ICONIC: Biologic and clinical activity of first in class ICOS agonist antibody JTX-2011 +/- nivolumab (nivo) in patients with advanced cancers

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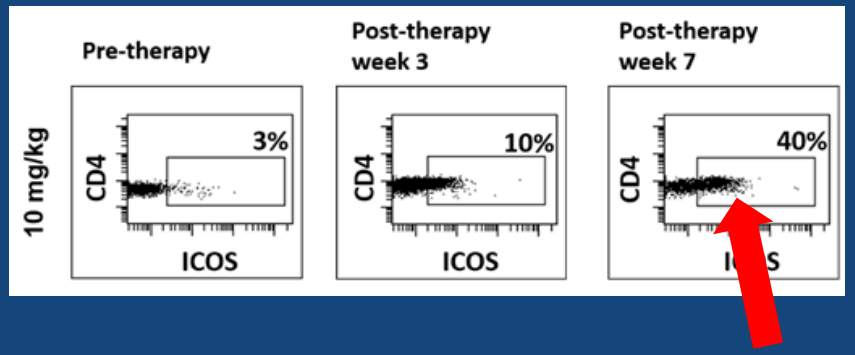
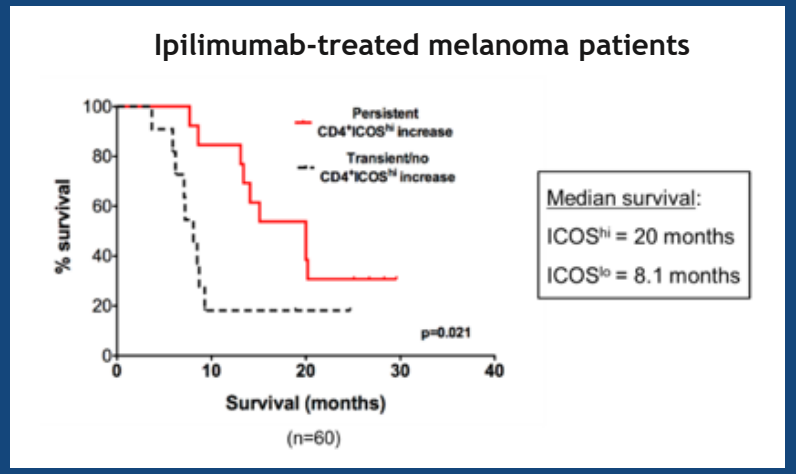
Why Choose ICOS as a Target?

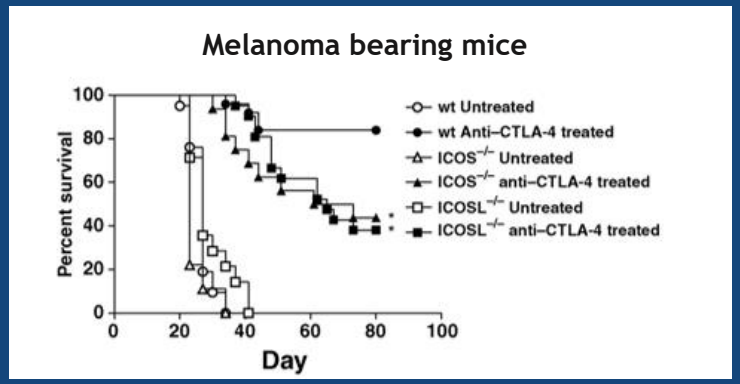
- ICOS: Inducible CO-Stimulator of T cells
  - Expression on T cells associated with favorable outcome with ipilimumab
  - Preclinical data show functional importance of host ICOS
  - Upregulated by variety of agents – ideal combination target



- ICOS induced on peripheral CD4 (and CD8) T cells post-ipilimumab therapy



- Persistent upregulation on CD4 T cells associated with improved clinical outcomes



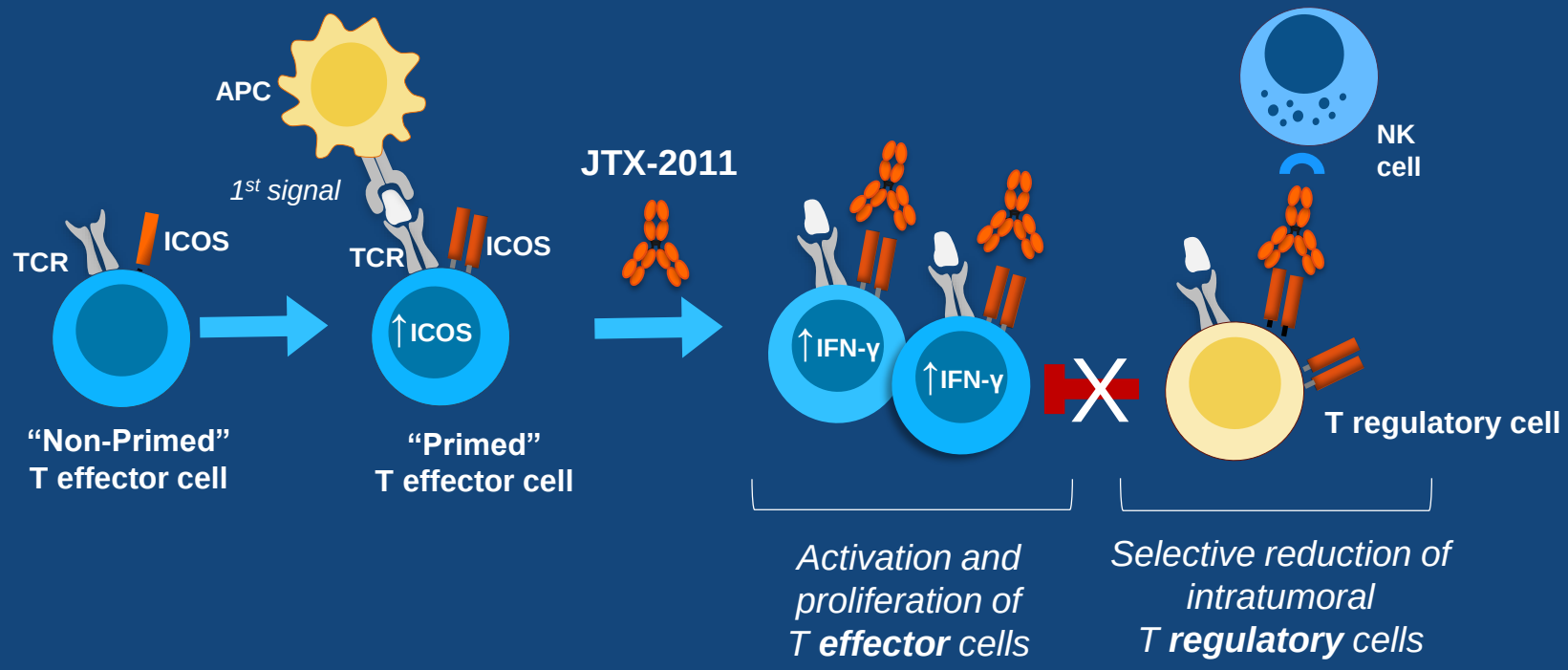
- Impaired tumor rejection In $ICOS^{-/-}$ and $ICOSL^{-/-}$ mice treated with anti-CTLA-4 therapy

