

# Efficacy of Anti-ICOS Agonist Monoclonal Antibodies in Preclinical Models Provides a Rationale for Clinical Development for cancer immunotherapy

- Michael J Briskin, Ph.D.
- Jounce Therapeutics

SITC 2015

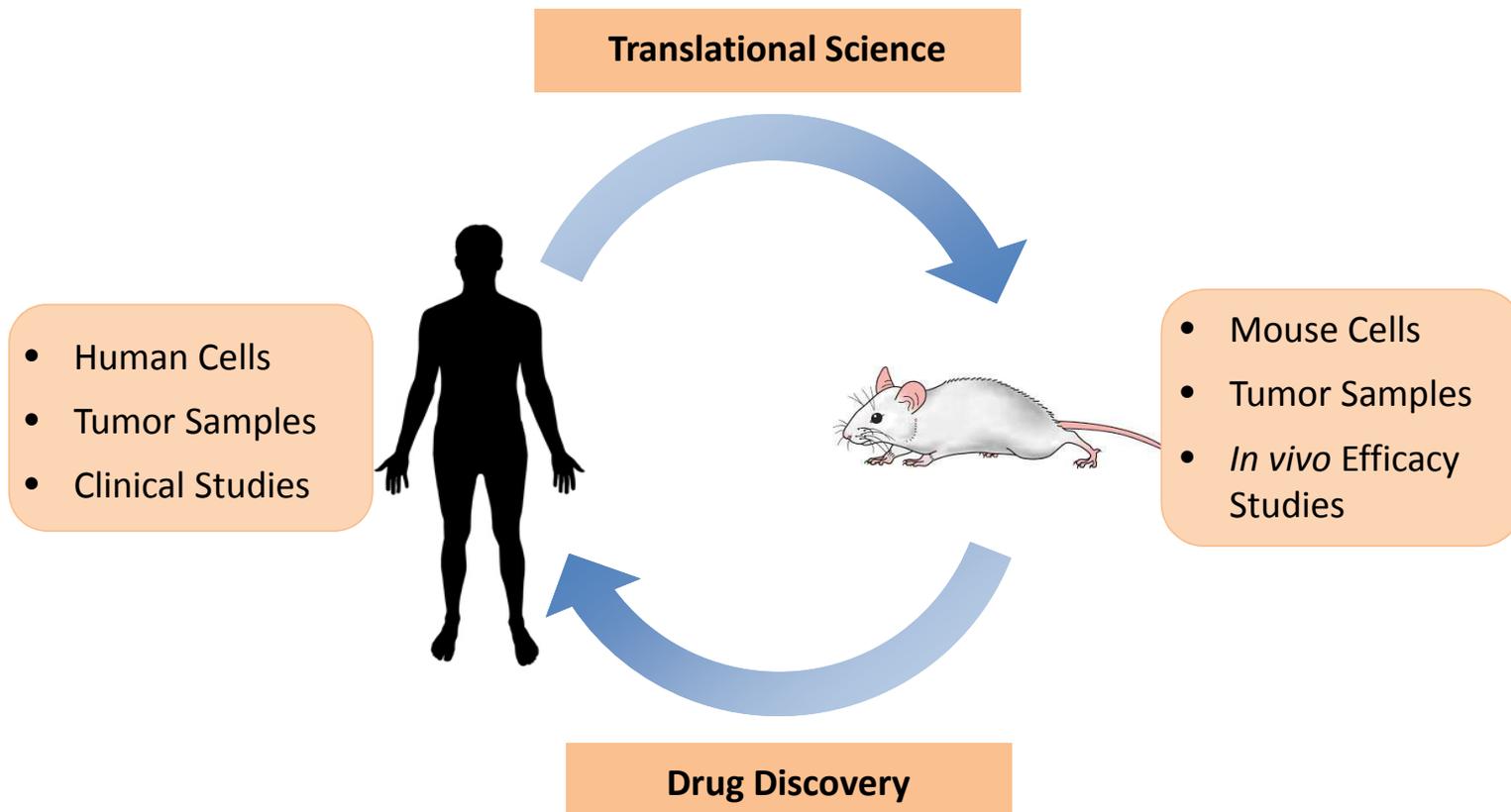
# Disclosures

*Dr. Michael J. Briskin*

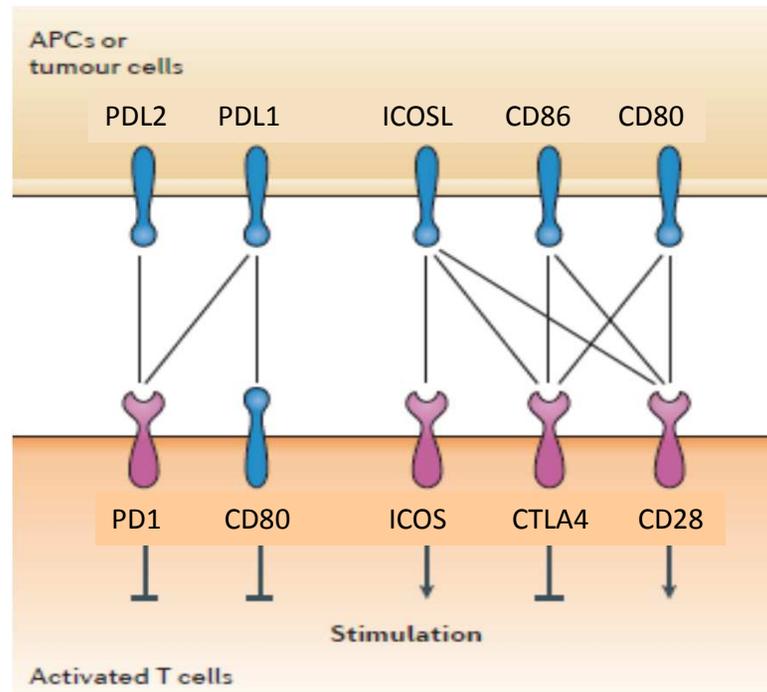
The following relationships exist related to this presentation:

