 50 mg/kg; highest dose tested in cynomolgus monkey IND-enabling GLP toxicology study

Activity of ICOS Antibody is Tumor-centric: No Depletion of Tregs in the Periphery

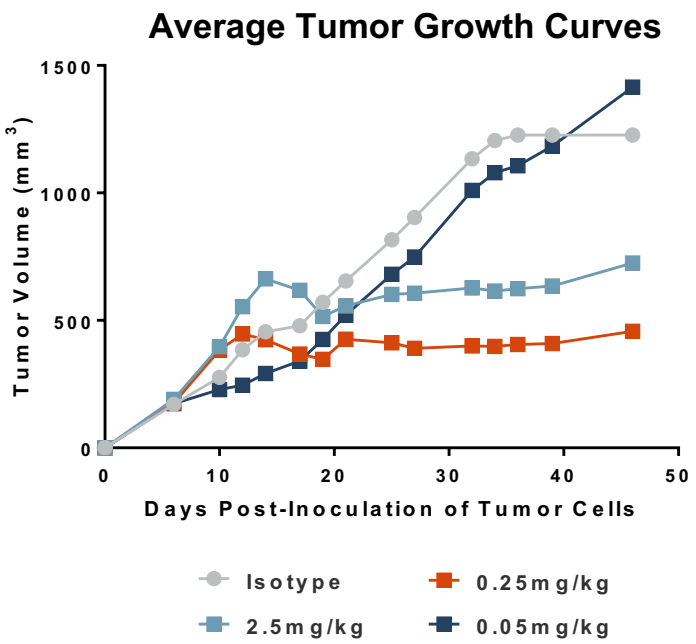


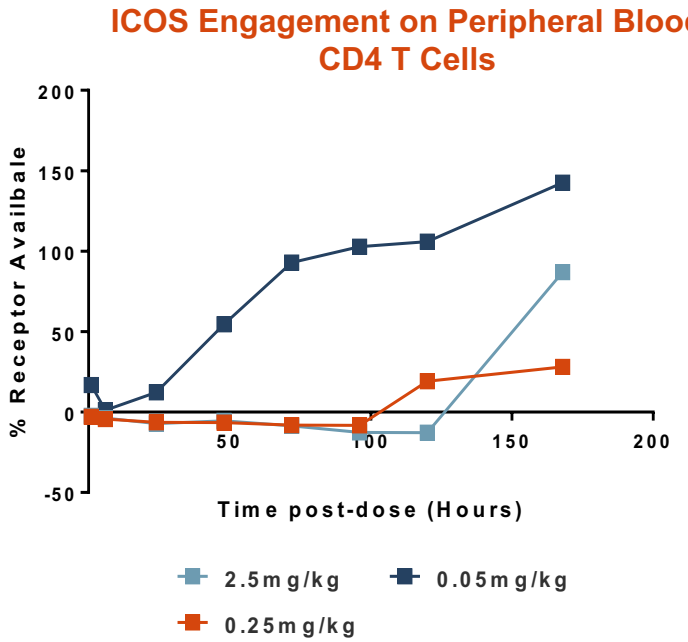
Cytokine Storm Not Predicted from *in vitro* and *in vivo* Studies

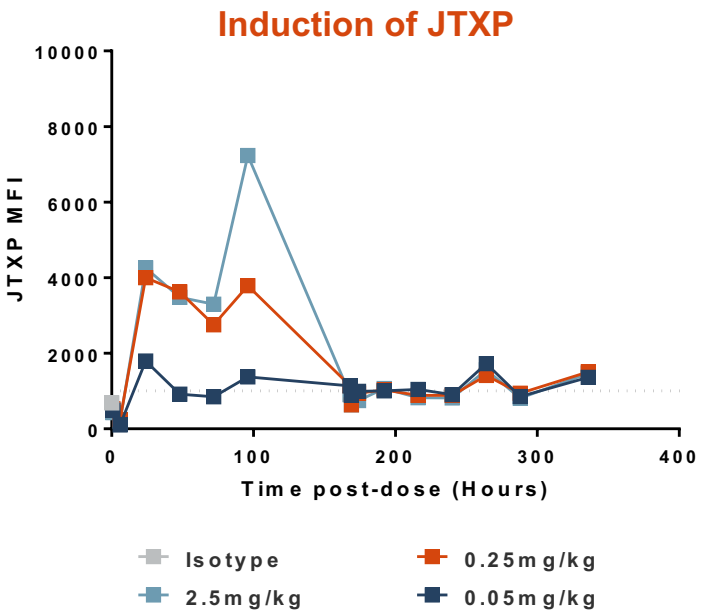
- No cytokine storm in GLP toxicology studies
- No cytokine induction by JTX-2011 alone or in combination with Opdivo® in human whole blood assays