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

Fu et al. Cancer Res (2011)

JTX-2011: Preclinical Rationale for ICOS Agonist IgG1 Antibody

Shifting the balance of T cells towards antitumor activity



- Monotherapy efficacy in mouse tumors with high % ICOS expressing immune cells
- Enhanced efficacy in combination with PD-1 and CTLA-4 inhibitors
- Period of sustained target engagement required for preclinical antitumor efficacy
- Tumor-centric pharmacology with no reduction in peripheral immune cell subsets in mice

ICONIC Phase 1 and 2 Objectives

Phase 1

Primary: JTX-2011 alone and in combination with nivo

- Safety and tolerability
- MTD and RP2D

Secondary

- PK/PD for JTX-2011
- PK for nivo

Exploratory: JTX-2011 alone and in combination with nivo

- Preliminary efficacy by RECIST 1.1 (CT scans q9w)*
- Peripheral blood
  - Gene signatures
  - Immune cell subsets
- Paired tumor biopsies (PK/PD cohorts)
  - Gene signatures
  - Immune cell subsets
- Putative predictive biomarkers of response

Phase 2

Primary: JTX-2011 alone and in combination with nivo

- Preliminary efficacy by RECIST 1.1 (CT scans q9w)*
- Confirm safety and tolerability
- Confirm MTD and RP2D

Secondary

- Confirm PK/PD for JTX-2011
- Confirm PK for nivo

Exploratory: JTX-2011 alone and in combination with nivo

- Peripheral blood
  - Gene signatures
  - Immune cell subsets
- Putative predictive biomarkers of response
  - Archival and fresh pre-treatment biopsies
    - ICOS expression
    - Gene signatures

* Investigator assessed; to be confirmed by central review

ICONIC Study Design

Phase 1

All solid tumors, no enrichment for ICOS expression

JTX-2011
0.003-1.0 mg/kg IV q3w

- Dose Escalation
- PK/PD Expansions

JTX-2011
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 where PK/PD predicts anticipated clinically effective dose

Phase 2

Enriched for pts with high ICOS expression

JTX-2011
0.3 mg/kg IV q3w

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

JTX-2011
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

ICONIC Patient Demographics

	JTX-2011		JTX-2011 + nivo	
Parameter	Phase 1	Phase 2	Phase 1	Phase 2
n	40	29	31	87
Median age, yrs (Range)	63 (24, 78)	67 (31, 81)	56 (29, 80)	62 (37, 85)
ECOG 0/1, n (%)/n (%)	8 (20%) / 32 (80%)	2 (7%) / 27 (93%)	8 (26%) / 22 (71%)*	25 (29%) / 60 (71%)*
Tumor types	8-TNBC,4-Colon,3-Melanoma,3-Oropharynx, 2-Sarcoma,2-Prostate, 2-Renal,2-Endometrial, 2-Unknown Origin, 12-Other Solid Tumors	8-Gastric, 5-NSCLC, 4-HNSCC, 12-Other Solid Tumors (TNBC, Ovarian, Pancreatic, Neuroendocrine, Rectal, Melanoma, Endometrial, Bladder, Unknown, Sublingual)	5-TNBC,4-Colon, 3-Gastric,2-Sarcoma, 2-Endometrial,2-Breast, other, 2-Rectal,2-Cervix,2-Esophageal (squam), 7- Other Solid Tumors	29-Gastric, 23-HNSCC, 19-TNBC, 13-NSCLC, 2-Melanoma, 1-Endometrial
≥3 Prior therapy for metastatic disease, n (%)	32 (80%)	21 (72%)	23 (74%)	46 (54%)#

Safety population: all subjects who received at least one dose of JTX-2011; *ECOG status not available on all subjects; #Prior therapy data not available on all subjects

ICONIC Phase 2 Characteristics

Tumor type	HNSCC		NSCLC		TNBC	Gastric		Other Solid Tumors	
	JTX-2011	JTX-2011 + nivo	JTX-2011	JTX-2011 + nivo	JTX-2011 + nivo	JTX-2011	JTX-2011 + nivo	JTX-2011	JTX-2011 + nivo
n*	4	23	5	13	19	8	29	12	3
Prior therapy for metastatic disease, n#(%)	n=4	n=22	n=5	n=12	n=19	n=8	n=29	n=11	n=3
≤1	0	2 (9%)	0	1 (8%)	3 (16%)	2 (25%)	6 (21%)	0	0
2	0	7 (32%)	2 (40%)	3 (25%)	5 (26%)	1 (13%)	11 (38%)	2 (18%)	1 (33%)
3	1 (25%)	7 (32%)	3 (60%)	3 (25%)	3 (16%)	5 (63%)	4 (14%)	3 (27%)	0
≥4	3 (75%)	6 (27%)	0	5 (42%)	8 (42%)	0	8 (28%)	6 (55%)	2 (67%)
Prior IO, n# (%)	4 (100%)	22 (100%)	5 (100%)	12 (100%)	1 (5%)	1 (13%)	6 (21%)	7 (64%)	3 (100%)
Prior IO Refractory, n (%)	2 (50%)	12 (55%)	2 (40%)	1 (8%)	1 (5%)	0	1 (3%)	2 (18%)	1 (33%)
Brain mets, n* (%)	1 (25%)	2 (9%)	0	3 (23%)	3 (16%)	0	2 (7%)	0	1 (33%)
Liver mets, n* (%)	1 (25%)	5 (22%)	1 (20%)	4 (31%)	10 (53%)	6 (75%)	18 (62%)	6 (50%)	1 (33%)

*Safety population: all subjects who received at least one dose of JTX-2011
#Patients for whom prior therapy information is available