- Current VP of research at Jounce Therapeutics

## Jounce Translational Approach: Iterative Clinical and Preclinical Data to Pursue Relevant Targets and Drive Programs



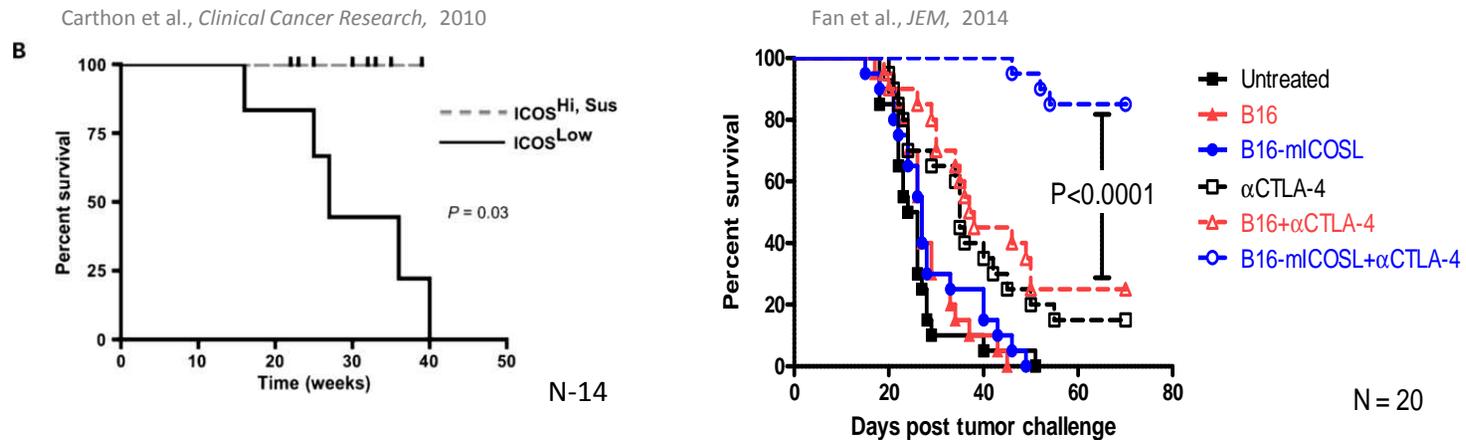
## ICOS: A Member of the B7/CD28-Superfamily



Adapted from Yao *et al.*  
Nature (2013)

- ICOS is up-regulated on activated CD4<sup>+</sup> T effector and CD4<sup>+</sup> T regulatory cells
- Its ligand (ICOSL) is expressed on APCs and B cells
- ICOS ligation via ICOSL stimulates activation of Teff cells
- ICOS binding to ICOSL on B cells leads to antibody production

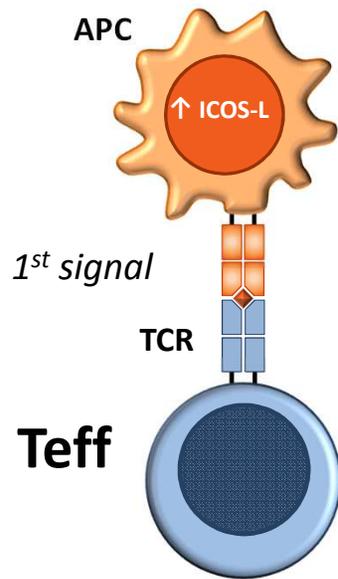
## ICOS is Up-regulated on CD4<sup>+</sup> T cells of Patients Who Respond to Anti-CTLA-4 Therapy: Clinical Observations Translated to a Pre-clinical Model



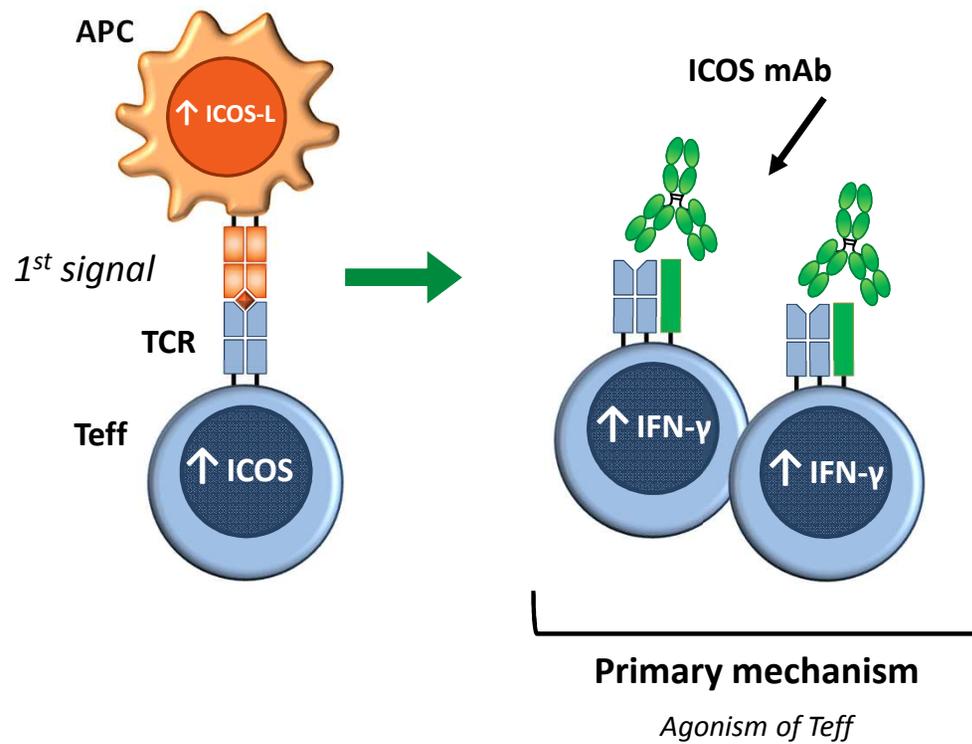
- Sustained increase in ICOS on peripheral CD4<sup>+</sup> T cells associated with positive clinical outcome
- Increase in ICOS<sup>+</sup> TILs also observed post-anti-CTLA-4 treatment
- In a pre-clinical tumor model. ICOS agonism in the context of anti-CTLA-4 mAb results in enhanced mouse survival