Pharmacodynamic Biomarker: Target Engagement in Mouse

Efficacy in Syngeneic Mouse Tumor Model Correlates with Duration of ICOS Target Engagement







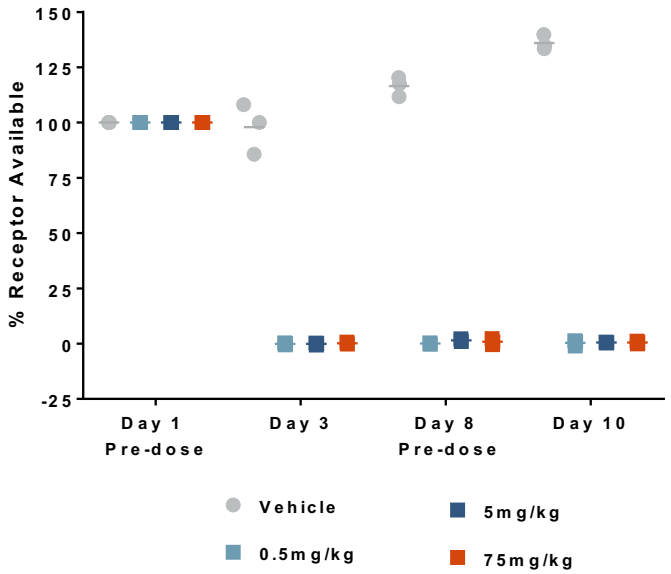
	0.05mg/kg	0.25mg/kg	2.5mg/kg
Tumor Free Mice	1/10	5/10	5/10

Preclinical Pharmacokinetics and Pharmacodynamics

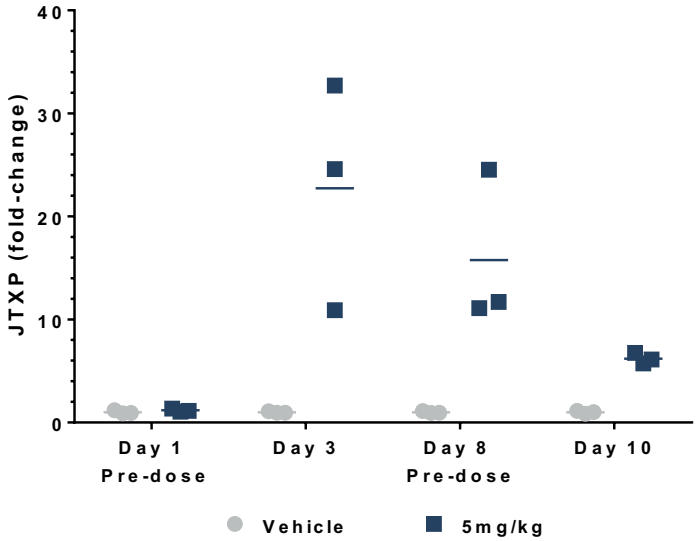
PK and PD in Cynomolgus Monkey Preclinical Studies

- Pharmacokinetics:
  - T1/2 = 5-12 days in ADA-negative monkeys
- Pharmacodynamic readouts
  - Target engagement: ICOS is fully engaged for the duration of the dosing interval at all doses
  - JTXP induction: JTXP is induced on monkey cells in peripheral blood