JTX-2011 is Well Tolerated Alone and Combined with nivo

Related AEs*	JTX-2011				JTX-2011 + nivo			
	Phase 1: all doses (n=40) n (%)		Phase 2 (n=29) n (%)		Phase 1 all doses (n=31) n (%)		Phase 2 (n=87) n (%)	
	All TEAEs	Grade 3/4	All TEAEs	Grade 3/4	All TEAEs	Grade 3/4	All TEAEs	Grade 3/4
Any related TEAE	**23 (58)**	**7 (18)**	**19 (66)**	**3 (10)**	**22 (71)**	**3 (10)**	**63 (72)**	**8 (9)**
Fatigue	3 (8)	0	6 (21)	0	5 (16)	1 (3)	17 (20)	0
Nausea	5 (13)	0	1 (3)	0	8 (26)	0	16 (18)	0
Infusion related reaction	3 (8)	0	4 (14)	1 (3)	9 (29)	0	12 (14)	0
Decreased appetite	4 (10)	0	2 (7)	0	2 (7)	0	11 (13)	0
Chills	4 (10)	0	0	0	1 (3)	0	8 (9)	0
Pyrexia	4 (10)	0	0	0	0	0	8 (9)	0
Diarrhea	4 (10)	3 (8)	0	0	2 (7)	0	5 (6)	0
Pruritus	4 (10)	0	1 (3)	0	1 (3)	0	4 (5)	0
Vomiting	1 (3)	0	0	0	2 (7)	0	6 (7)	0
AST increased	2 (5)	1 (3)	1 (3)	1 (3)	1 (3)	0	2 (2)	1 (1)
Anemia	3 (8)	3 (8)	2 (7)	0	0	0	1 (1)	0
Hypophosphatemia	0	0	0	0	0	0	2 (2)	2 (2)
Hypoxia	0	0	0	0	0	0	2 (2)	2 (2)

- DLTs on mechanism at 1.0 mg/kg JTX-2011 alone (Grade 3 AST/ALT, Grade 3 pleural effusion)
- 2 possibly related Grade 5 AEs with JTX-2011 + nivo: increased bilirubin, encephalopathy

*all related TEAEs experienced by ≥ 5% of pts or Gr 3/4 events experienced by > 1 pt listed in order of decreasing frequency of Total related AEs

JTX-2011 Pharmacokinetics and Pharmacodynamics

Phase 1

- **RP2D 0.3 mg/kg mono and combo based on:**
  - Safety
  - Sustained Target Engagement in peripheral blood through Cycle 1
- Dose dependent increase in IFN-gamma with JTX-2011 at 1-6 hours after first dose
- No significant impact on peripheral immune cell subsets for JTX-2011 or JTX-2011 + nivo
- No impact of nivo on JTX-2011 PK

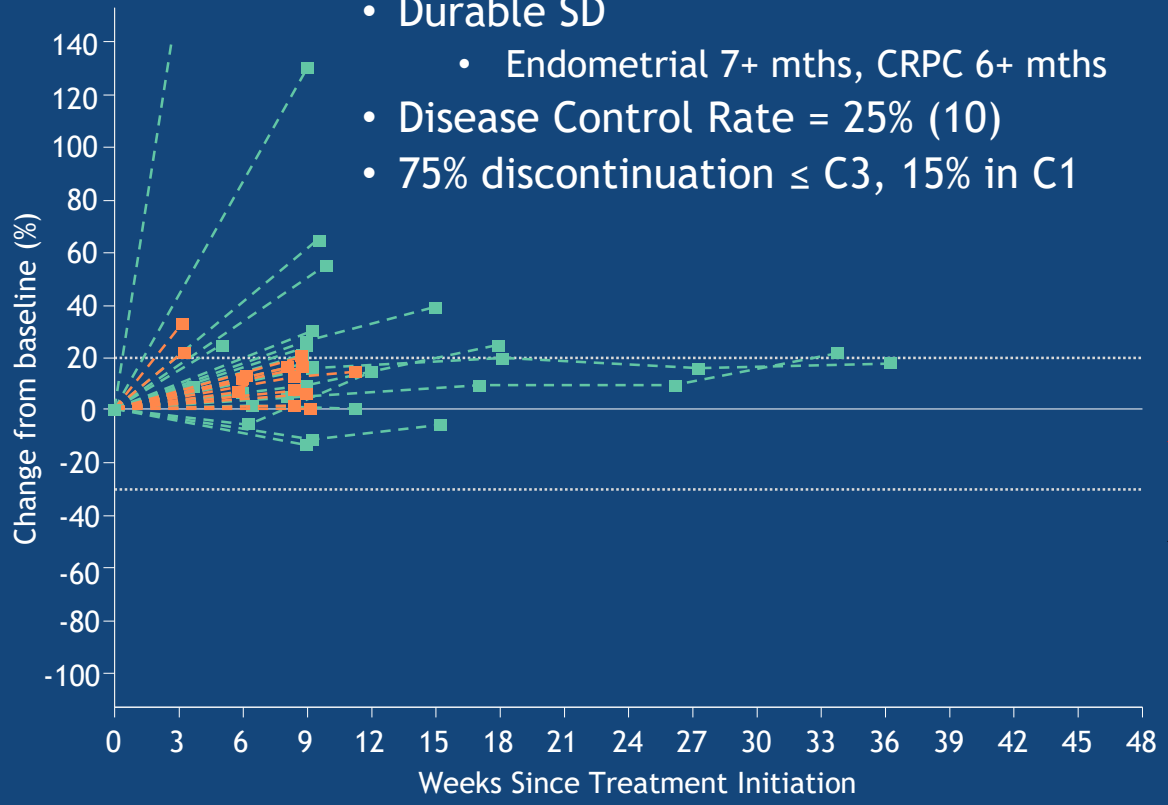
Phase 2

- **RP2D 0.3 mg/kg mono and combo confirmed:**
  - Sustained Target Engagement beyond Cycle 1
- No significant change in IFN-gamma after first dose with JTX-2011 or JTX-2011 + nivo
- No significant impact on peripheral immune cell subsets for JTX-2011 or JTX-2011 + nivo
- No impact of nivo on JTX-2011 PK
- Nivo PK: Cmin (mean)
  - C1D15 = 18.3 mcg/mL
  - C1D22/C2D1 = 14.6 mcg/mL
  - C5D1 = 30.1 mcg/mL