**Hypothesis: Up-regulated ICOS activates an immune-based anti-tumor response to provide therapeutic benefit**

# Mechanisms of a Jounce Anti-ICOS Antibody

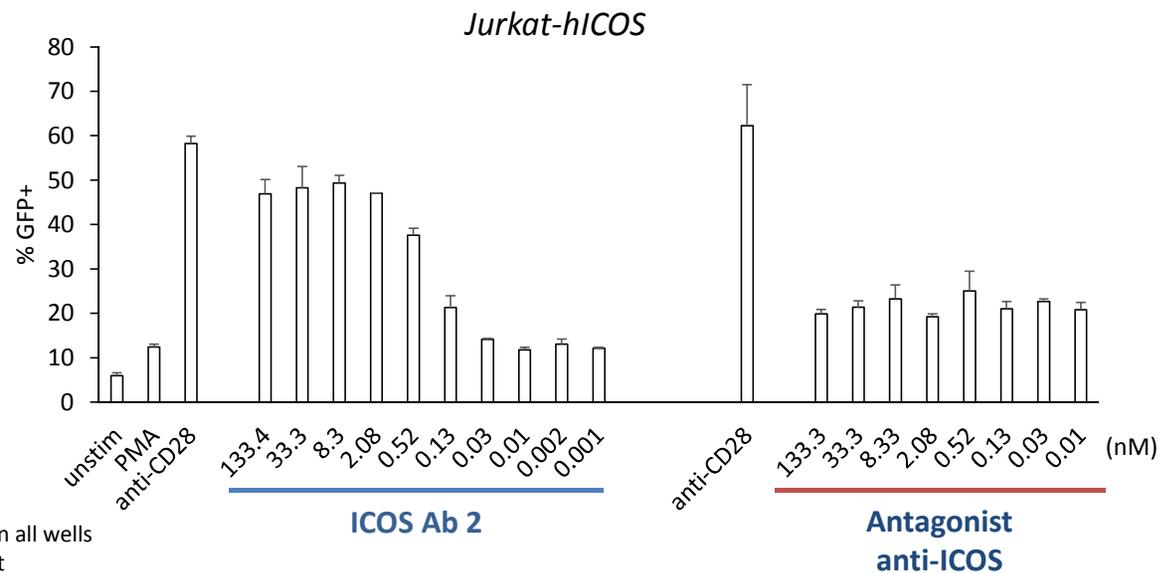


# Mechanisms of Jounce Anti-ICOS Antibodies



# Anti-ICOS mAb Displays Agonistic Activity

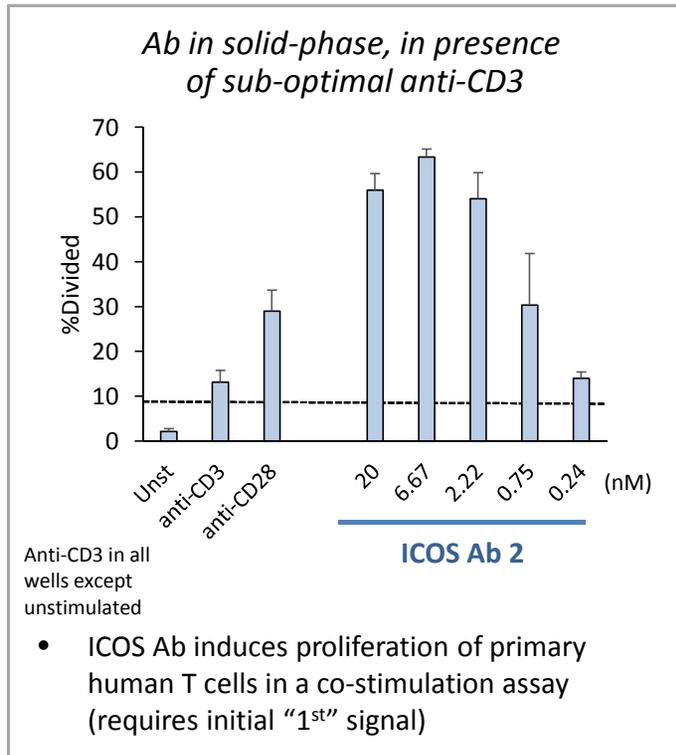
## Effect of Anti-ICOS mAbs on Jurkat ICOS-Reporter Assay:



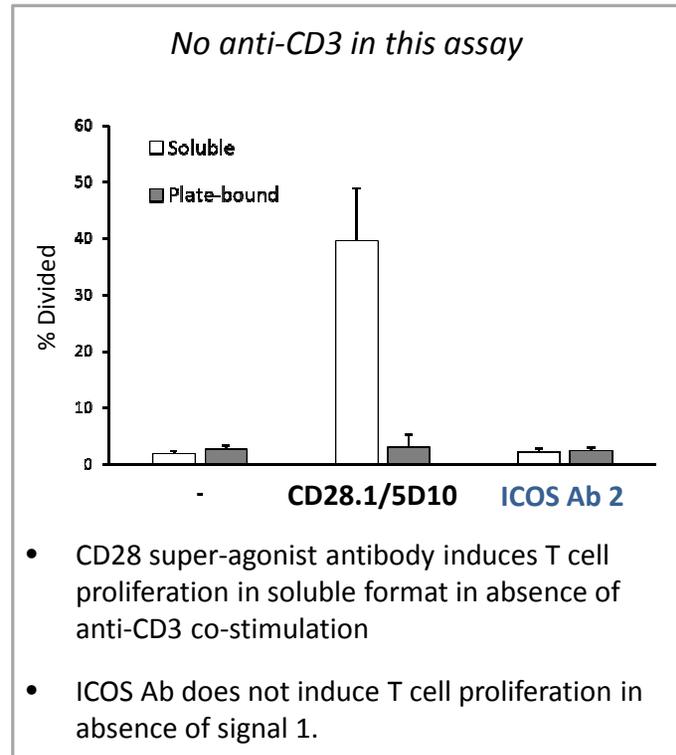
- Anti-ICOS antibody displays agonist activity in Jurkat cell reporter assay with GFP readout
- A published antagonist anti-ICOS has no agonist activity