ICOS Engagement on Peripheral Blood CD4 T Cells



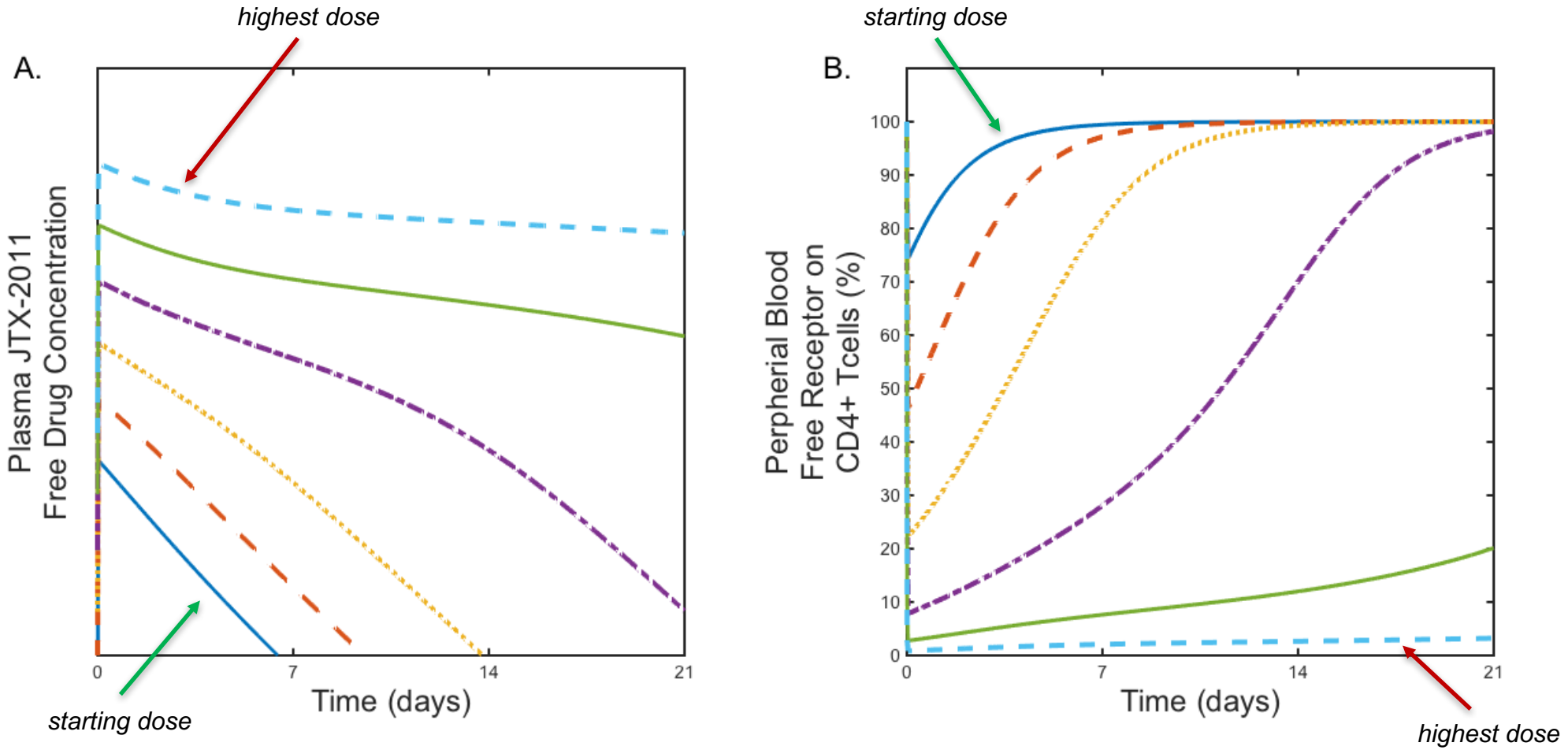
Induction of JTXP



Non-GLP tox study dosed up to 75 mg/kg with no toxicity observed

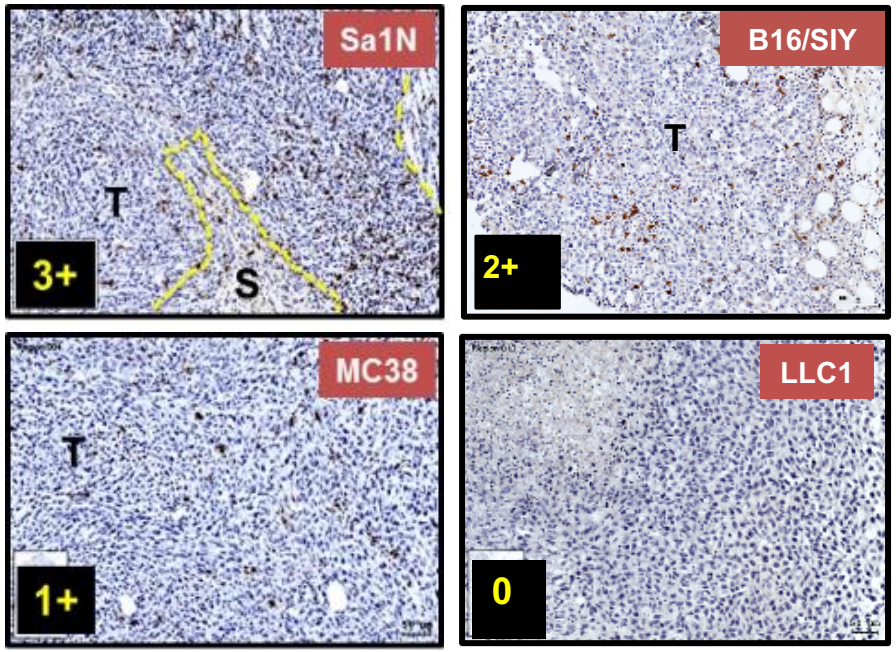
Preclinical QSP Modeling of JTX-2011

Predictions for PK and Target Engagement in First-in-Human Study



Patient Selection Strategy Supported by Mouse Models