JTX-2011 Monotherapy: Clinical Activity

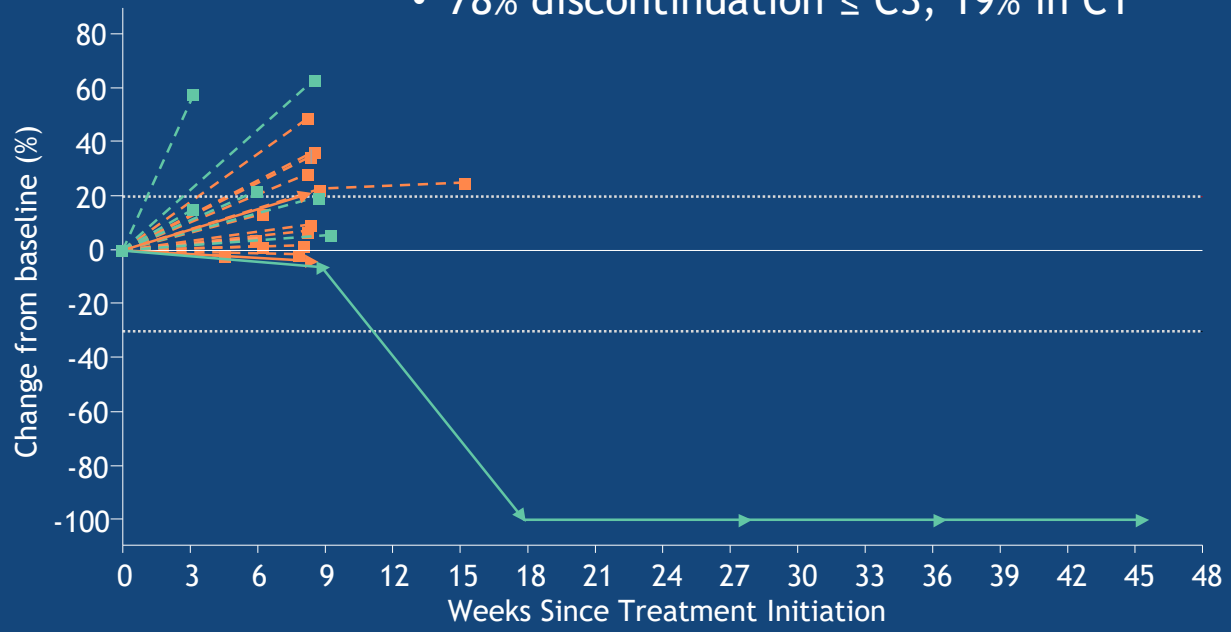
Phase 1 (n=40*)

- Durable SD
  - Endometrial 7+ mths, CRPC 6+ mths
- Disease Control Rate = 25% (10)
- 75% discontinuation ≤ C3, 15% in C1



Phase 2 (n=27*)

- Ongoing RECIST PR in 1/8 gastric
  - Gastric 8.5+ mths
- Disease Control Rate = 19% (5)
- 78% discontinuation ≤ C3, 19% in C1



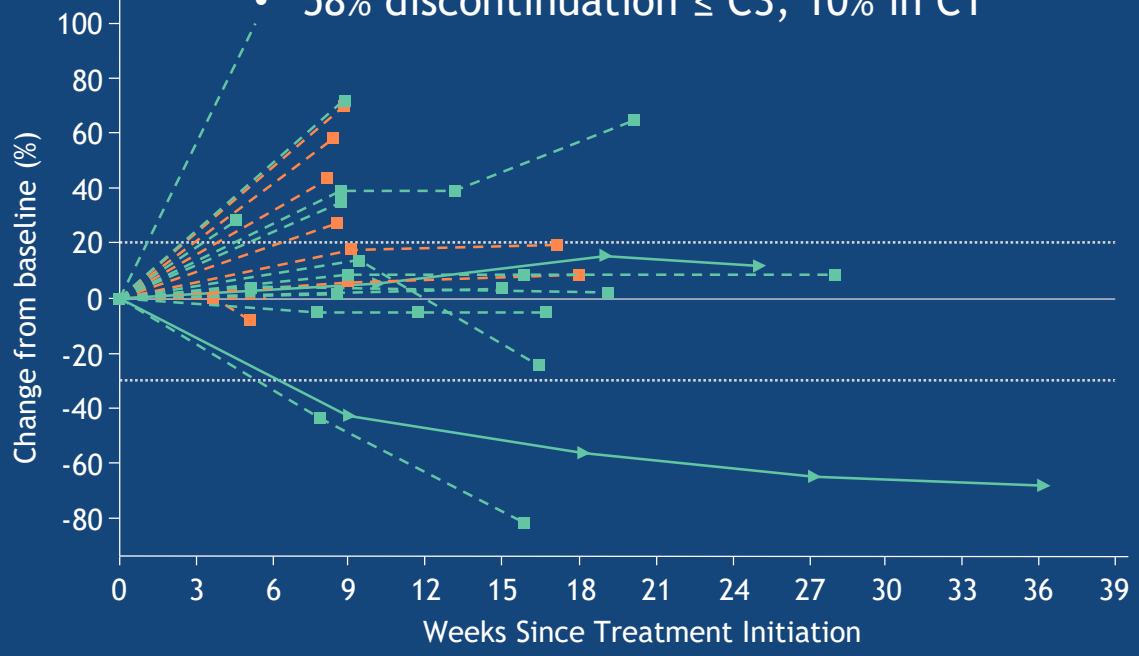
Ongoing
Off-treatment
PD-1 inhibitor naive
PD-1 inhibitor failure

*Evaluable= Dosed and ≥ 1 scan or discontinued treatment, Disease Control Rate= confirmed PR + SD ≥ 9 wks

