Lessons Learned from a Clinical Trial Targeting ICOS

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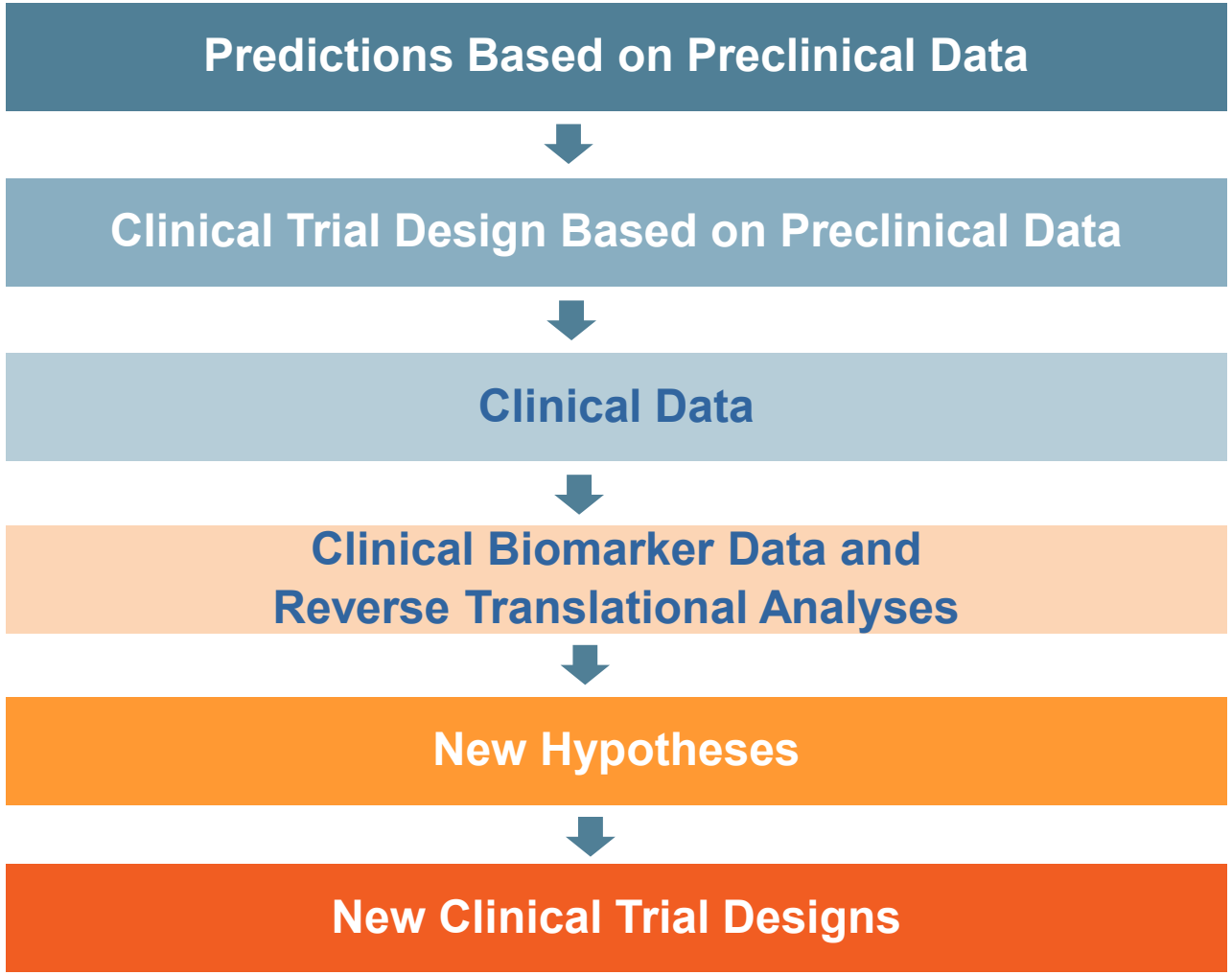
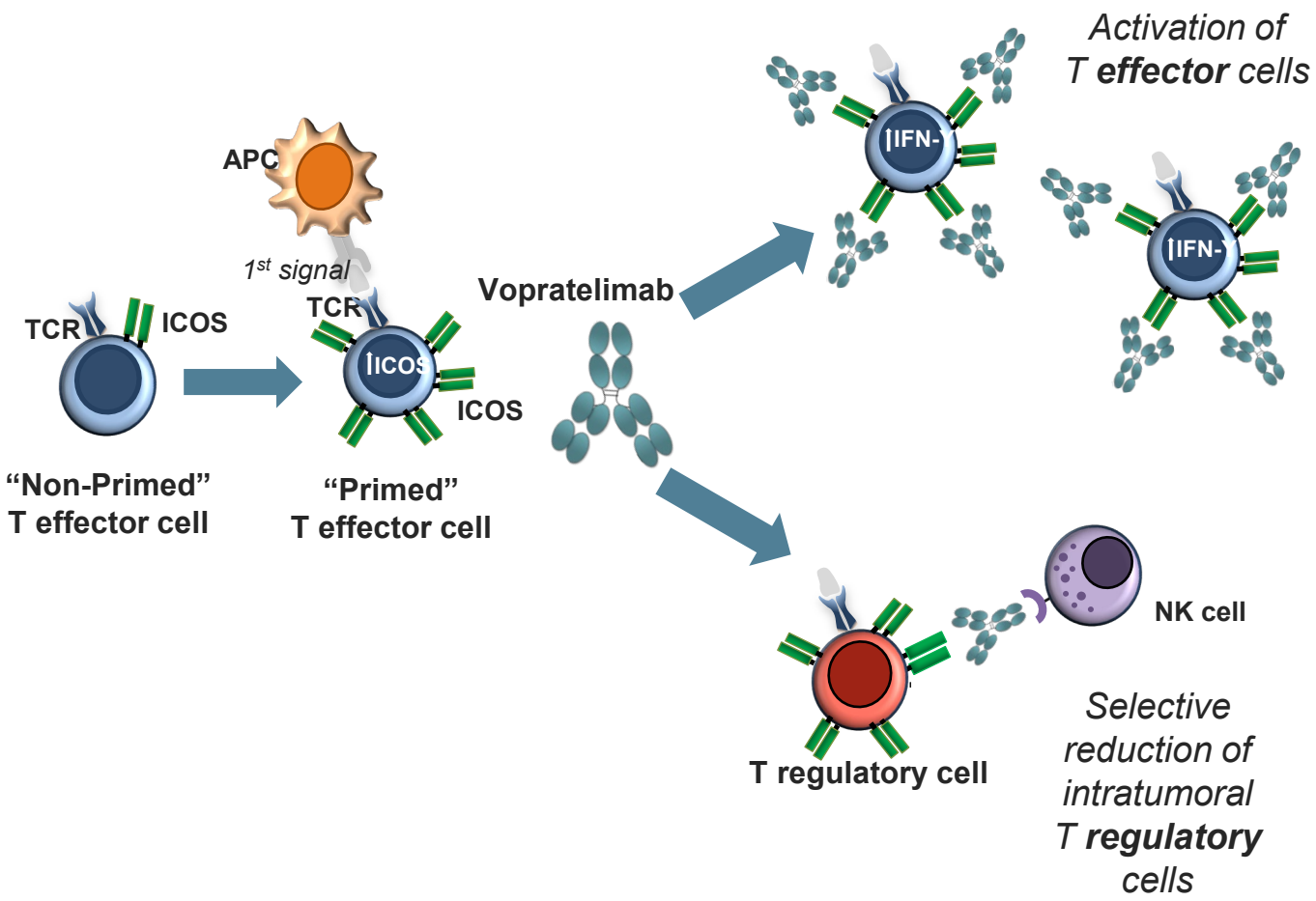
Lessons Learned from a Clinical Trial Targeting ICOS



Predictions Based on Preclinical Data

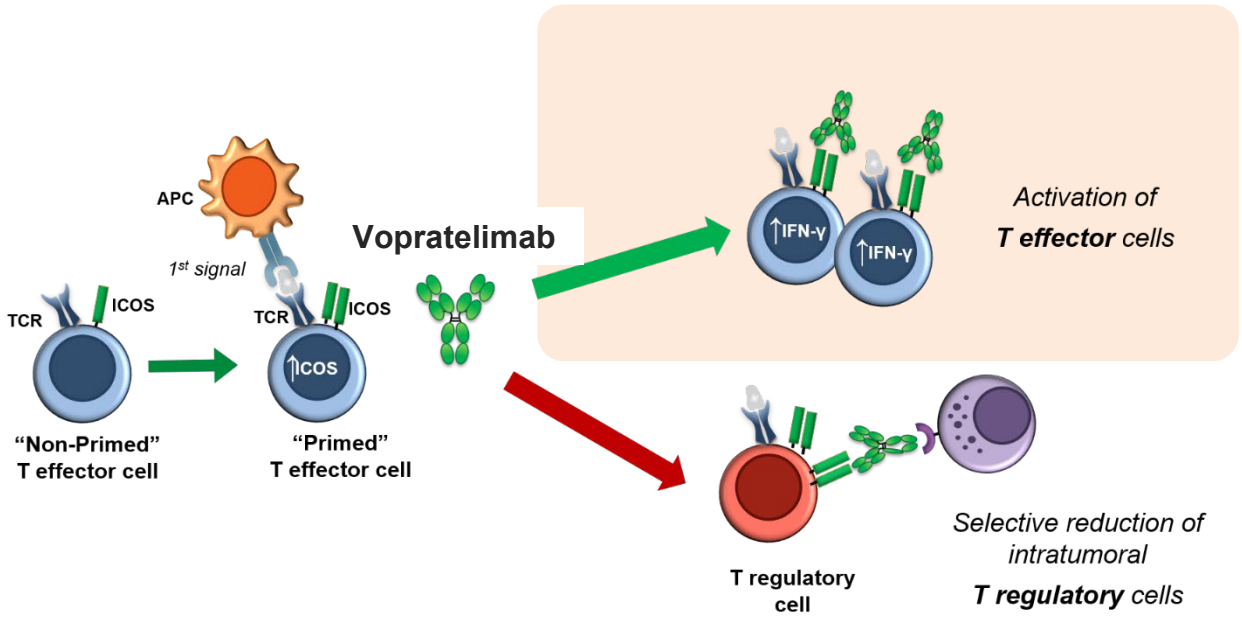
Vopratelimab (JTX-2011): IgG1 Agonist Monoclonal Ab Targets ICOS



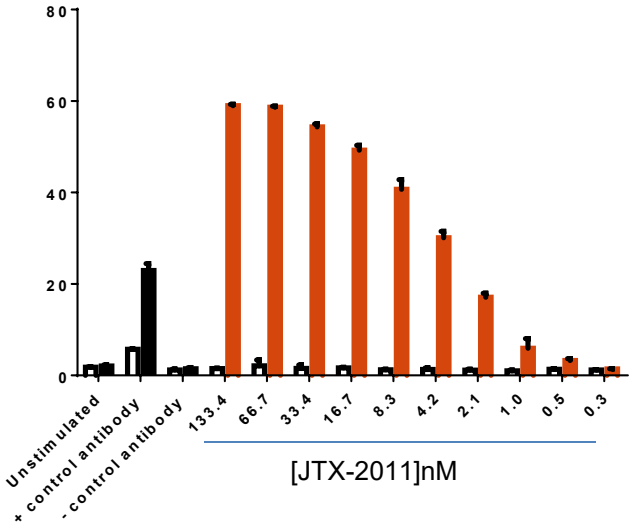
Predictions from Preclinical Data

- Dual MOA
  - Activation and proliferation of CD4 T effector cells
    - Requires T cell priming
  - Selective reduction of intra-tumoral T regulatory cells
    - No effect on peripheral T regs
- Requirements for Monotherapy Efficacy
  - Functional Fc
  - Sustained Target Engagement
  - High ICOS IHC score