## Anti-ICOS Displays Agonist but NOT Super-Agonist Activity

### Anti-ICOS is Agonistic On Anti-CD3-Activated CD4+ T Cells

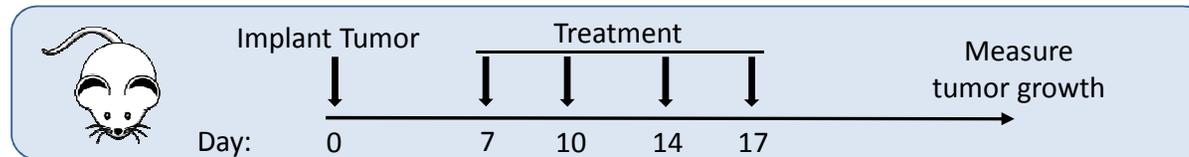


### Anti-ICOS is NOT Super-Agonistic on CD4+ T Cells

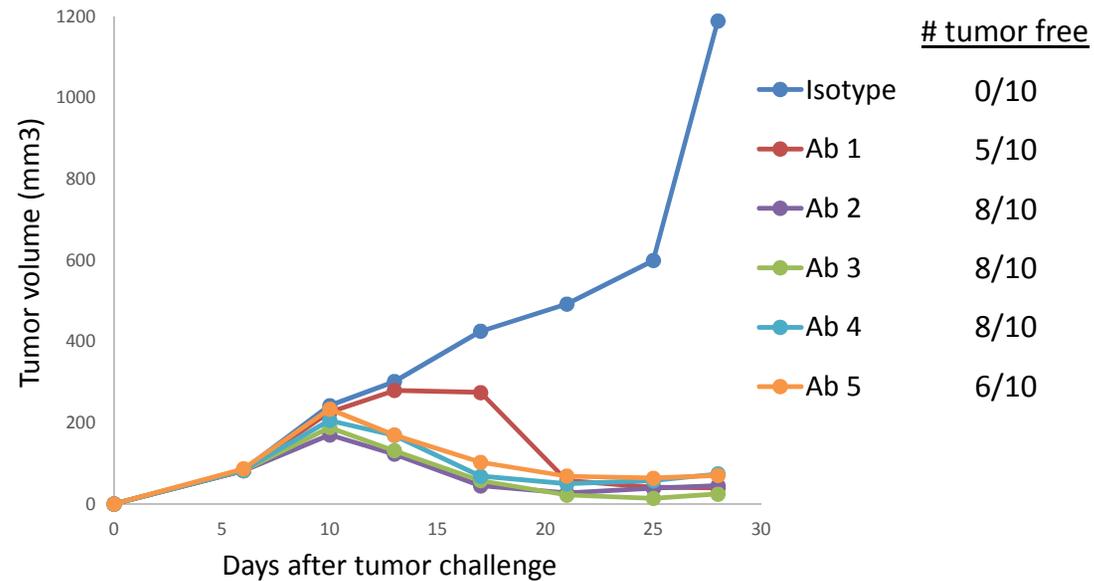


# Select Anti-ICOS mAbs are Efficacious in a Syngeneic Tumor Model

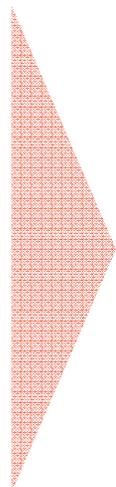
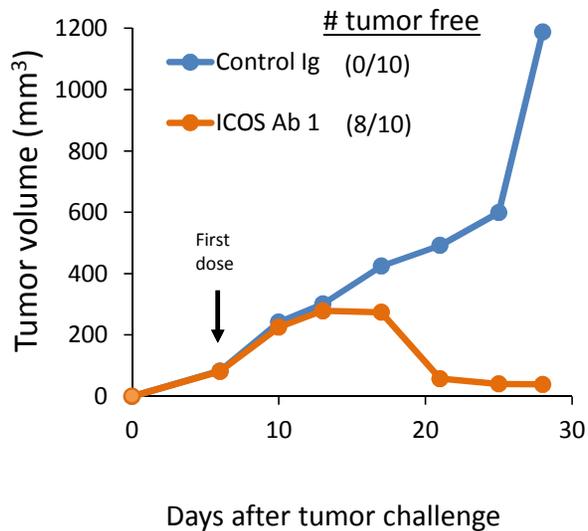
## Experimental Design:



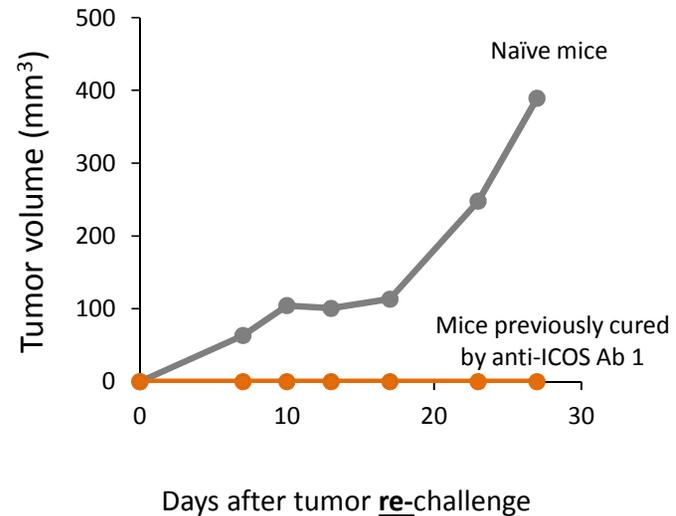
## Average Tumor Volume Over Time:



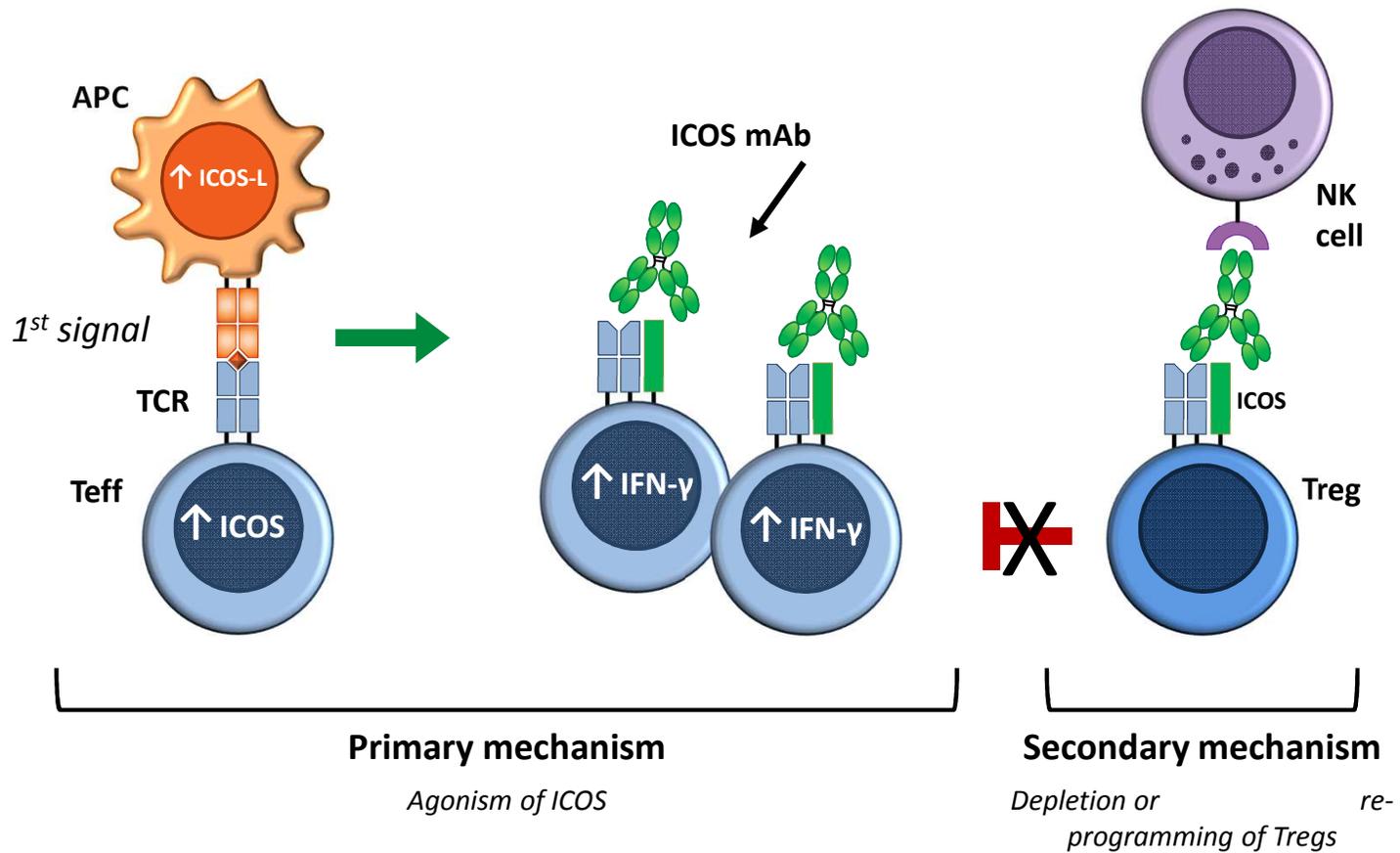
# ICOS Antibodies Create Durable Effects