JTX-2011 + nivo: Clinical Activity

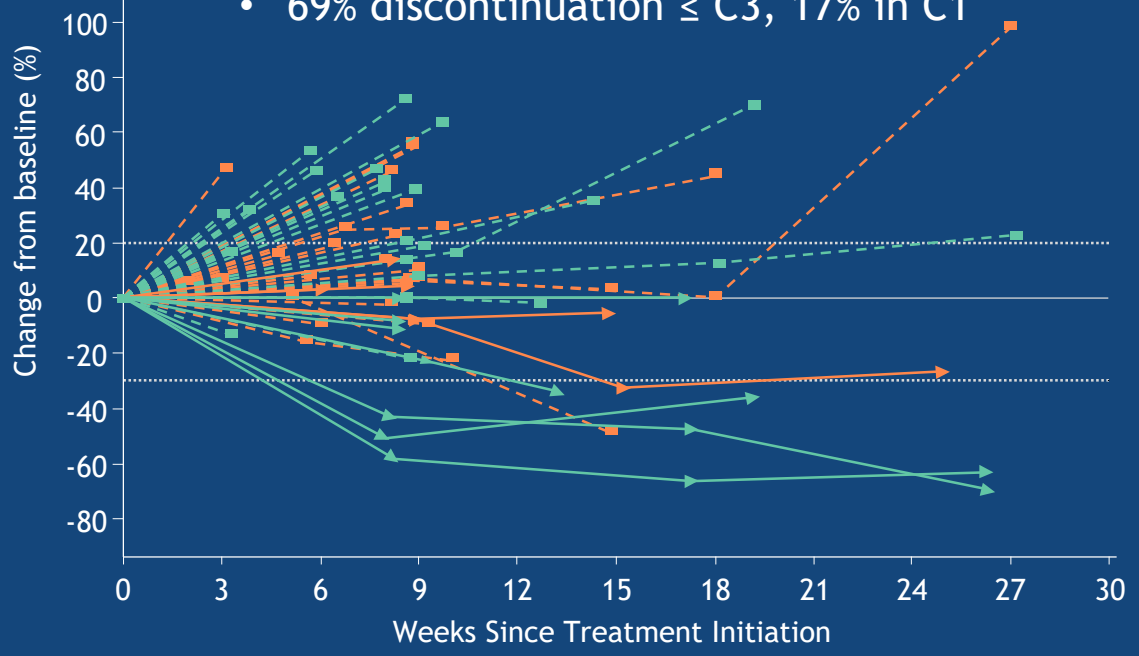
Phase 1 (n=31*)

- Ongoing RECIST PR in 1/4 gastric
  - Gastric 11+ mths (JTX-2011 0.1 mg/kg)
- Disease Control Rate = 29% (9)
- 58% discontinuation ≤ C3, 10% in C1



Phase 2 (n=75*)

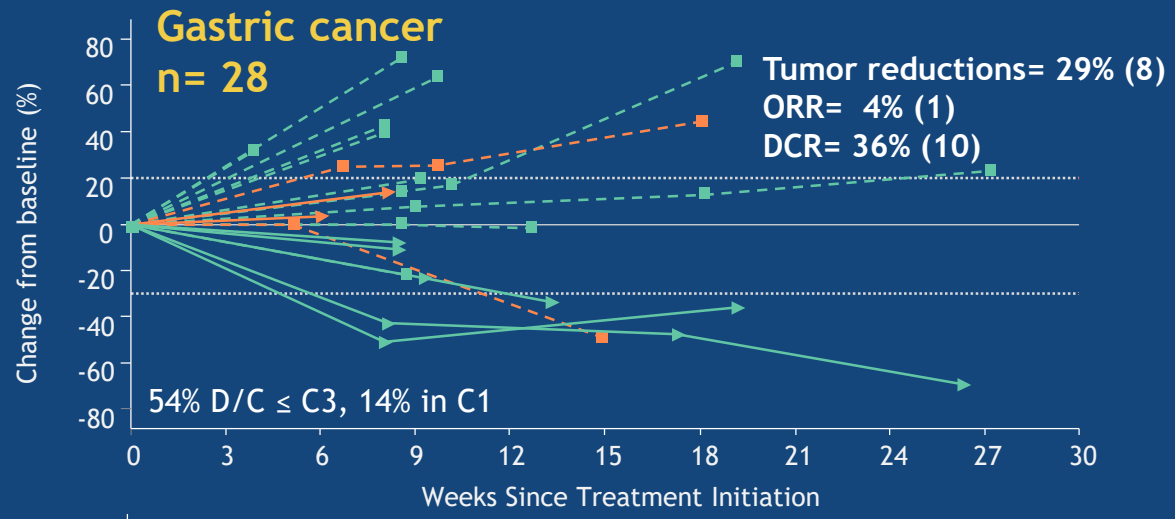
- Ongoing RECIST PRs and/or SD
  - Gastric, TNBC, NSCLC
- Disease Control Rate = 32% (24)
- 69% discontinuation ≤ C3, 17% in C1