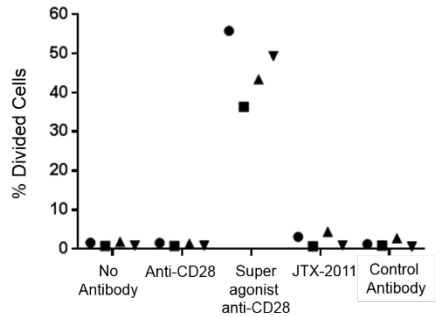
Vopratelimab Preclinical Data:
Activation and Proliferation of CD4 T effector Cells Requires Initial Priming



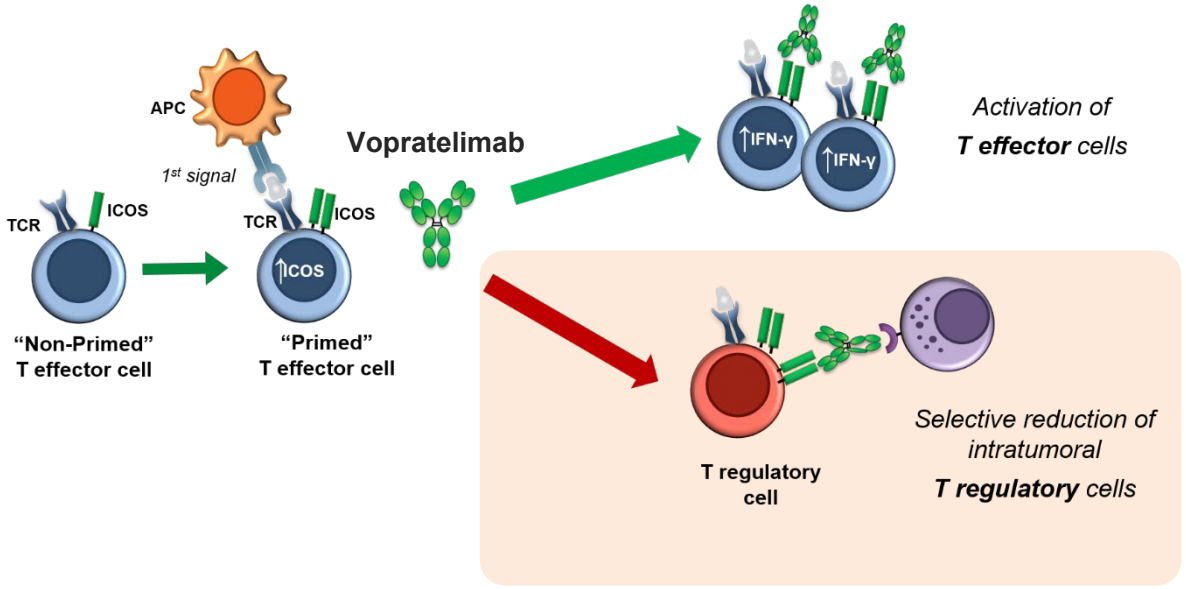
Activation of *primed* human CD4+ T effector cells



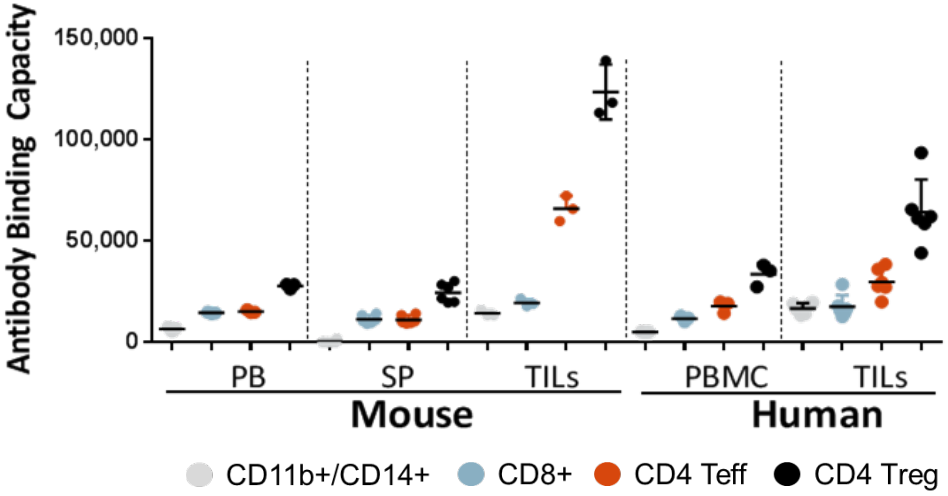
No activation of *unprimed* CD4+ T effector cells



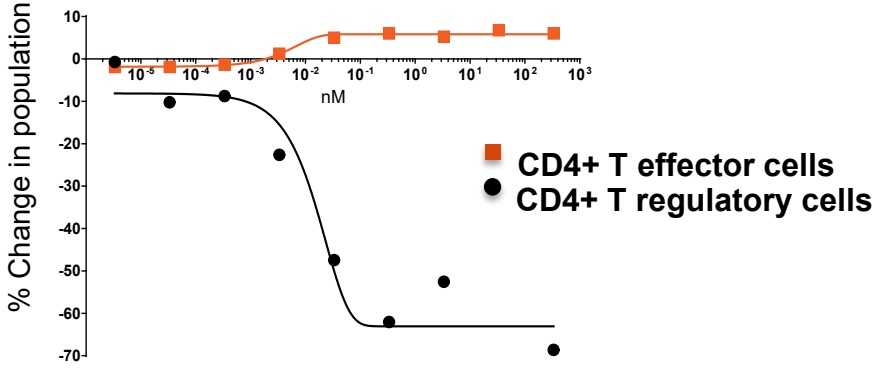
Vopratelimab Preclinical Data: Selective Reduction of Intra-tumoral T regs in Mice
No Reduction of T effectors or Peripheral T regs



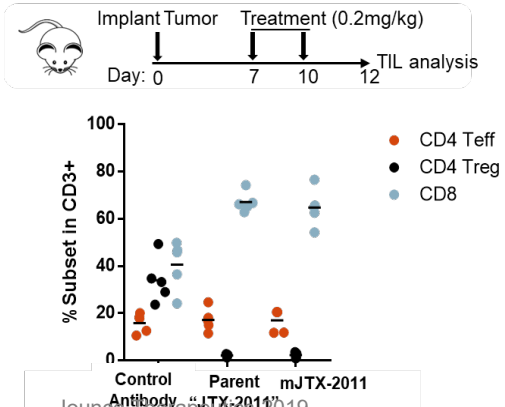
ICOS expression highest on intratumoral Tregs



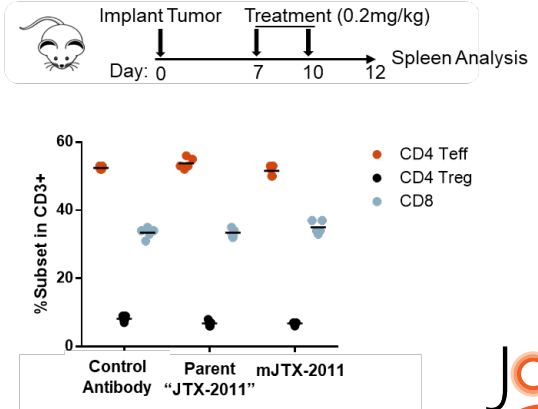
Selective reduction of human CD4+ Tregs



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

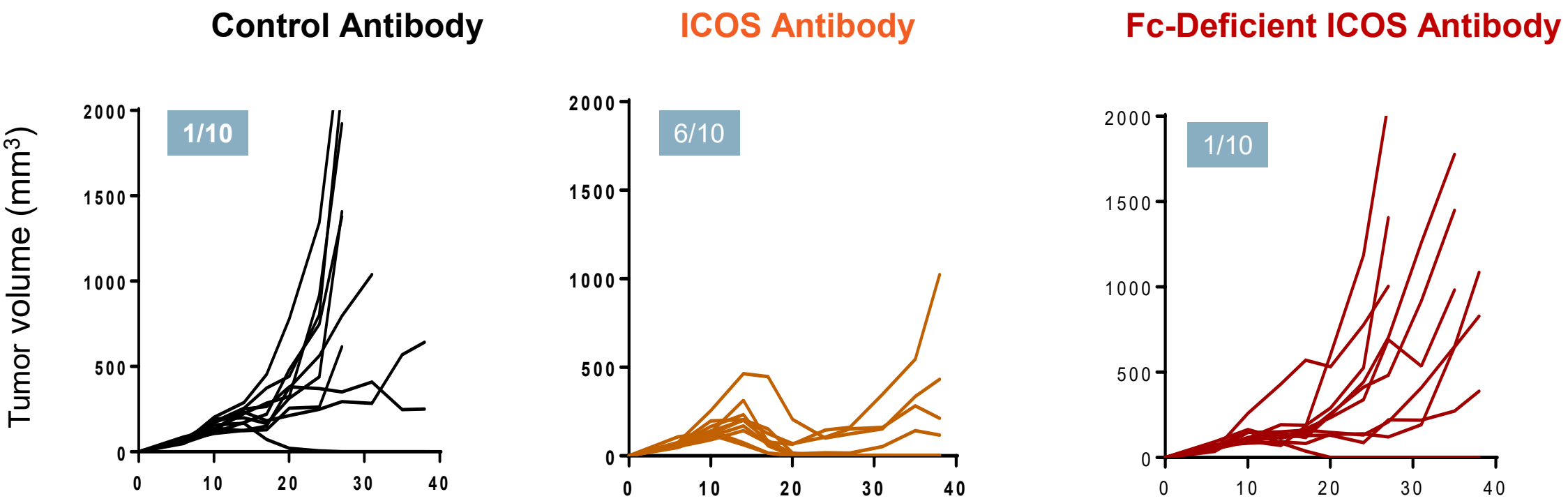


Mouse JTX-2011 does not reduce spleen T regulatory cells *in vivo*



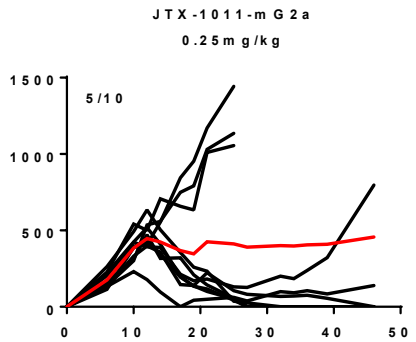
Vopratelimab Preclinical Data: Fc Effector Function is Required for Optimal Anti-Tumor Activity

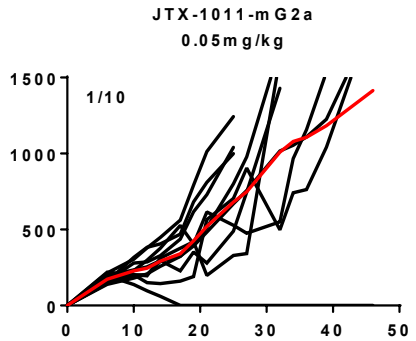
Loss of Activity with Fc Deficient Version of Antibody