Better Single-Agent Efficacy in Tumors Expressing Higher Levels of Intra-Tumoral ICOS



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	-	-

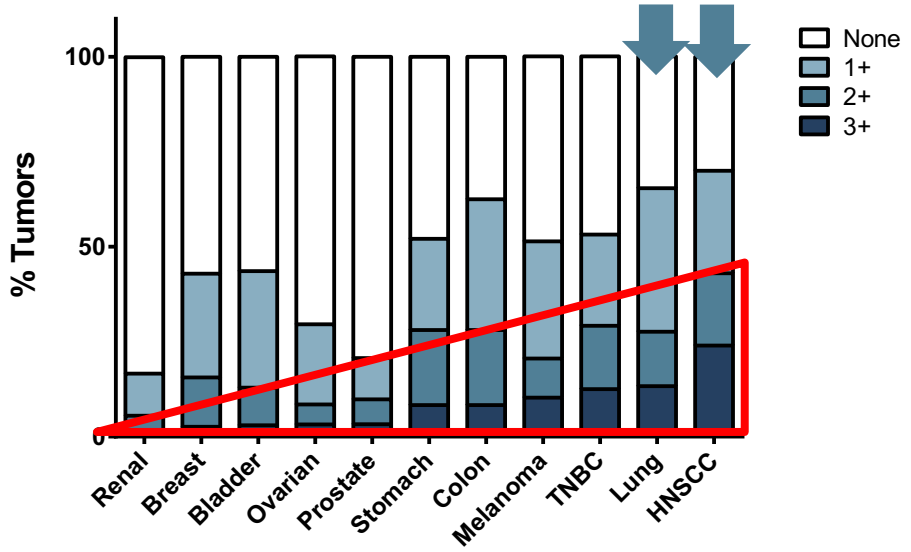
++++ indicates 61-100% tumor regression
+++ indicates 41-60% tumor regression
++ indicates 21-40% tumor regression
+ indicates 10-20% tumor regression
- indicates no tumor regressions