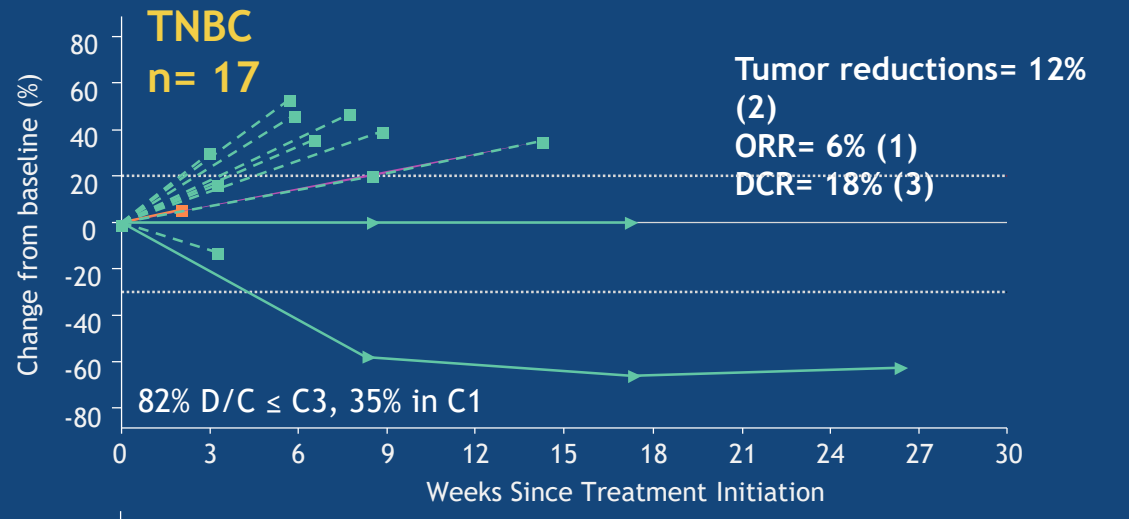


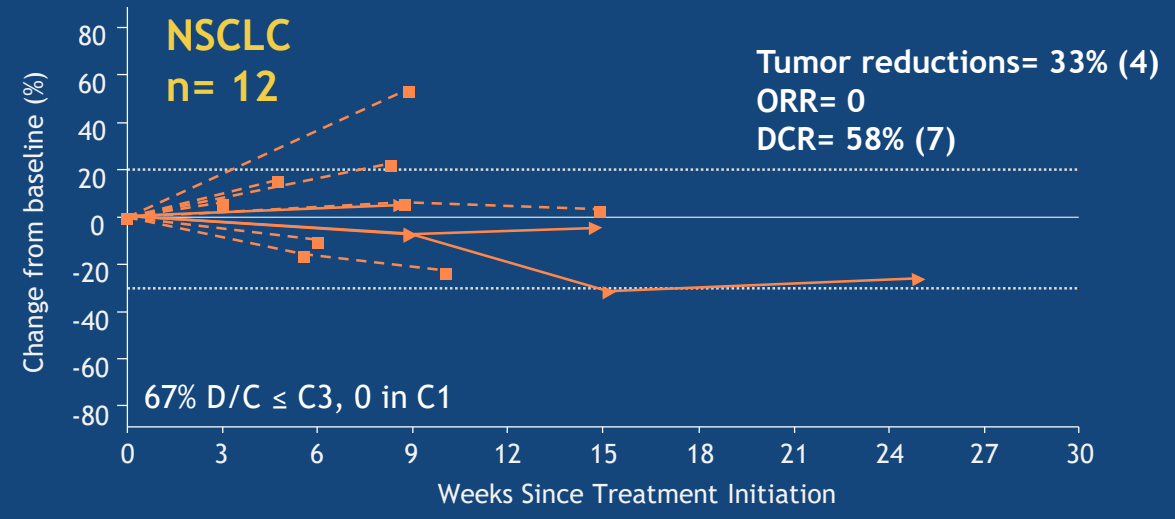
Ongoing
Off-treatment
PD-1 inhibitor naive
PD-1 inhibitor failure

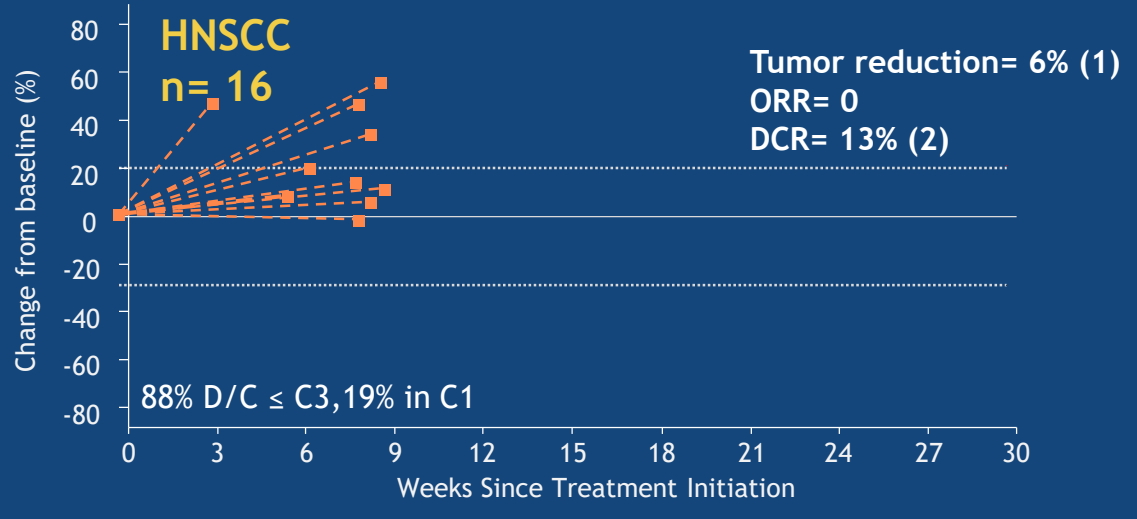
*Evaluable= Dosed and ≥ 1 scan or discontinued treatment, Disease Control Rate= confirmed PR + SD ≥ 9 wks

JTX-2011 + nivo: Ongoing Disease Control in Gastric, TNBC and NSCLC









Ongoing
Off-treatment
PD-1 inhibitor naive
PD-1 inhibitor failure

n= Dosed and ≥ 1 scan or discontinued treatment; Disease Control Rate= confirmed PR + SD ≥ 9 wks; D/C= discontinued

ICOS Expression in ICONIC Patient Tumor Samples

- Preliminary data suggests relationship between archival and fresh pre-Tx biopsy ICOS scores may vary:
  - May reflect the inducible nature of ICOS
  - May reflect differences in ICOS expression between primary tumor, nodal, and visceral metastases

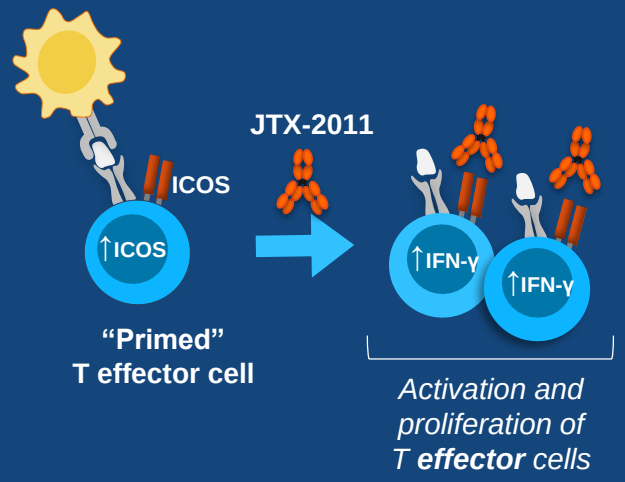
- Preliminary analysis of evaluable fresh pre-treatment biopsies:
  - Rates of disease control and tumor reductions appear higher in patients with high ICOS score

All evaluable matched archival and fresh tumor biopsies (Phase 1 and Phase 2)	n (%)
# matched pairs archival and fresh	58
# of samples that do not change	33 (57%)
# of archival ICOS low to fresh ICOS high	16 (28%)
# of archival ICOS high to fresh ICOS low	9 (15%)