*Animals cured of tumors are immune to tumor re-challenge*

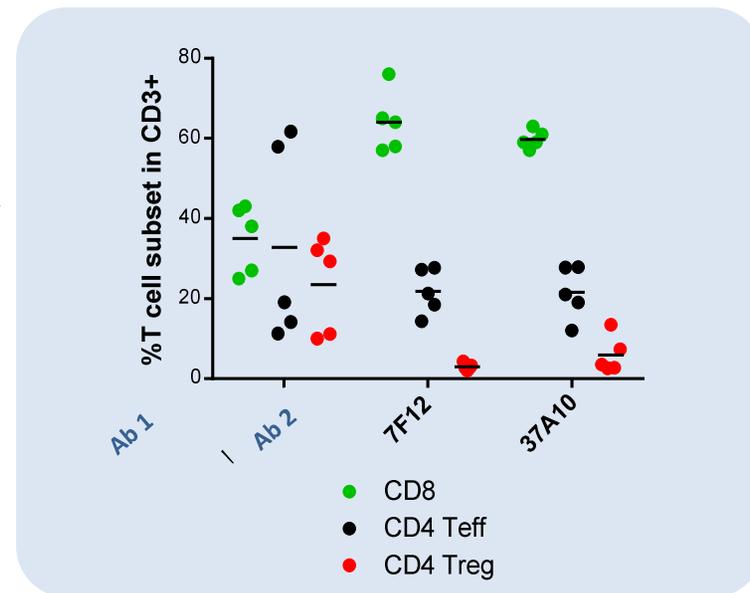
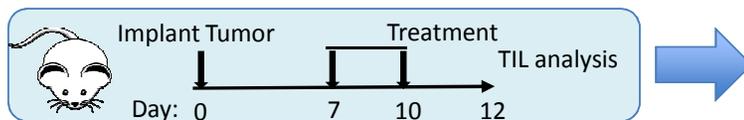


# Mechanisms of Jounce Anti-ICOS Antibodies



## Treatment with Anti-ICOS Antibodies Results in Reduction in FoxP3+ Tregs in Tumors

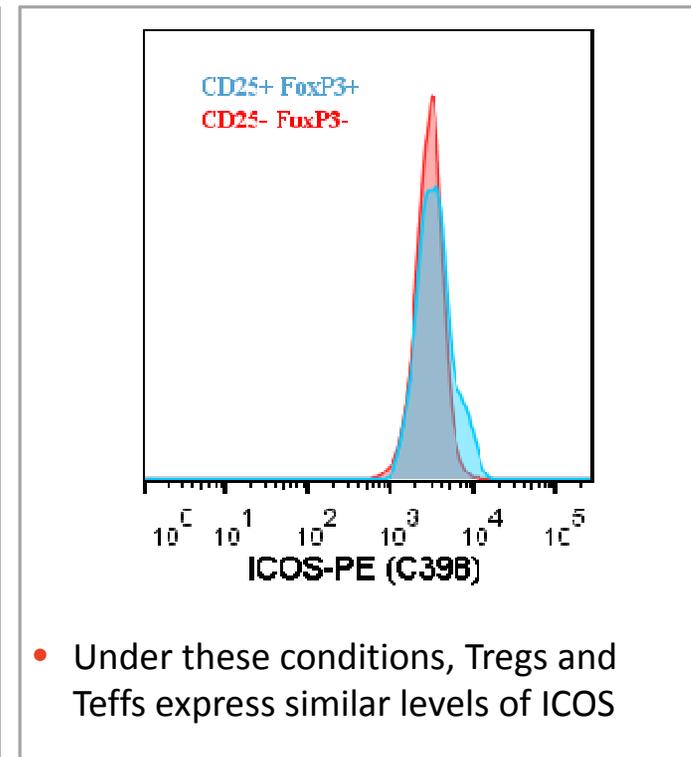
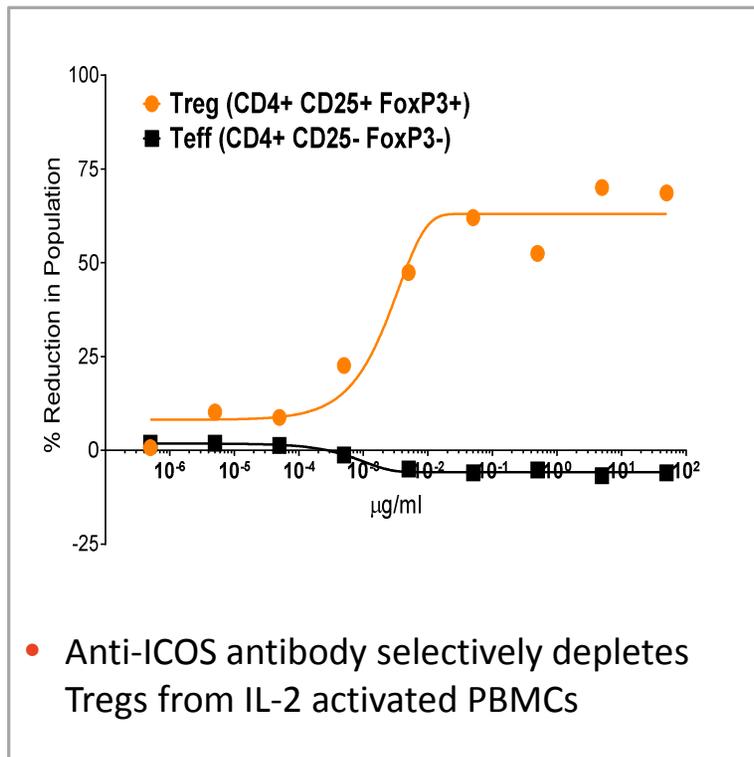
### *Selective reduction of Tregs in vivo:*