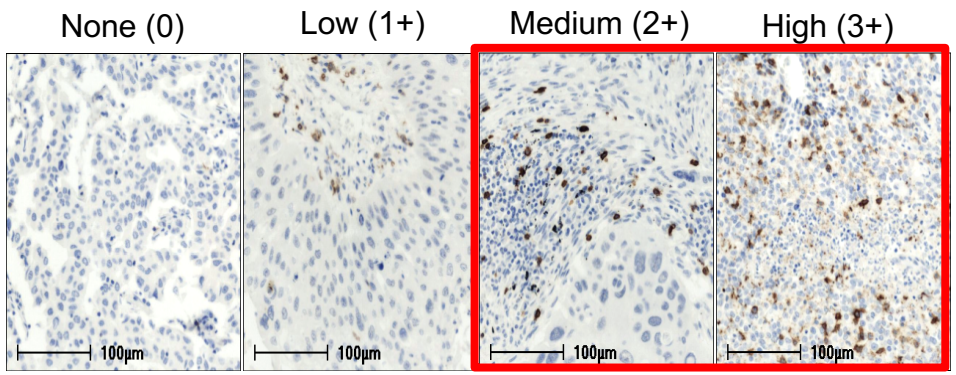
*Intra-tumoral levels of ICOS+ T cells increases post PD-1 treatment

Indication Selection & Patient Enrichment

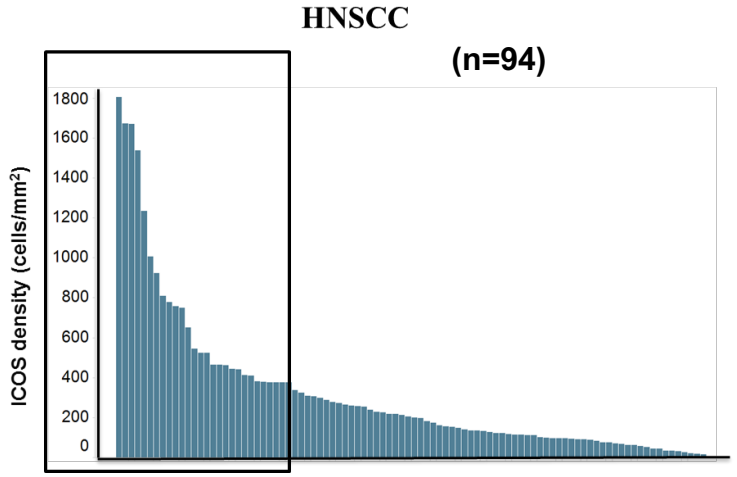
ICOS Immunohistochemistry (IHC)

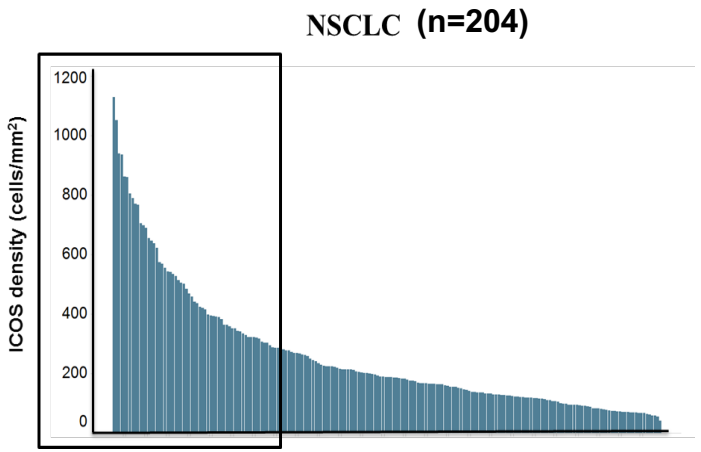
1 ICOS protein levels vary across indications