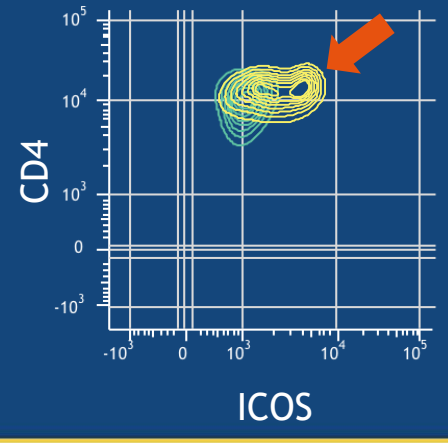
Preliminary efficacy measure	All evaluable subjects with fresh tumor biopsies		
	All	ICOS High	ICOS Low
n	67	45	22
Response (n)	1	1	0
Disease control (n)	14	11	3
Tumor reductions (n)	9	7	2

ICOS Expression in ICONIC Patient Peripheral Blood Samples

Tumor Reductions Associated with Emergence of ICOS^{hi} CD4+ T cell Population



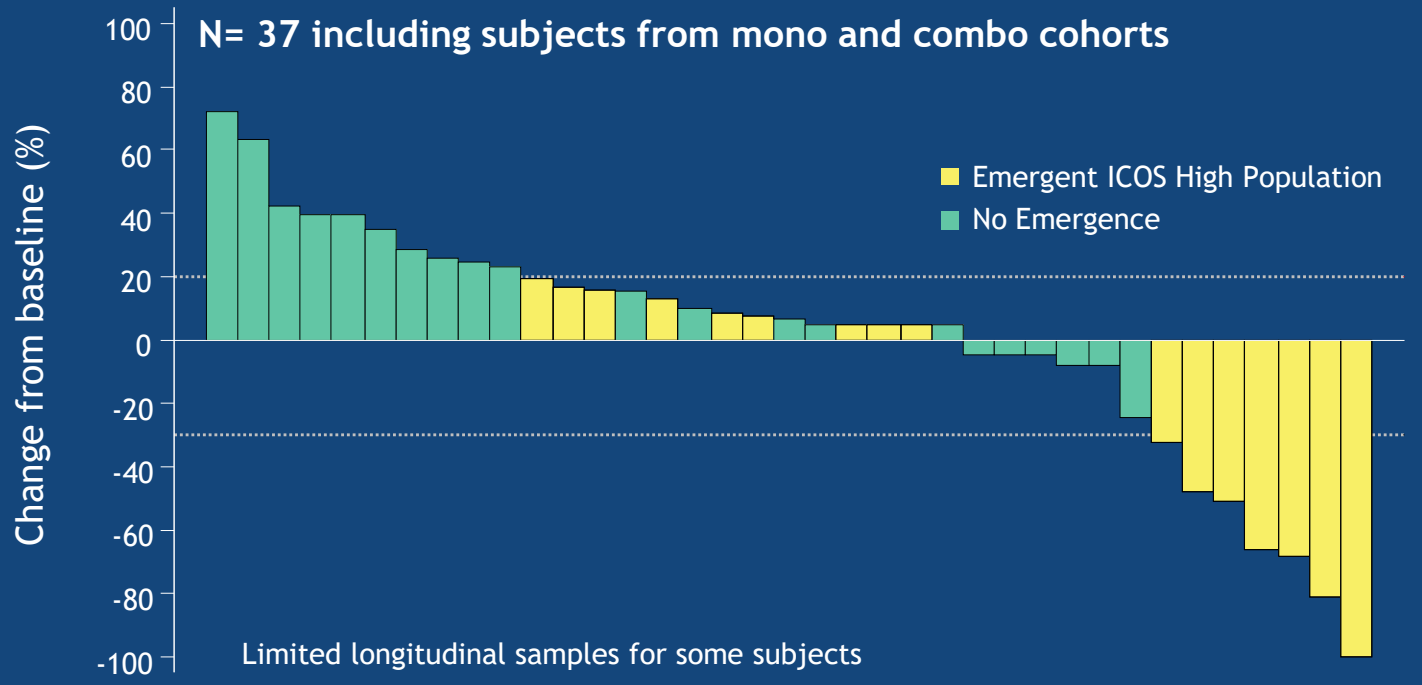
ICOS expression assessed in peripheral blood



Blood samples collected at multiple timepoints

Emergence of ICOS^{hi} CD4+ T cell population

- Observed in 7/7 subjects with target PR*
- Not observed in 10/10 subjects with PD*



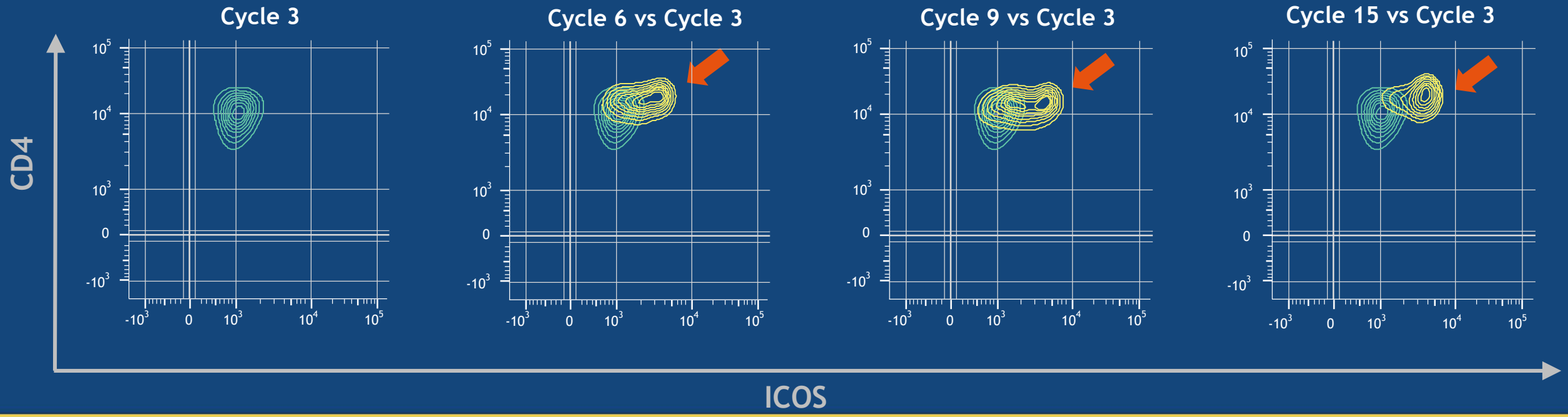
*Best response observed for target lesion