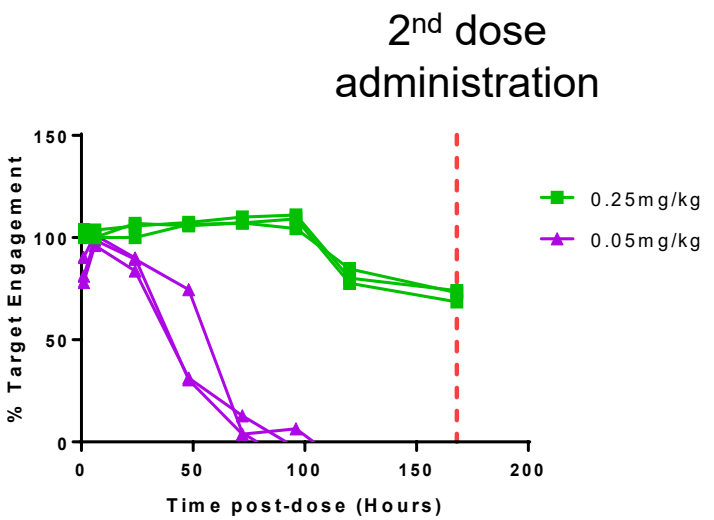


Vopratelimab Preclinical Data:
Sustained Target Engagement Required for Optimal Efficacy

In vivo monotherapy efficacy corresponded to doses at which a period of target engagement was maintained

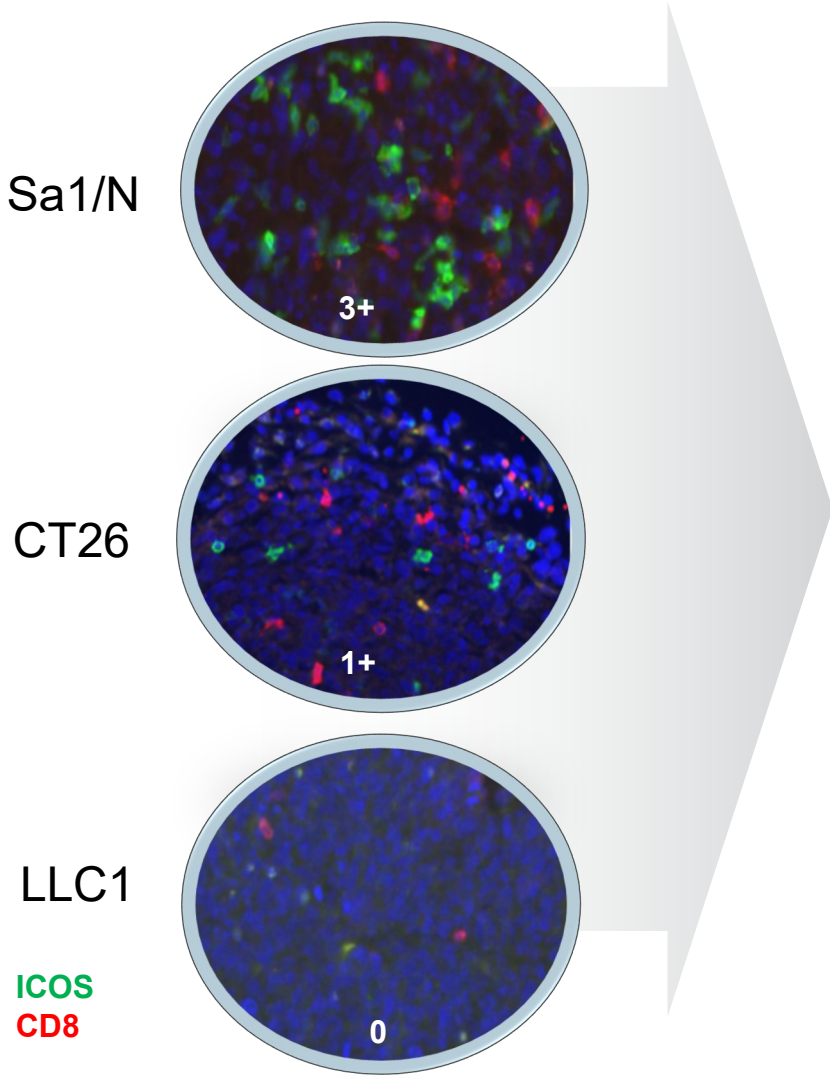






Vopratelimab Preclinical Data: High ICOS IHC Score Required for Optimal Efficacy

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



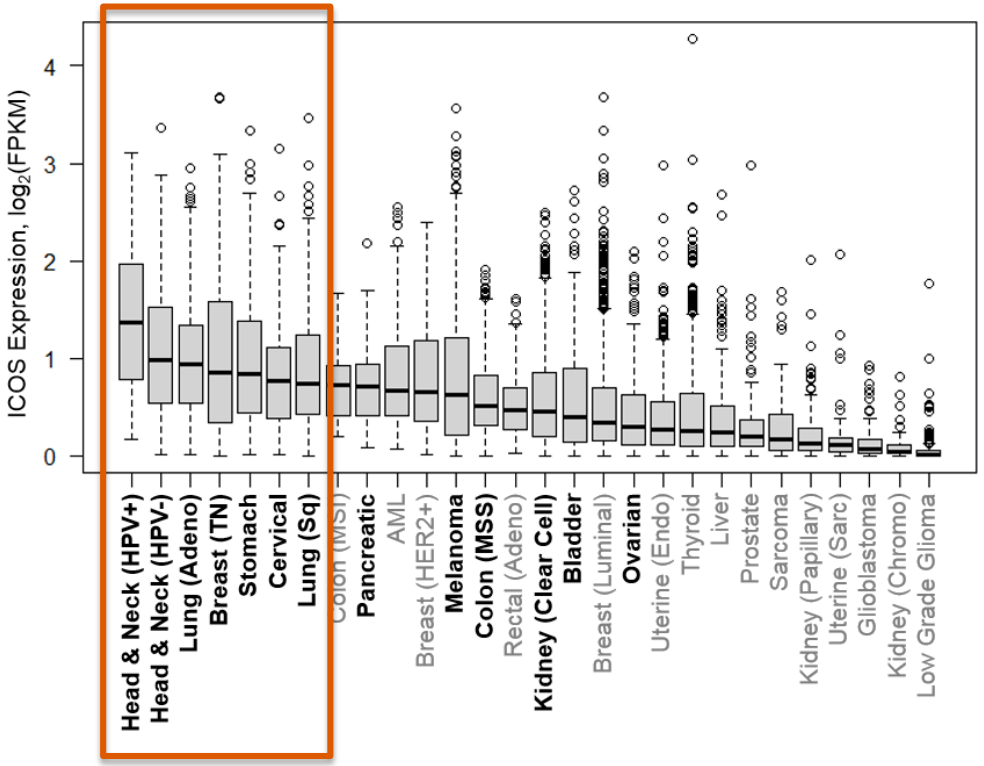
Tumor Line	ICOS IHC Score (at Baseline)	Single Agent Efficacy	Combination Efficacy (+ anti-PD-1)
Sa1/N	3+	++++	ND
B16-SIY	2+	+++	++++
MC38	1+	+	+++*
CT26	1+	+	++++
EMT6	1+	+/++	+/-
LLC1	0	-	-

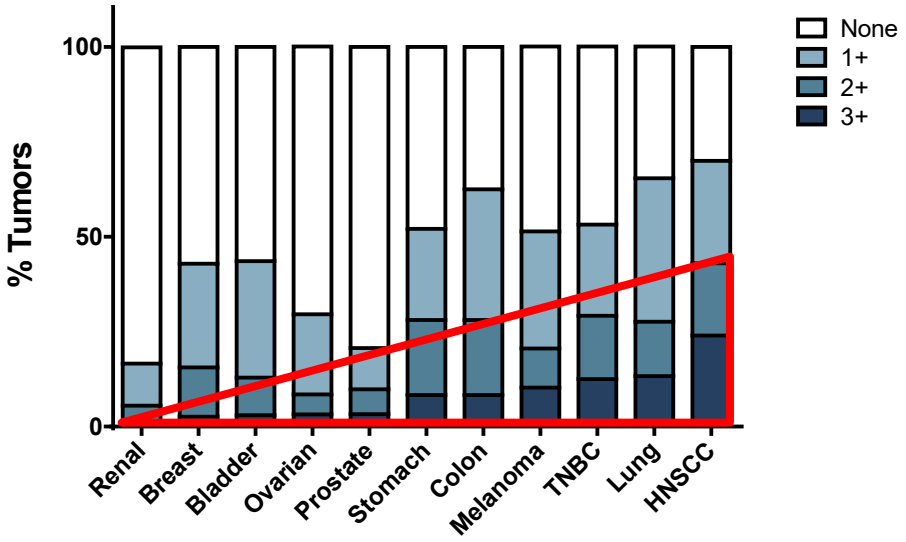
++++ indicates 61-100% tumor regression
+++ indicates 41-60% tumor regression
++ indicates 21-40% tumor regression
+ indicates 10-20% tumor regression
- indicates no tumor regressions

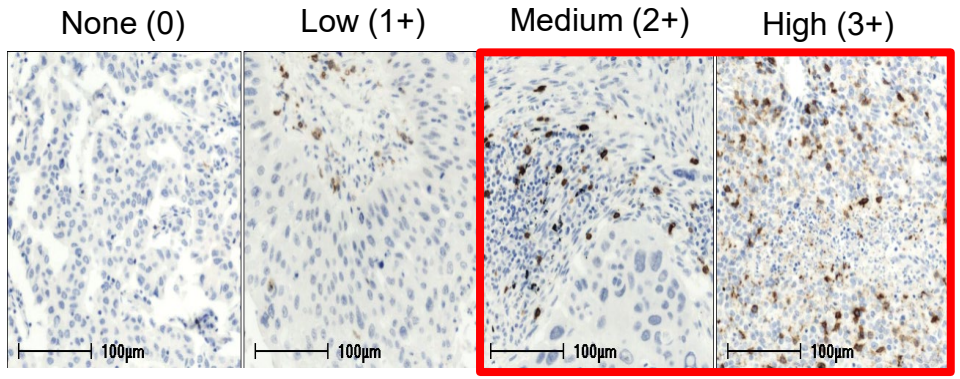
*Intra-tumoral levels of ICOS+ T cells increases post PD-1 treatment

Clinical Trial Design Based on Preclinical Data

Vopratelimab: Phase 2 Indication Selection & Patient Enrichment Based on Intra-tumoral ICOS RNA and IHC Data







ICONIC: Adaptive Study Design

Phase 1

All solid tumors, no enrichment for ICOS expression

vopratelimab 0.003-1.0 mg/kg IV q3w

Dose Escalation

PK/PD Expansions

vopratelimab 0.01-0.3 mg/kg IV q3w + nivo 240 mg IV q3w

Dose Escalation

PK/PD Expansions

Phase 2 Triggered Upon: Identification of safe dose with ≥ 70% TE

Phase 2

Enriched for pts with high ICOS expression

vopratelimab 0.3 mg/kg IV q3w

- NSCLC*
- HNSCC*
- Any solid tumor type
- Gastric*
- Additional tumor types based on emerging science

vopratelimab 0.3 mg/kg IV q3w + nivo 240 mg IV q3w

- NSCLC*
- HNSCC*
- TNBC
- Melanoma*
- Gastric*
- Additional tumor types based on emerging science

*Required to have failed PD-1 inhibitor in FDA-approved indications

Clinical Data

ICONIC: Demographics and Safety

- Heavily pre-treated patients in Phase 1 and Phase 2

	vopratelimab		vopratelimab + nivo	
Parameter	Phase 1	Phase 2	Phase 1	Phase 2
n	40	30	31	100
ECOG 0/1, n (%)/n (%)	8 (20%) / 32 (80%)	2 (7%) / 28 (93%)	8 (26%) / 22 (71%)*	30 (31%) / 68 (70%)*
≥3 Prior therapy for metastatic disease, n (%)	32 (80%)	24 (80%)	23 (74%)	60 (60%)

- vopratelimab is safe and well-tolerated alone and in combination with nivo
  - Related Grade 3/4 AEs in Phase 2 12% with vopratelimab or vopratelimab + nivo
  - Phase 1: DLTs on mechanism at 1.0 mg/kg vopratelimab alone
    - Grade 3 AST/ALT, Grade 3 pleural effusion
  - Phase 2: Two possibly related Grade 5 AEs with vopratelimab + nivo
    - Increased bilirubin, encephalopathy