2 ICOS protein levels within high ICOS indications vary across individual patients

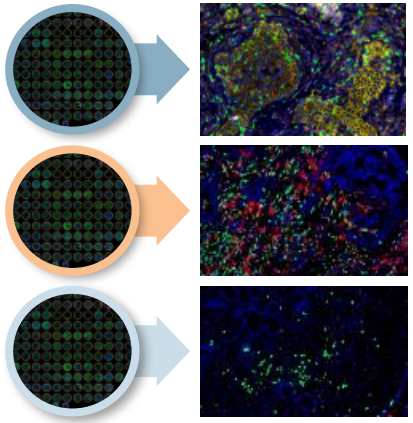




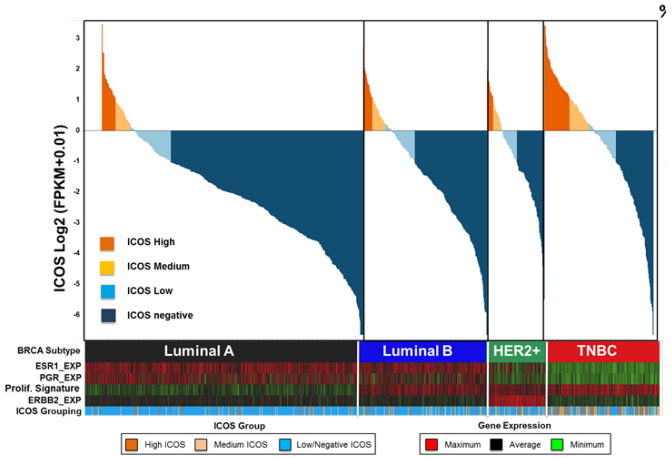
Integrated Approach to Understanding ICOS in the Context of Immune Oncology Landscape

Collaborations with premier Institutions

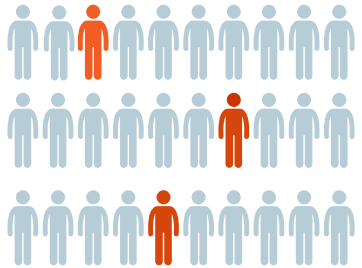
1000s of human tumors interrogated



Integrated TCGA and Internal Data Analysis



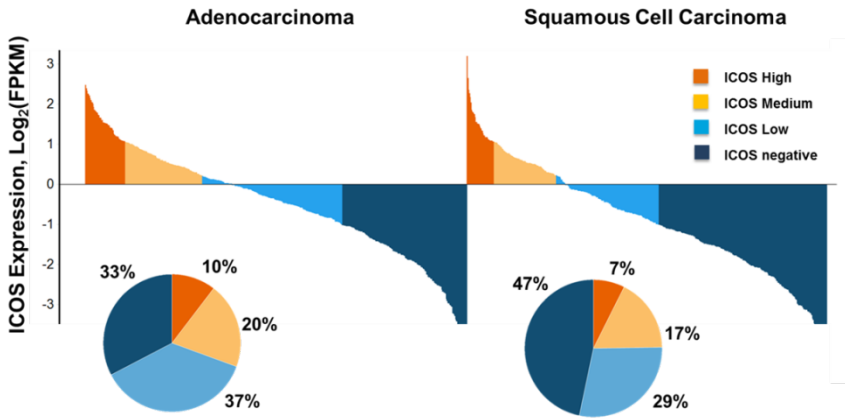
Patient enrichment for our clinical trials



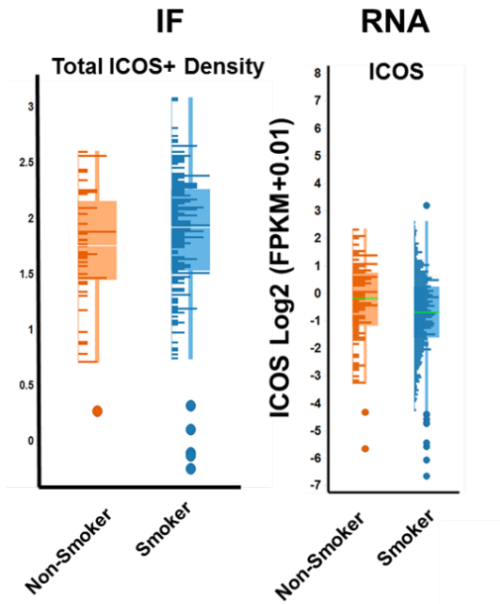
Translational Science Platform Informs Biomarker Strategy