JTX-2011 Monotherapy RECIST PR in Gastric Cancer

Tumor reduction associated with emergence of ICOS^{hi} T cell population

- 51yo female diagnosed with advanced gastric cancer June 2016
- 3 prior lines of therapy, IO naïve
- JTX-2011 therapy began May 2017; Durable RECIST PR 8.5+ mths (ongoing)

Emergence of peripheral ICOS^{hi} CD4 T cell population

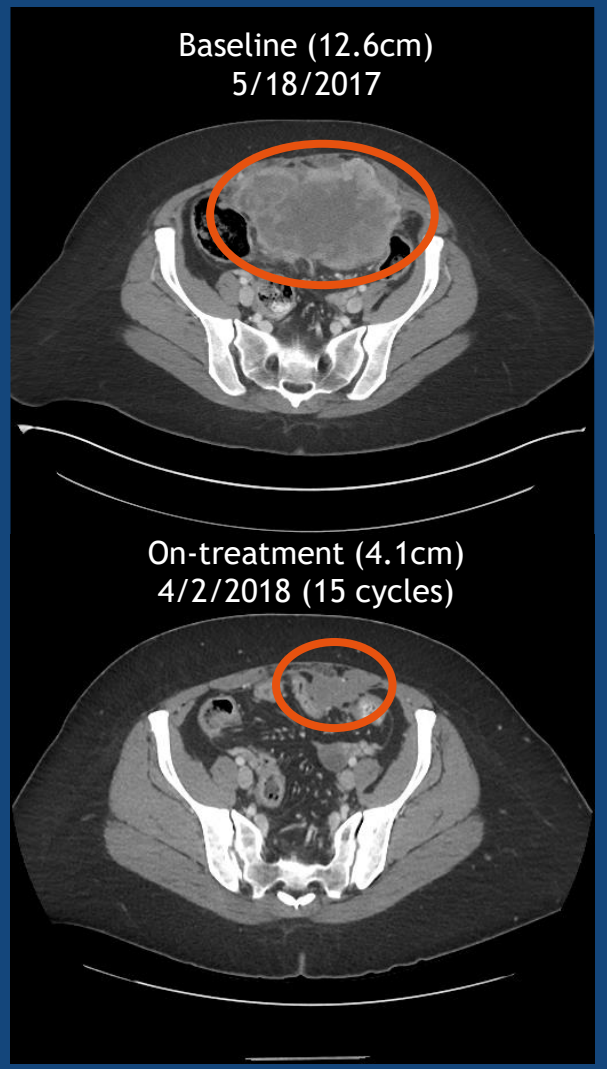


Data cut-off April 4, 2018

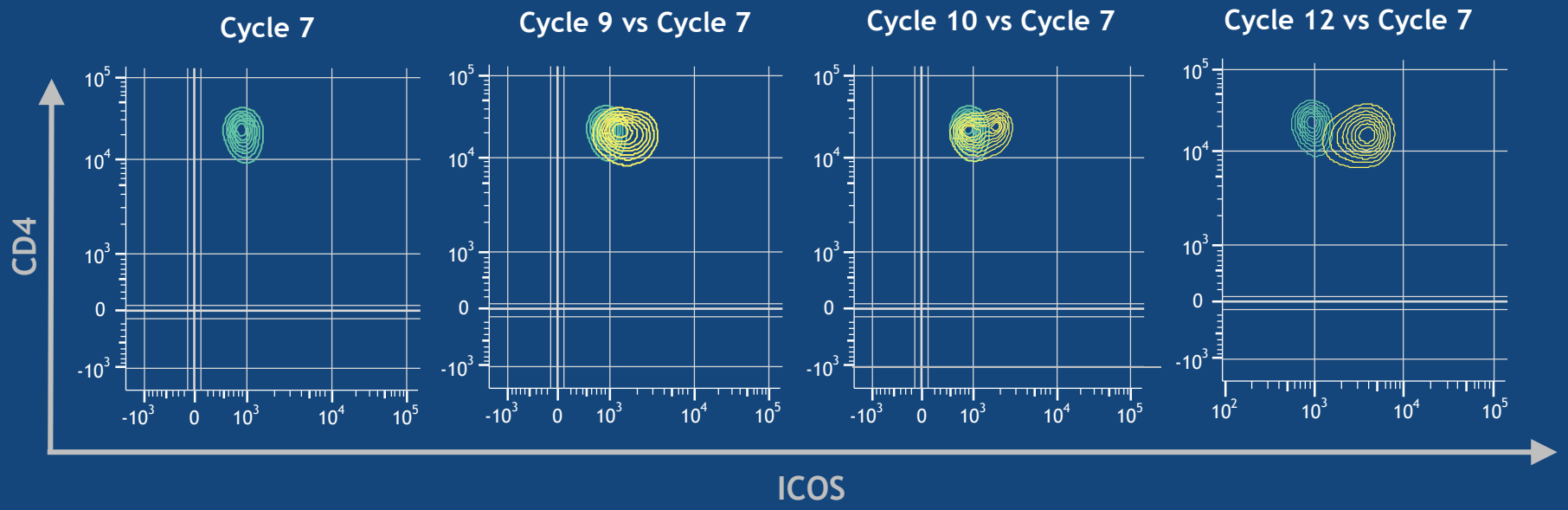
JTX-2011+ nivo RECIST PR in Gastric Cancer

Tumor reduction associated with emergence of ICOS^{hi} T cell population

- 43yo female diagnosed with MSS gastric adenocarcinoma in Dec 2013
- 6 prior lines of therapy, IO naive
- JTX-2011 therapy (0.1mg/kg) + nivo (240mg q3w) began May 2017; Durable RECIST PR 11+ mths (ongoing)
- ICOS target saturation sustained over 21-day dosing cycle



Emergence of peripheral ICOS^{hi} CD4+ T cell population



Conclusions

- Safety and tolerability demonstrated in heavily pre-treated patients
  - JTX-2011 0.3 mg/kg well tolerated as monotherapy and with nivo 240 mg q3w
- RECIST partial responses and stable disease in advanced cancers
  - Gastric cancer- mono and combo PRs
  - TNBC- combo PR
  - NSCLC- combo stable disease and tumor reductions in PD-1 inhibitor failures
- Potential on-mechanism ICOS biomarker identified
  - Emergence of $ICOS^{hi}$ CD4 T-cell population, which appears to associate with antitumor activity
- Ongoing clinical trial includes a planned combination with ipilimumab

The ICONIC investigators would like to thank:

All patients and their families

The clinical study teams and participating centers

Jounce Therapeutics