Safety population: all subjects who received at least one dose of vopratelimab
*ECOG status not available on all subjects
#Prior therapy data not available on all subjects

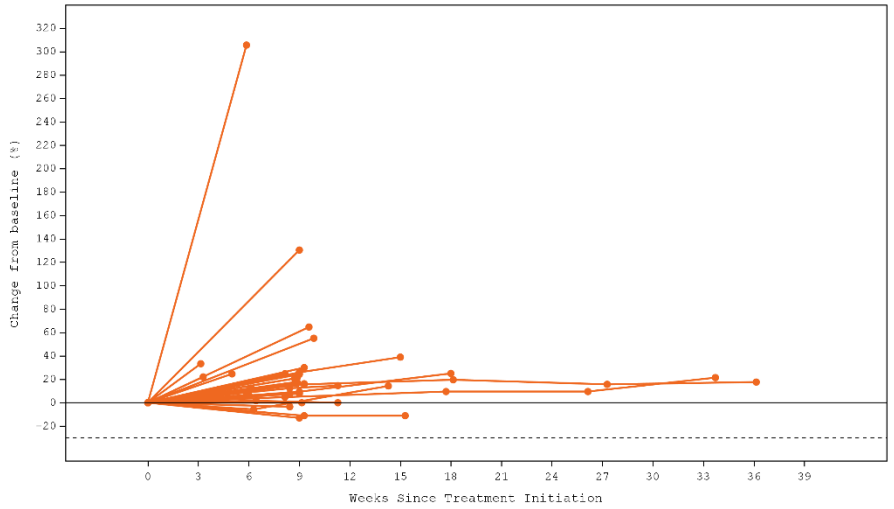
Data cut-off Jan 17, 2019

ICONIC Efficacy

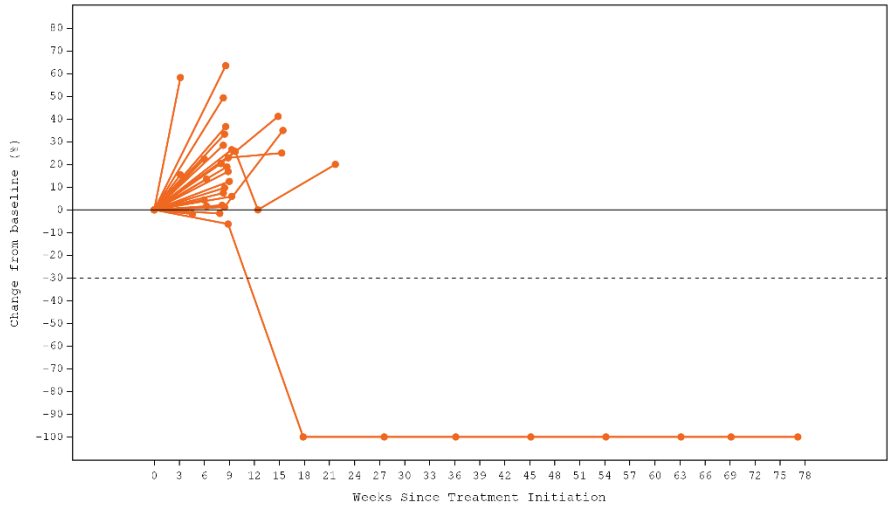
Vopratelimab monotherapy

CR=0
PR=0
SD=15 (21.4%)

Phase 1 vopratelimab (n=40)



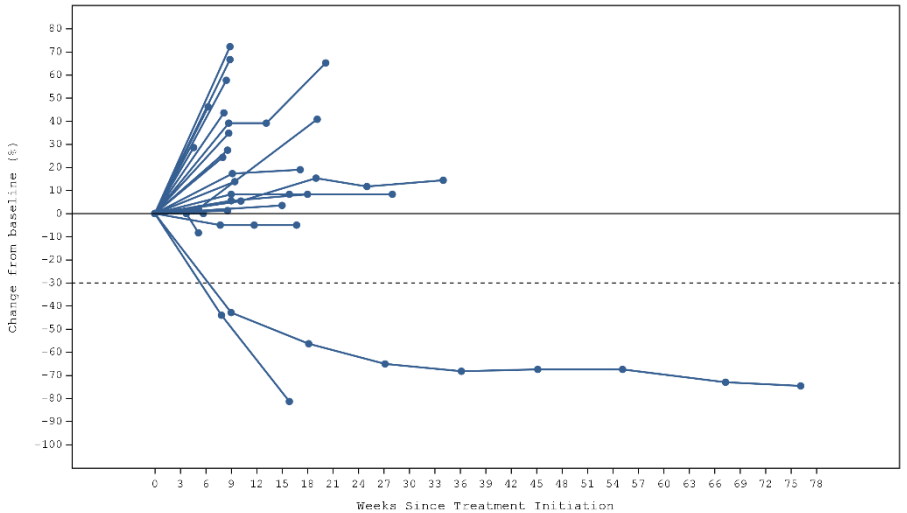
Phase 2 vopratelimab (n=27)



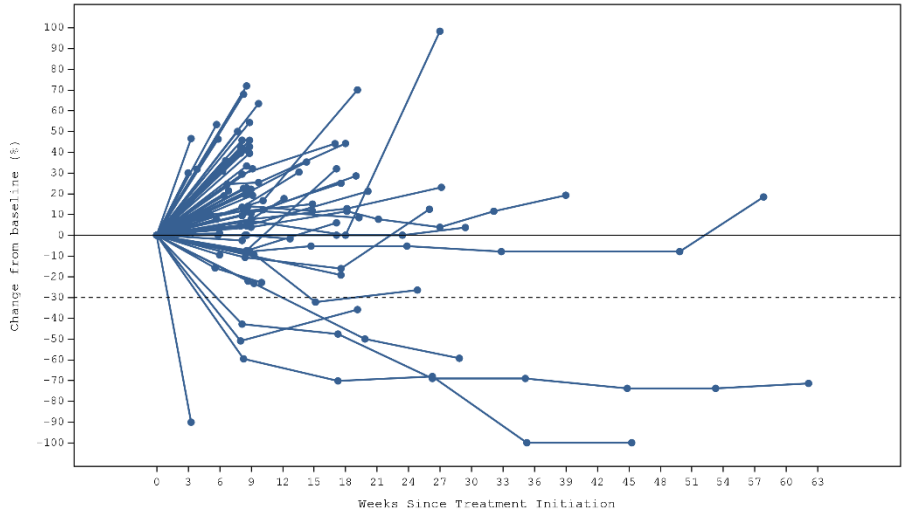
Vopratelimab + nivo

CR=1 (0.8%)
PR=3 (2.3%)
SD=20 (15.4%)

Phase 1 vopratelimab + nivo (n=31)

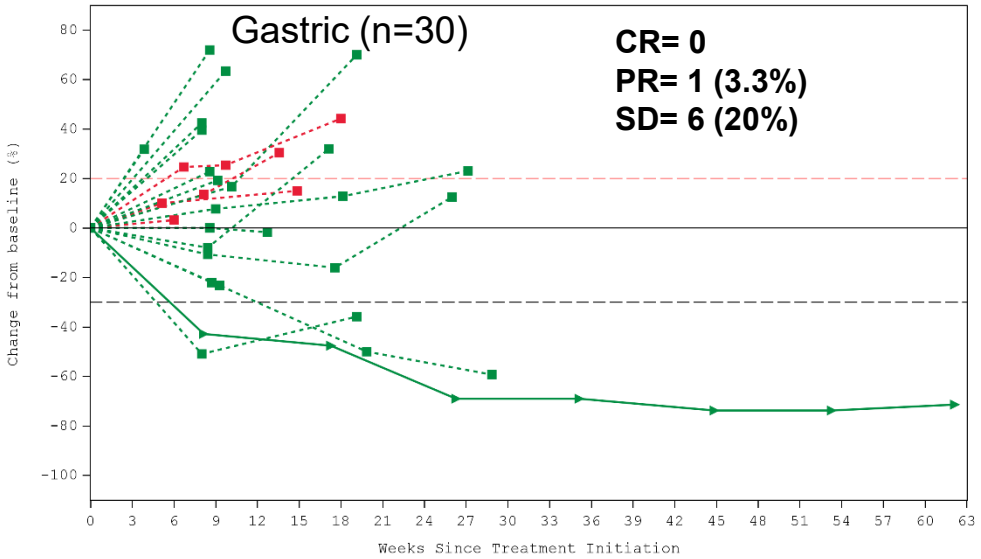


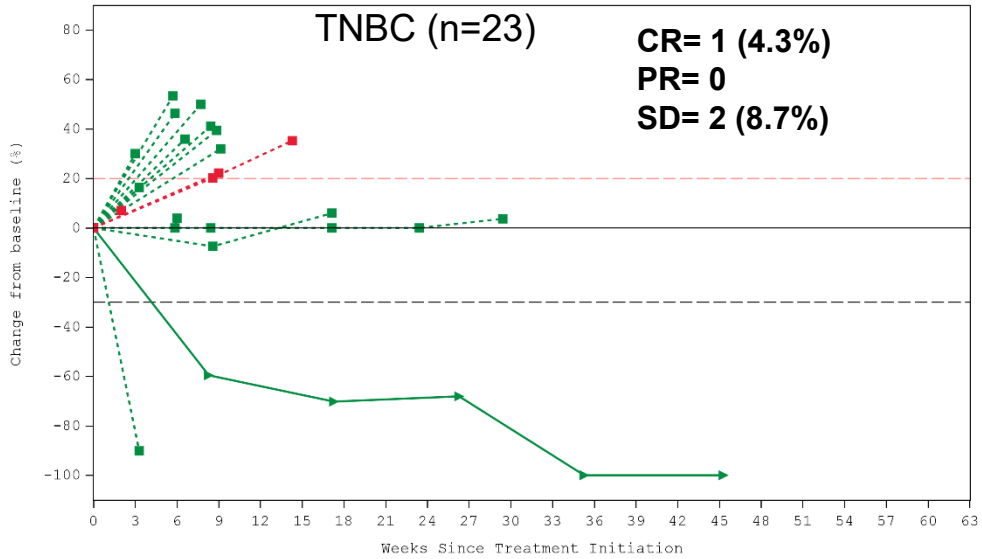
Phase 2 vopratelimab + nivo (n=100)