Example from NSCLC

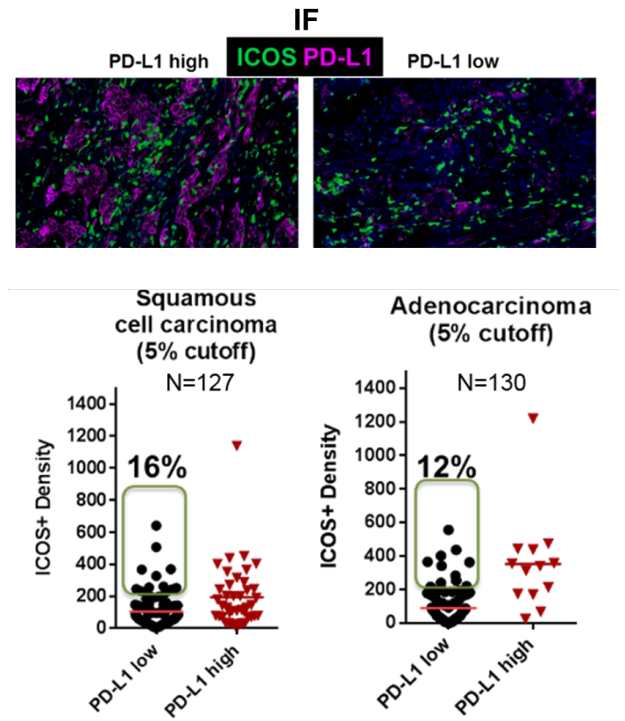
ICOS expression levels across subtypes of NSCLC tumors