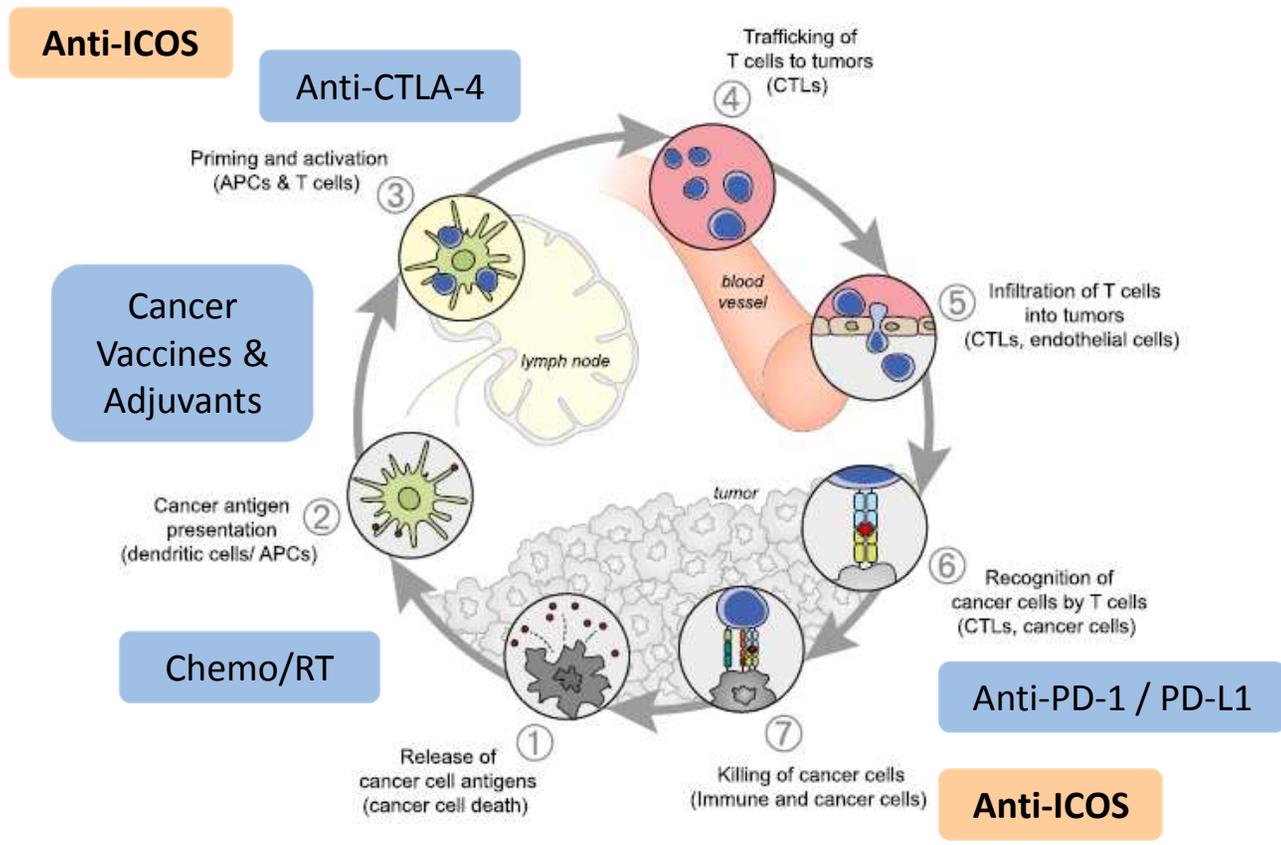
- Treatment with anti-ICOS mAbs reduces tumor-associated Tregs, but not Teffs
- CD8:Treg ratio is increased following anti-ICOS treatment
- No change in T cell subsets or ratios observed in spleen, lymph nodes, or peripheral blood (data not shown)