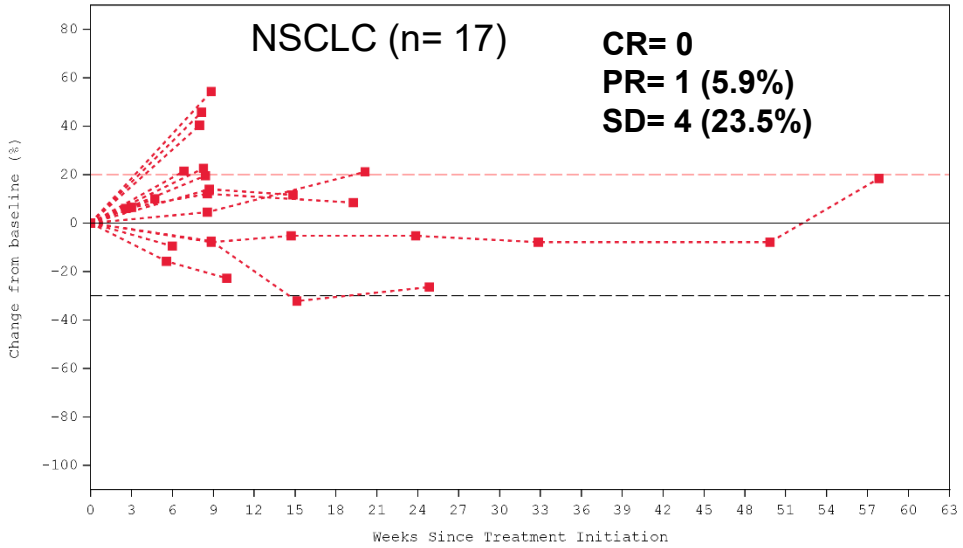


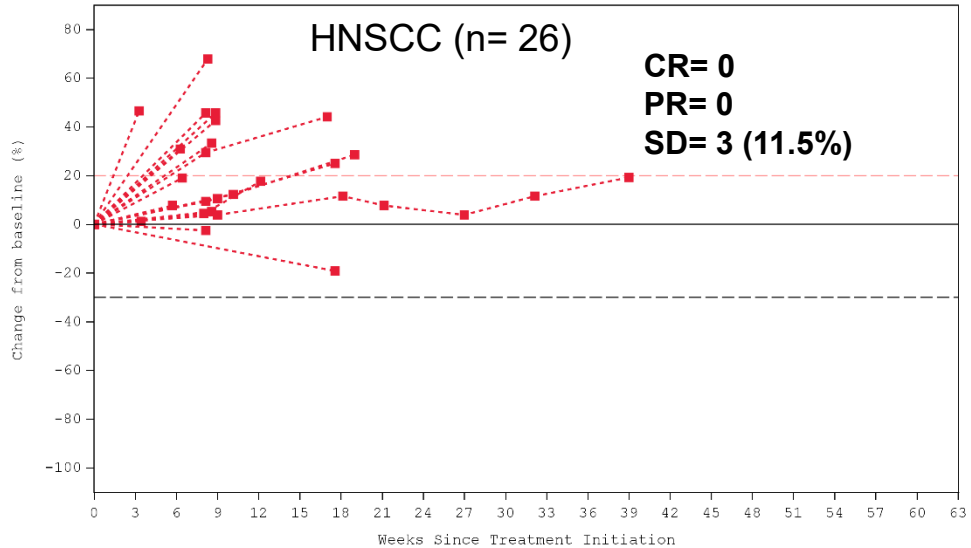
n= Dosed and ≥ 1 scan or discontinued treatment; Spider plot= Investigator measurements; CR, PR, SD= Central Radiology review; data cut-off March 4, 2019

Vopratelimab + nivo Phase 2: Durable Responses and Stable disease









n= Dosed and ≥ 1 scan or discontinued treatment; Durable= > 6 months; Spider plot= Investigator measurements; CR, PR, SD= Central Radiology Review; data cut-off March 4 2019

Ongoing — Off-treatment - - -

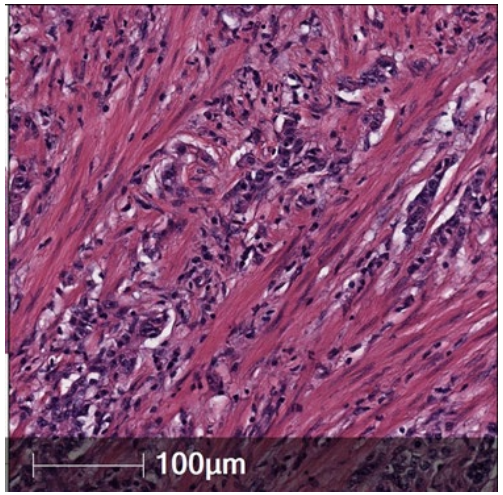
PD-1/L1 inhibitor naive — PD-1/L1 inhibitor failure —

Clinical Biomarker Data and Reverse Translational Analyses

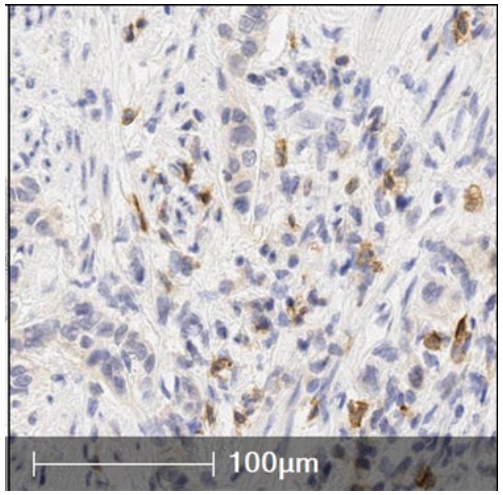
ICOS and PD-L1 IHC are not Correlated with Tumor Reductions

- Concordance between PD-L1 and ICOS scores in archival and fresh tumor tissue
- Neither ICOS score nor PD-L1 score are correlated with response

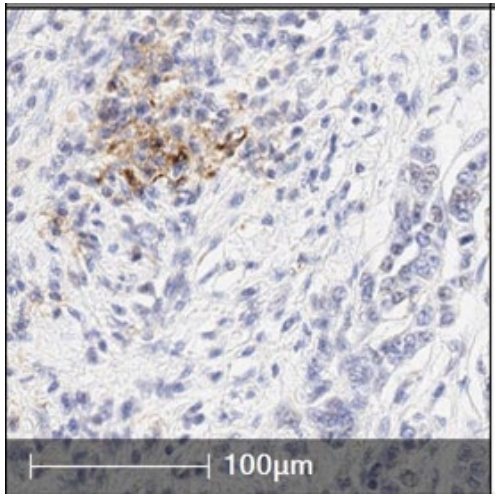
H&E



ICOS



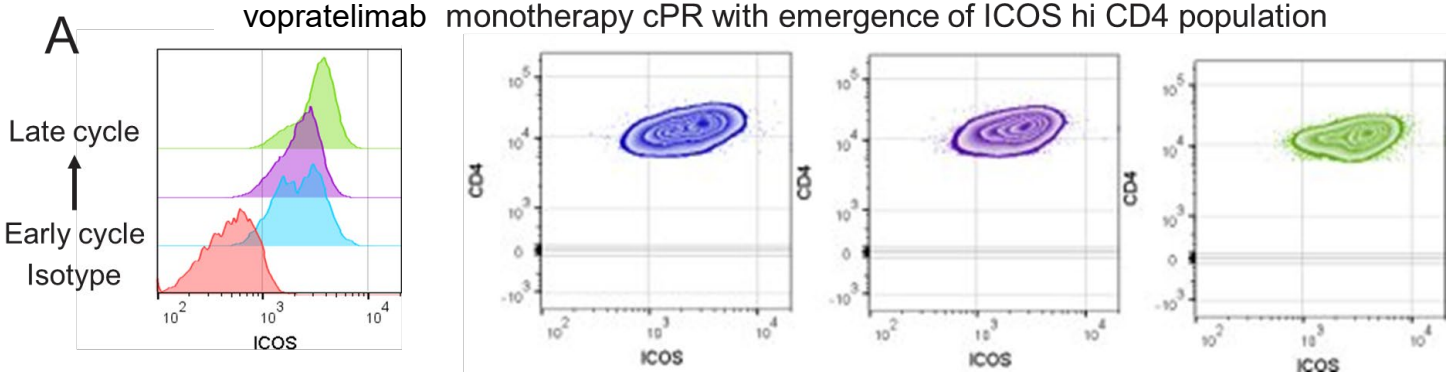
PD-L1



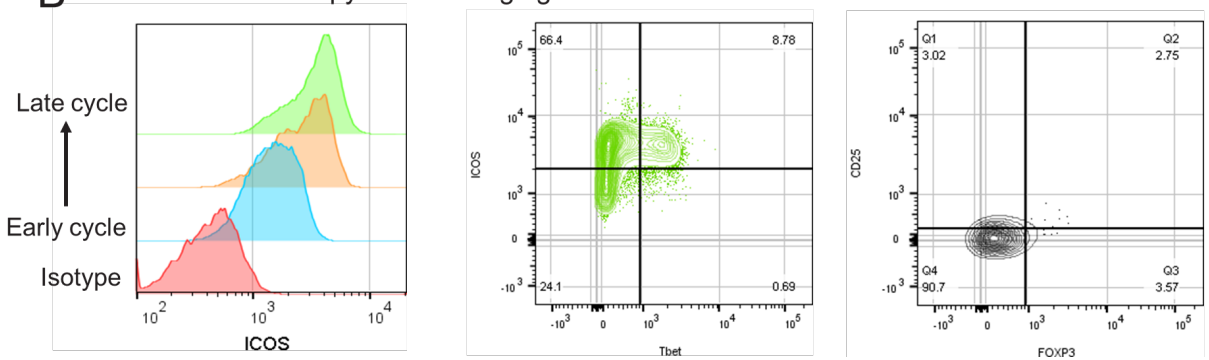
- ICOS IHC score is based on total tumor infiltrate ICOS positive immune cells
  - does not discriminate between Teff, Treg, and NK cells
  - does not measure ICOS density per immune cell

Emergence and Persistence of ICOS hi CD4 Teff is Observed in Responding* Subjects

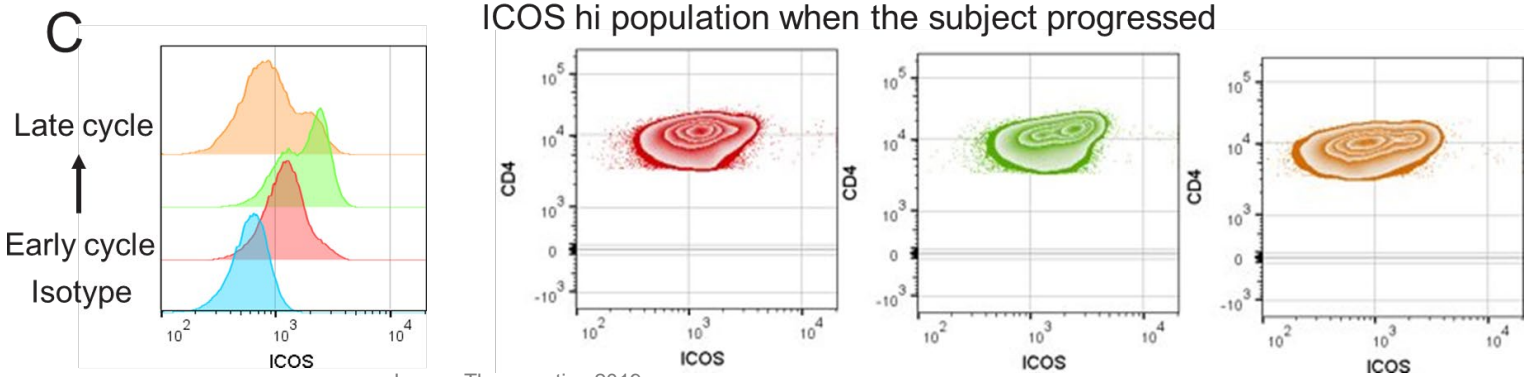
A vopratelimab monotherapy cPR with emergence of ICOS hi CD4 population



B Combination therapy cPR. Emerging ICOS hi CD4 T cells are FoxP3^{-} with a subset T-bet^{+}.