ICOS levels are not associated with smoker status

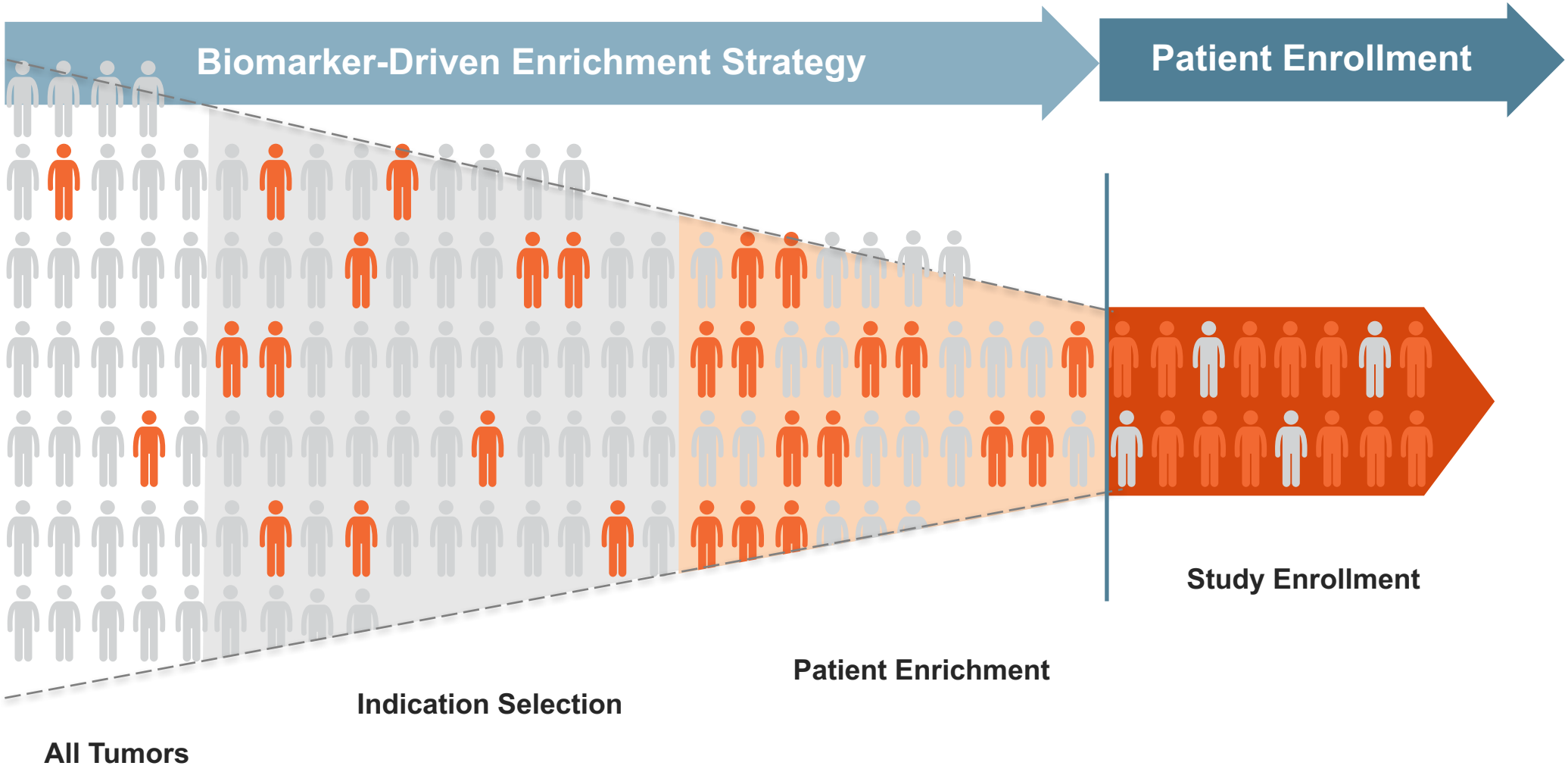


A subset of PD-L1 low tumors have high levels of ICOS expression



Biomarker-Driven Strategy for Patient Enrichment

Potential for Establishing Complementary and/or Companion Diagnostics



ICONIC: Adaptive, Biomarker-Driven Clinical Study

Phase 1/2 Preliminary Efficacy Proof-of-Concept

Phase 1
Safety, PK and PD

All-comers, no enrichment for ICOS expression
Dose escalate to anticipated clinically effective dose

A **Single Agent** → **Dose Escalation** → PK/PD Expansions

B **Combo with nivolumab** → **Dose Escalation** → PK/PD Expansions

Phase 2
Preliminary Efficacy

Enriched for patients with high ICOS expression

C **Single Agent**
- NSCLC
- HNSCC
- Any solid tumor type
- New indications based on emerging science*

D **Combo with Nivolumab**
- NSCLC
- HNSCC
- TNBC
- Melanoma
- Gastric
- New indications based on emerging science*

* *Additional indications, including niche indications, identified through Jounce Translational Science Platform*

Poster: CT035

JTX-2011: Agonist Monoclonal Antibody that Targets ICOS

ICOS: T cell Surface Protein Receptor with Strong Target Rationale

- Member of family of immune modulators that includes PD-1 and CTLA-4
- Potential importance of ICOS supported by key clinical observations
- Pharmacological activity is focused in the tumor

JTX-2011: Agonist Antibody Targeting ICOS

- Significant anti-tumor activity seen in preclinical studies
- Preclinical data supports use as both a single agent and in combination
- Safety, PK, and pharmacodynamic features in the monkey inform human FIH study
- Potential predictive biomarkers identified for patient enrichment strategies

ICONIC: JTX-2011 Phase 1/2 Clinical Trial

- JTX-2011 being evaluated as monotherapy and in combination with nivolumab
- Phase 1 to assess safety, PK and PD – ongoing
- Phase 2 will incorporate patient enrichment strategy

Thank You

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Jim Allison
Pam Sharma

THE UNIVERSITY OF CHICAGO

Tanguy Seiwart

Yale University

David Rimm

Jounce Therapeutics

Debbie Law
Elizabeth Trehu
Christopher Harvey
Heather Hirsch
Jason Reeves
Tyler Simpson
Lindsey Shallberg
Matt Wallace
Sriram Sathy
Robert Mabry
Amit Deshpande
Steve Sazinsky
Kutlu Elpek
Ellen Duong
Jenny Shu
Tong Zi

Applied Biomath

Joshua Apgar

ToxStrategies

Barbara Mounho-Zamora

Jounce® THERAPEUTICS