# Anti-ICOS mAbs Selectively Reduce Tregs vs Teffs

*Selective reduction of Tregs in vitro:*



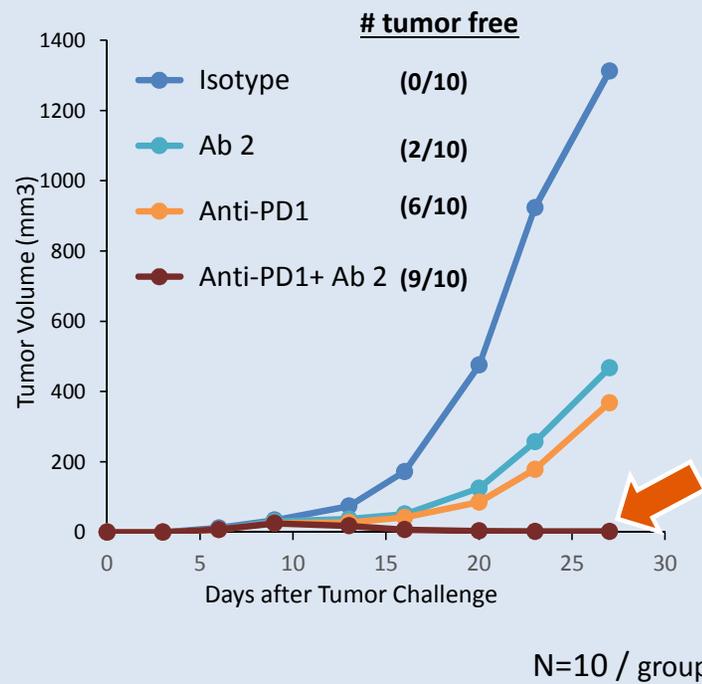
# Potential Combination Approaches



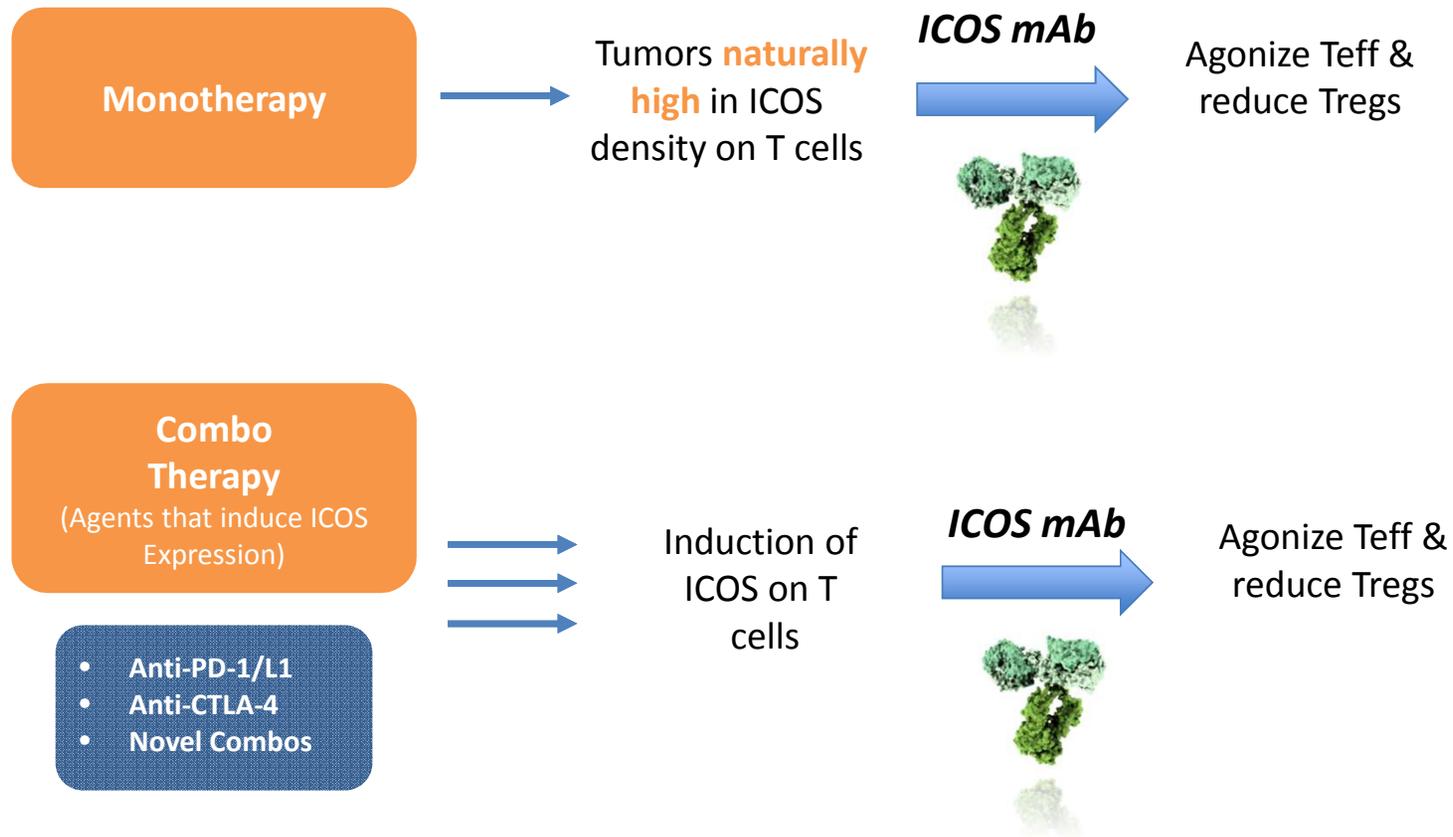
Chen and Mellman, *Immunity* (2013)

# ICOS and PD-1 Antibody Combination is Highly Effective

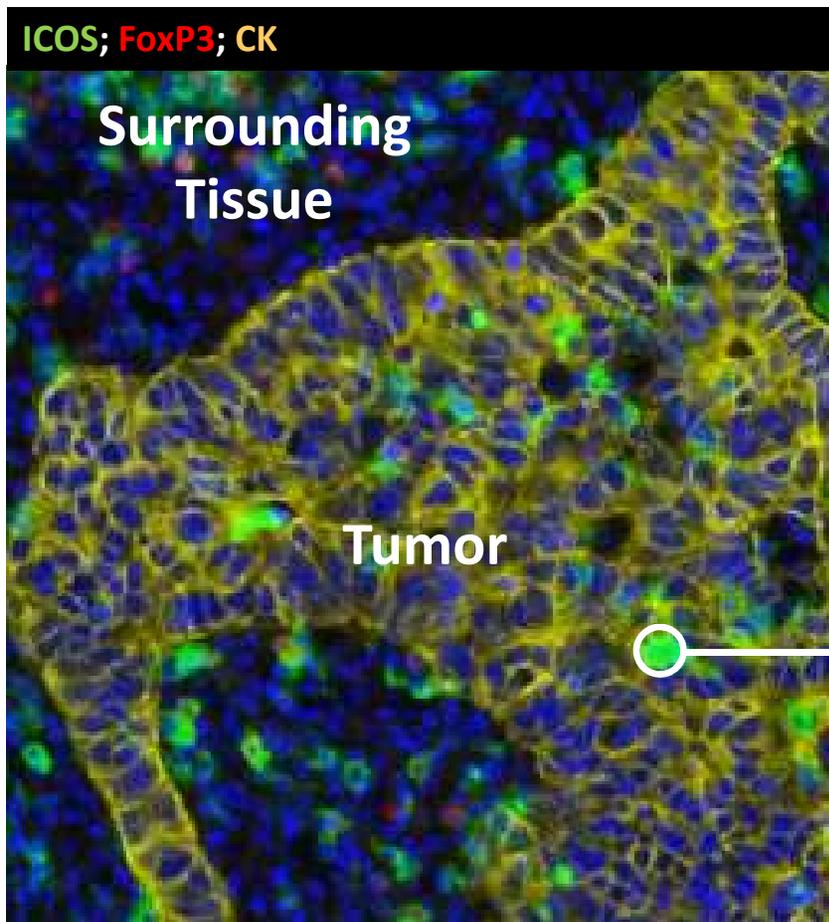
## Syngeneic tumor model in immunocompetent Mice



# Positioning ICOS Therapeutics



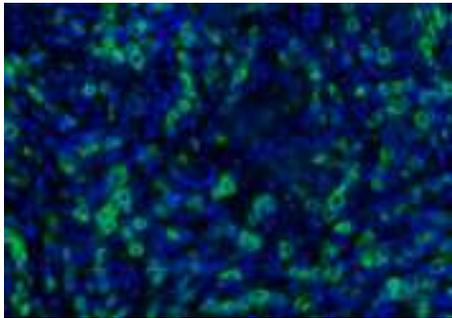
# Hypothesis: ICOS CD4 T cells are Essential for Response to Anti-ICOS Therapy



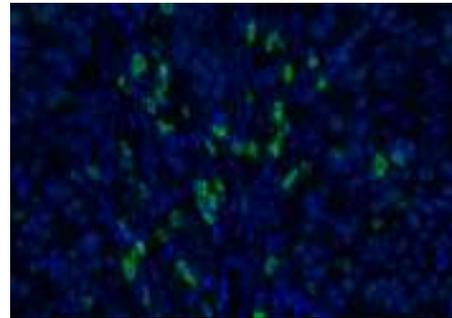
CD4 effector T cells  
expressing ICOS target  
within human tumors