Subject with stable disease shows emergence and then loss of ICOS hi population when the subject progressed



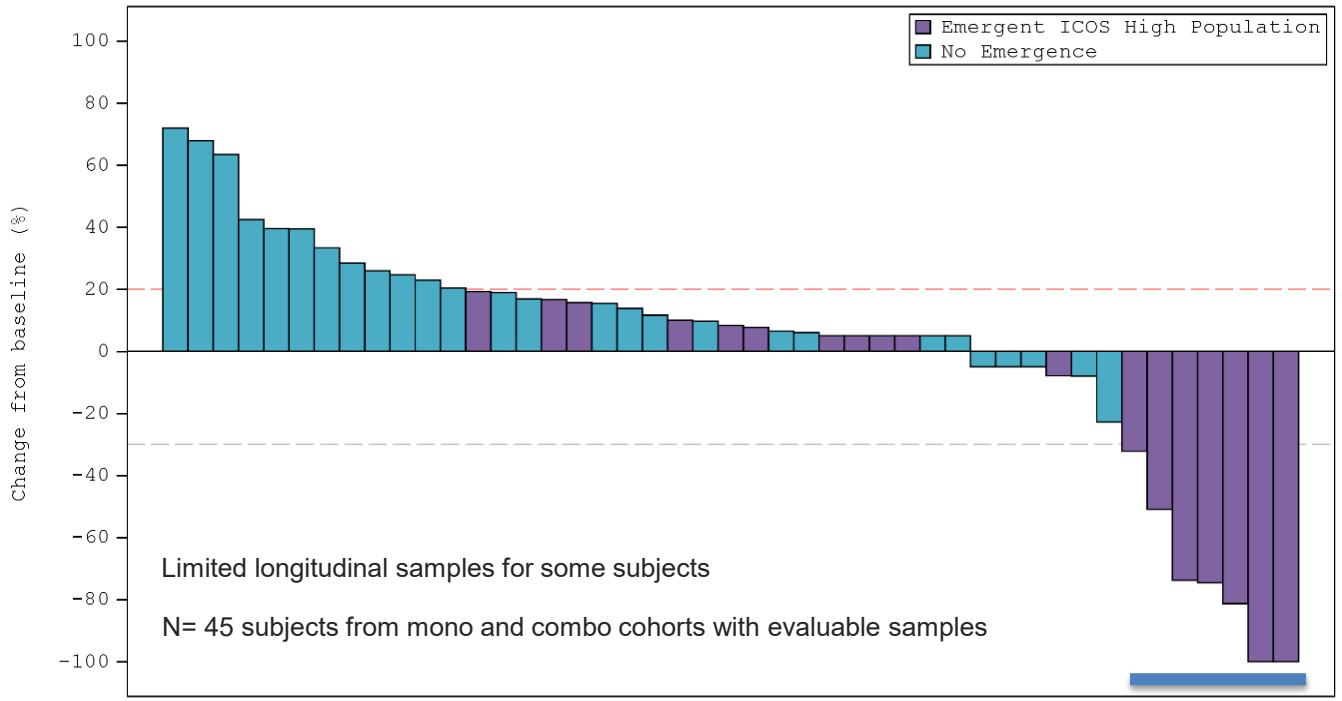
*based on investigator assessments

C. Harvey, SITC 2018

Anti-Tumor Activity Correlates with Vopratelimab Mechanistic Biomarker

ICOS hi CD4 Cells Emerge in Patients with Target Lesion Reductions*

- Observed in 7/7 subjects with target lesion PR
- Not observed in 12/12 subjects with progressive disease

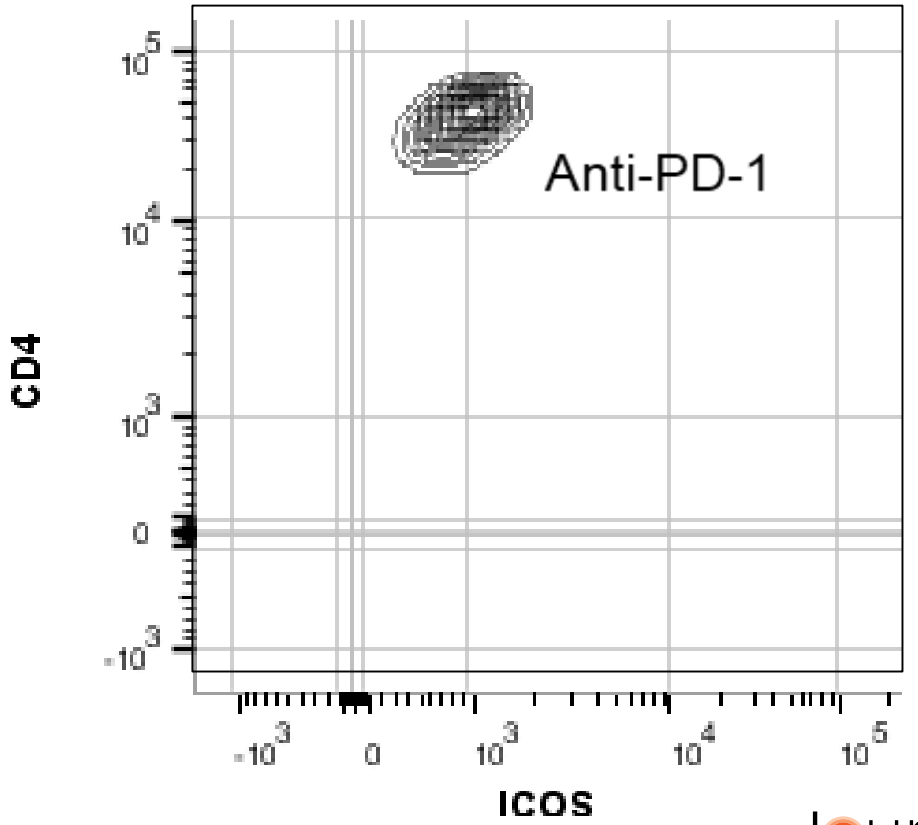


Data cut-off as of December 18, 2018

≥30% target lesion reduction

PD-1i Does Not Induce ICOS hi CD4 Cells

- 77 patients treated with PD-1/L1i monotherapy
- 6 confirmed responders
- 0 patients with ICOS hi CD4 cells



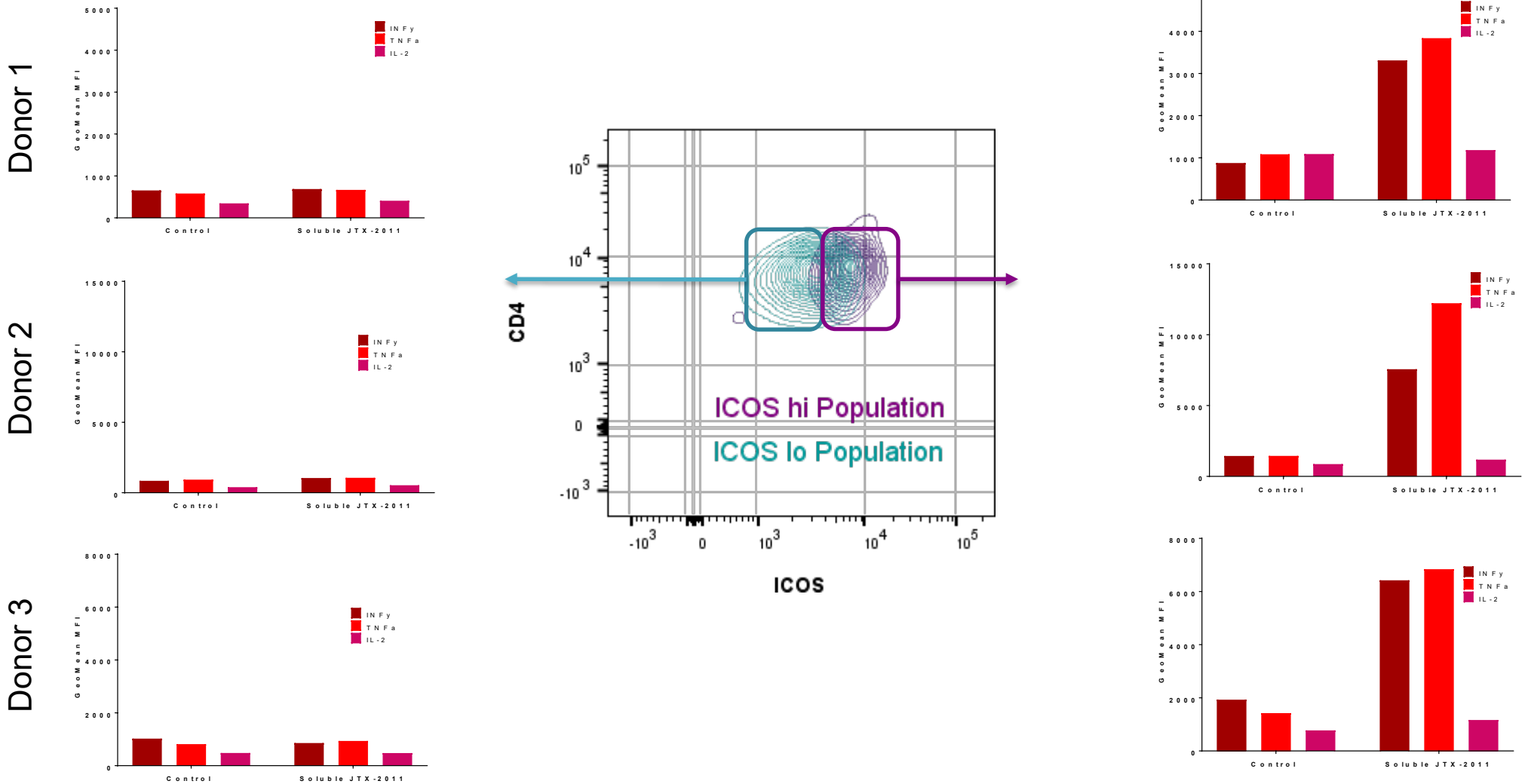
*Best response observed for target lesion, based on investigator assessments

Soluble vopratelimab Induces *ex vivo* Cytokine Responses **only** in ICOS hi CD4 T Cells