# Quantitative Evaluation of ICOS Across Human Tumor Types

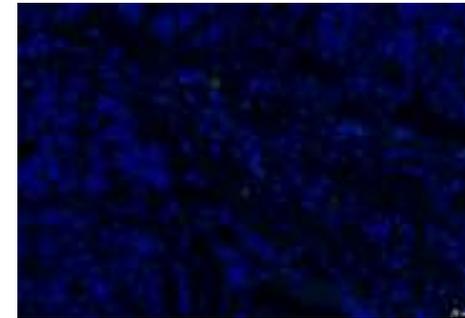
ICOS High



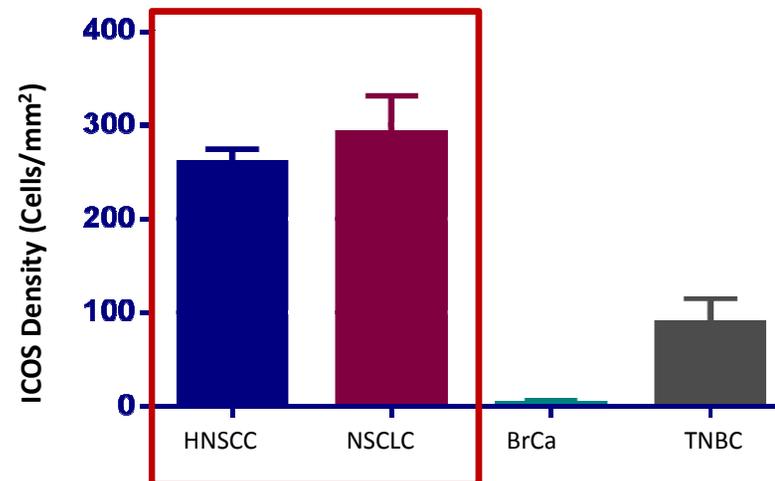
ICOS Medium



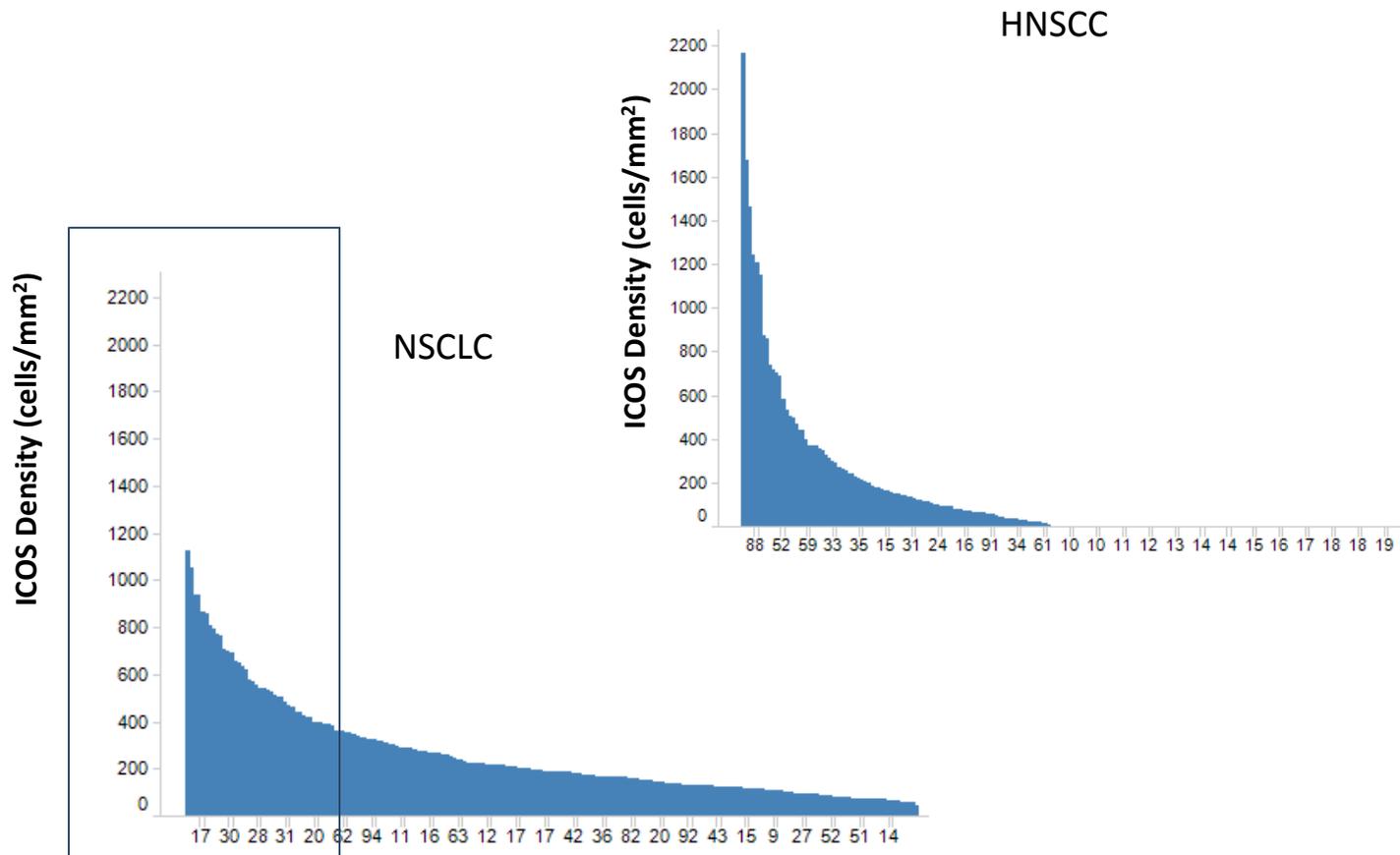
ICOS Low



100-200 tumors per indication or subtype



# ICOS Density in Individual Patients in NSCLC and HNSCC



# Summary

- Anti-ICOS antibodies were generated with dual function:
  - Agonistic activity on Teff cells
  - Capacity to selectively deplete Tregs
- Anti-ICOS antibodies are efficacious in syngeneic tumor models and induce durable protective immunity
- Anti-ICOS antibodies may be effectively combined with other immunotherapeutics, such as anti-PD1
- Immunohistochemical analysis of clinical samples has identified key indications for our lead ICOS therapeutic
  - Allows for patient enrichment and hypothesis testing in early clinical trials

# Acknowledgements

## **MD Anderson**

- Jim Allison
- Pam Sharma
- Ignacio Wistuba

## **University of Chicago**

- Tanguy Seiwart

## **Jounce Therapeutics**

- Jennifer Michaelson
- Kutlu Elpek
- Christopher Harvey
- Ellen Duong
- Tyler Simpson
- Jenny Shu
- Tong Zi
- Amit Deshpande
- Lindsey Shallberg
- Matt Wallace
- Sriram Sathy
- Robert Mabry
- Debbie Law