Consistent with vopratelimab need for primed CD4 T effectors

ICOS lo CD4 Cells

ICOS hi CD4 Cells

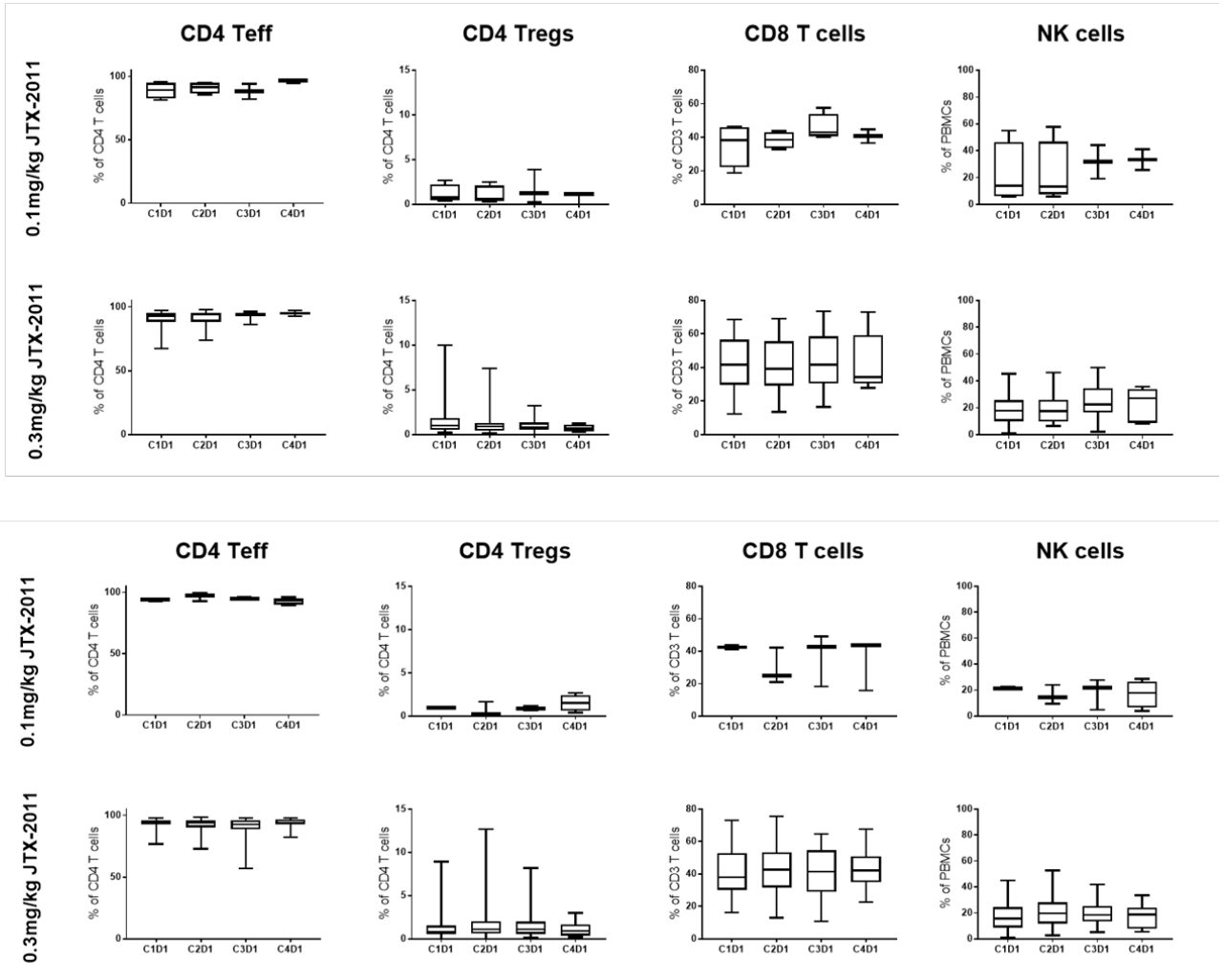


C. Harvey, SITC 2018

No Significant Changes in Peripheral Blood Immune Cell Subsets over 3 Cycles

Vopratelimab Monotherapy

Vopratelimab + Nivolumab Combination Therapy



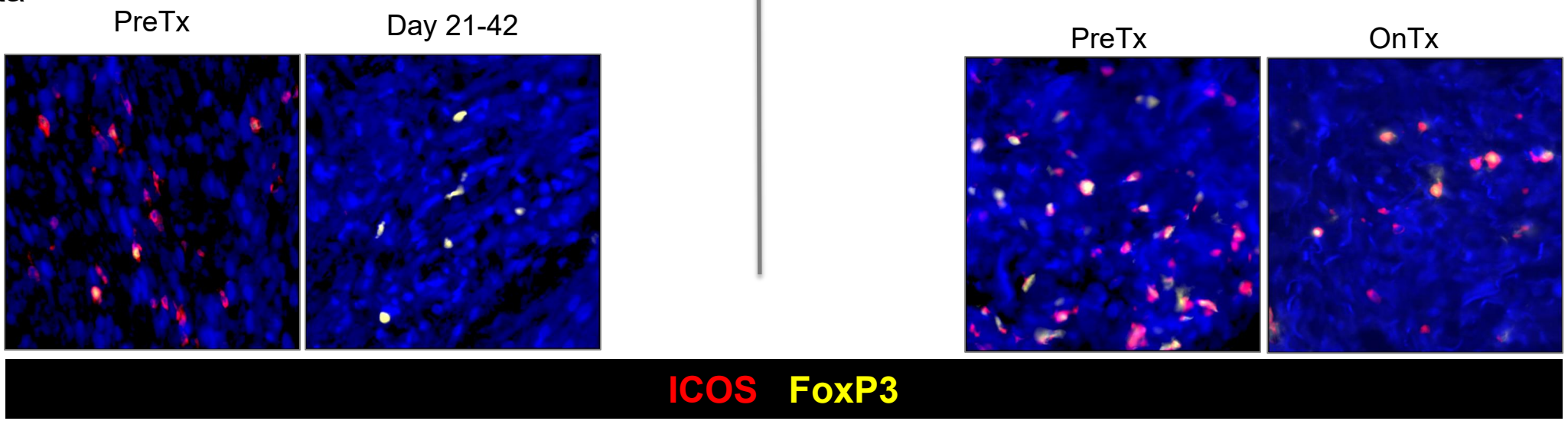
C. Harvey, SITC 2018

No Significant Change in Cycle 2 in Intra-tumoral Immune Cell Subsets, Including Tregs

ICOS staining is significantly reduced on intra-tumoral Treg, CD4eff, and CD8 cells with sustained exposure

- Loss of ICOS observed in 5/8 monotherapy and combination subjects, including 1 confirmed PR*
- All had trough concentrations ≥200 ng/mL (200- 1400)
- Sustained target saturation in all with available data

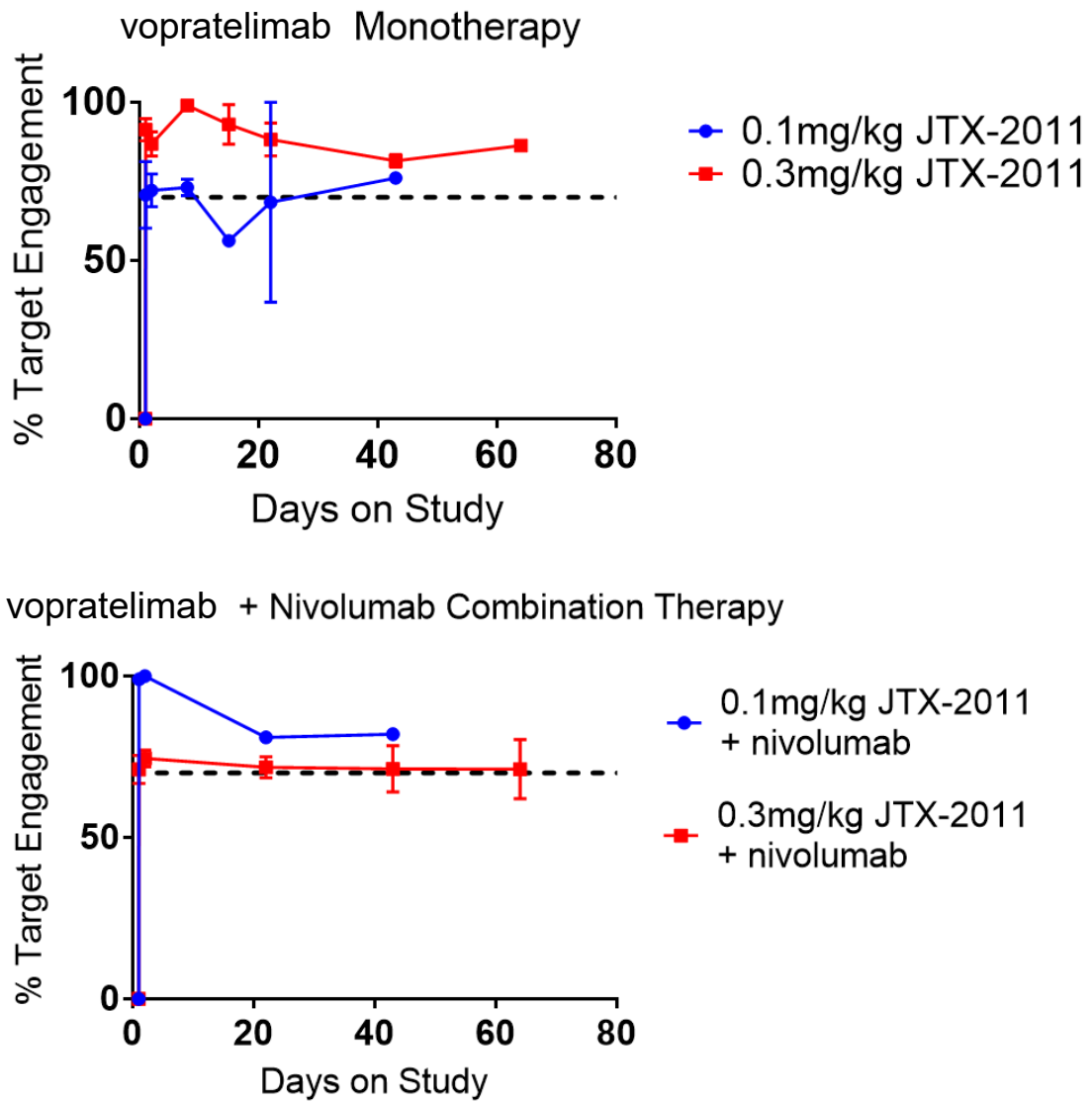
- Persistent ICOS observed in 3/8 subjects (no responders*)
- All had trough concentrations < 100 ng/mL (<20-<100)
- Target engagement data unavailable



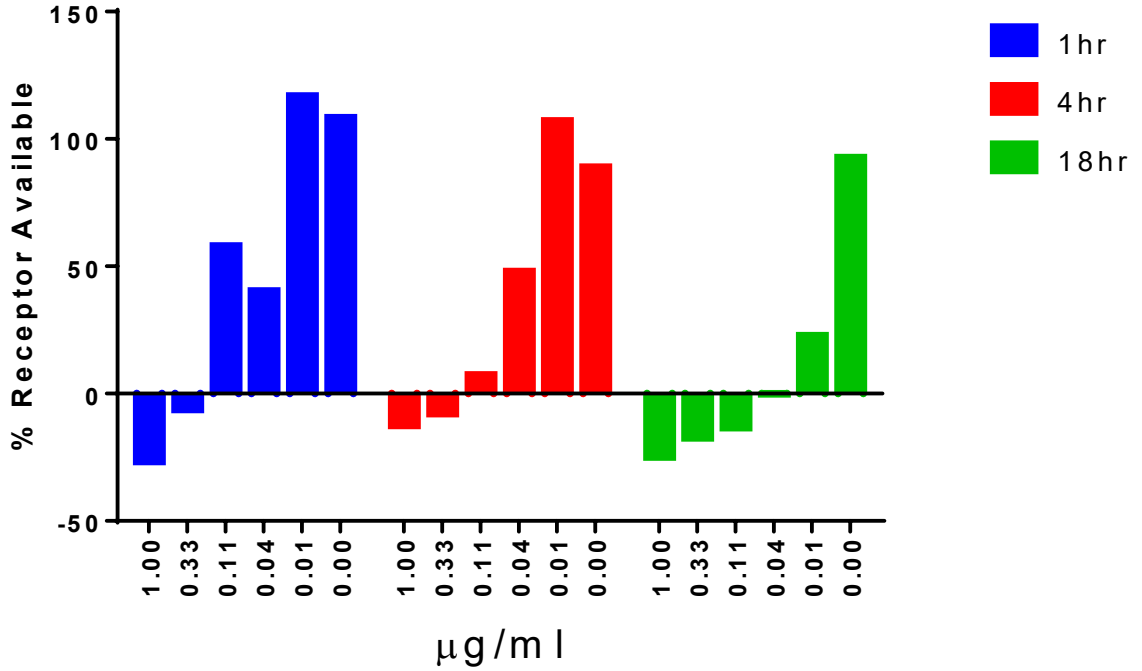
Is on treatment loss of ICOS staining due to down-regulation of the receptor due to sustained signaling and internalization (negative feedback)?

*Central radiology review

ICOS on Peripheral T cells Saturated at Doses above 0.1mg/kg q3w



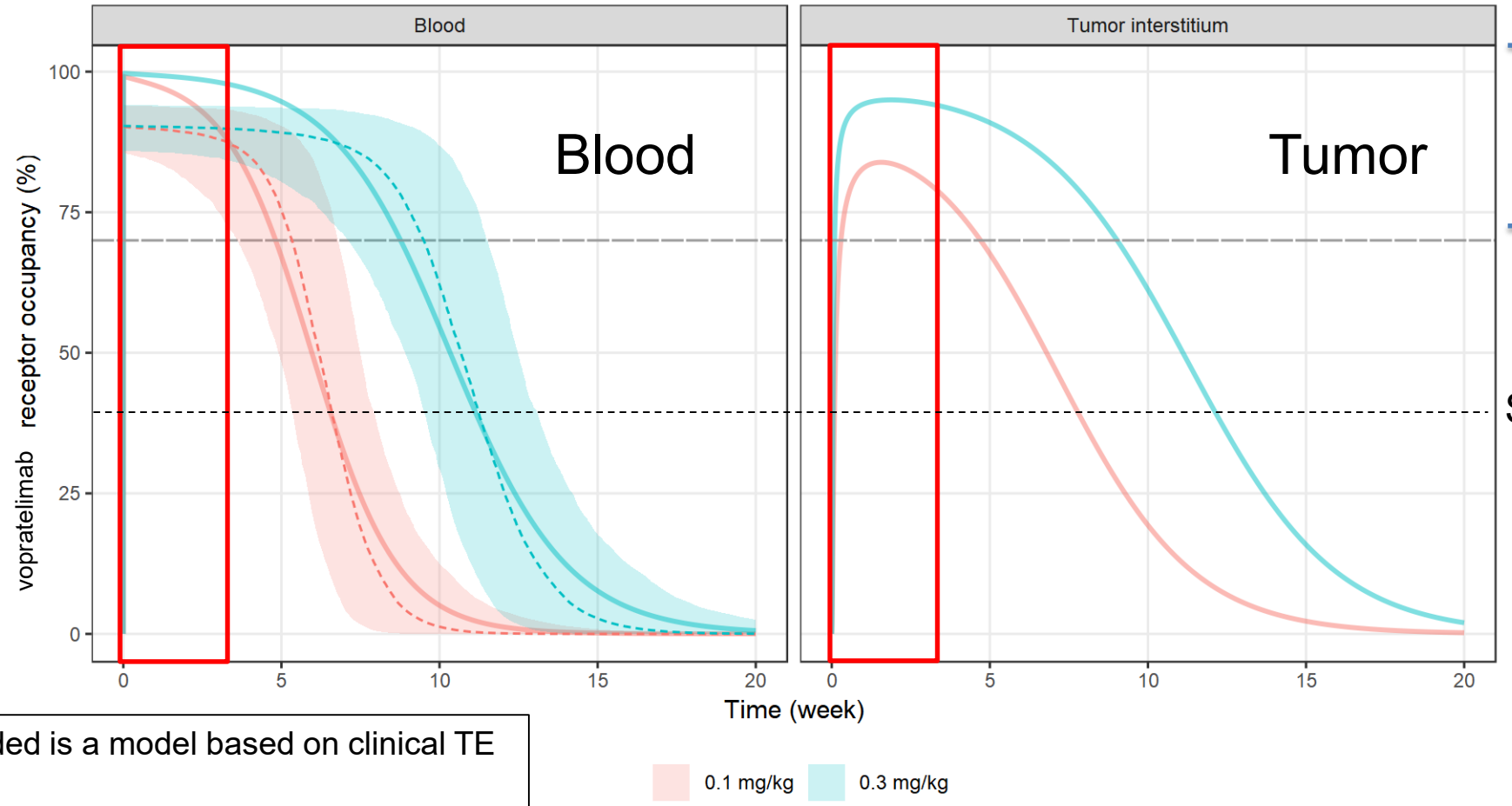
ICOS is internalized over time when bound by vopratelimab



- % available ICOS in whole blood at different concentrations of vopratelimab
- Incubated at 37 degrees for 1hr, 4hrs, or 18hrs

Target Saturation: How Long is Too Long?

Preliminary PK/PD modeling predicts prolonged saturation in both blood and tumor at 0.3 mg/kg q3w
Is a lower, less frequent dose advisable?



- Dotted/Shaded is a model based on clinical TE data
- Solid line is a model based on TE, vopra affinity, PK, and target distribution

*based on primary CD4+ cells

New Hypotheses

What have we learned from the clinic?

Preclinical Predictions

Dual MOA

- Activation and proliferation of CD4 T effector cells
  - Requires T cell priming
- Selection reduction of intra-tumoral Tregs
  - No effect on peripheral Tregs

Requirements for Efficacy

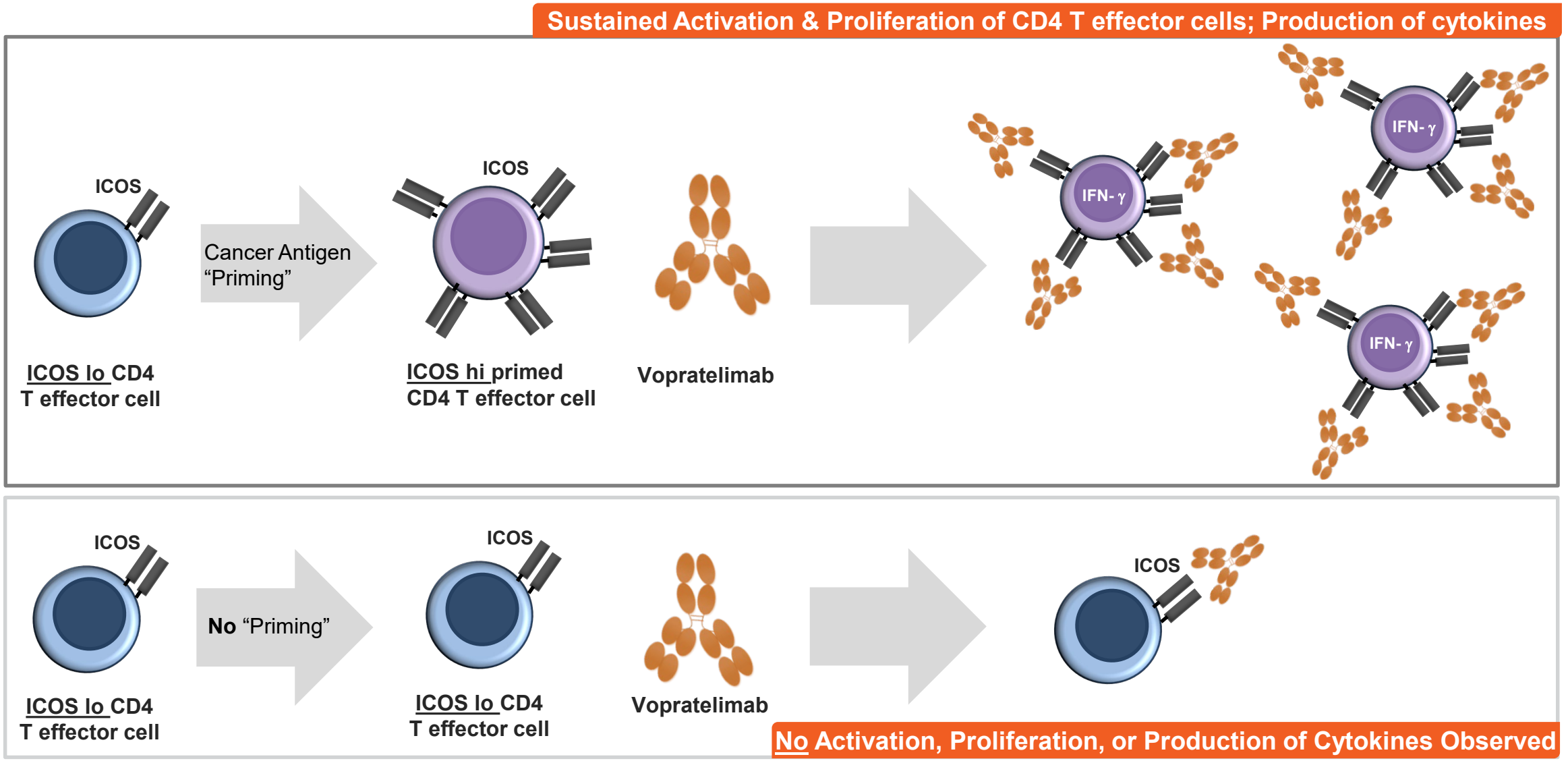
- Sustained Target Engagement
- High ICOS IHC score

Clinical Observations

MOA

- Activation and proliferation of primed CD4 T effector cells
  - Requires Priming/presence of ICOS hi CD4 T cells
- No apparent reduction of intra-tumoral Tregs to date
  - No effect on peripheral immune cell subsets
- Continuous Target Engagement may be too much stimulation
- ICOS IHC score not predictive of efficacy
  - High ICOS score may reflect high numbers of Tregs
  - ICOS IHC does not discriminate between ICOS lo and ICOS hi cells
- A better predictive biomarker is needed

Evolving Vopratelimab MoA Based on Reverse Translational Analyses of Clinical Data



New Clinical Trial Designs

Vopratelimab:
Reverse Translational Work Leads to Two Development Paths

New hypothesis: vopra will result in expansion, activation, and proliferation of primed ICOS hi CD4 T effectors

CTLA-4i Combination

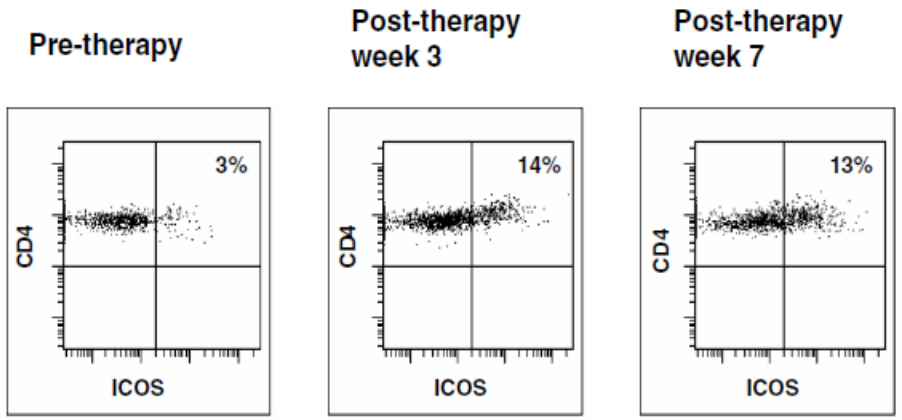
Prioritize combination agents that induce ICOS hi CD4 cells

Two Development Paths

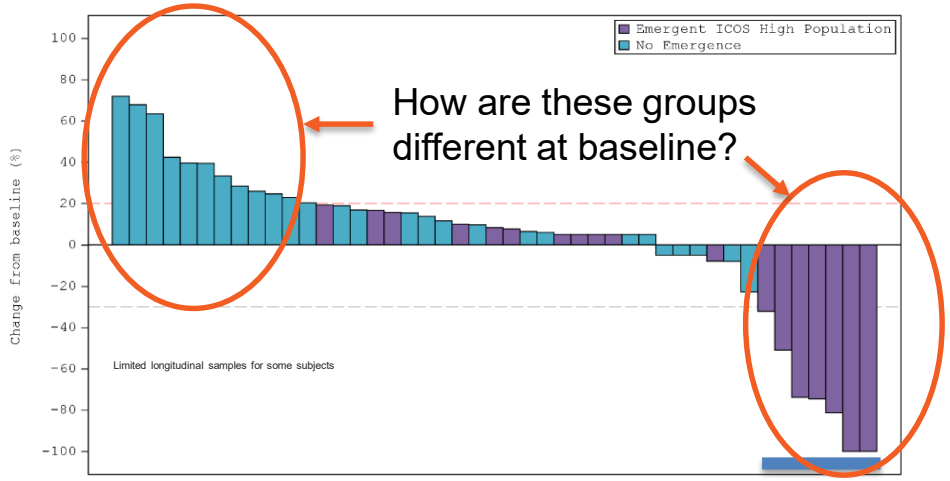
Predictive Biomarker

Identify baseline characteristics to predict which patients have pre-existing ICOS hi CD4 cells

Induction of ICOS by Ipilimumab



Carthon et al, Clin Can Res (2010)



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