Improved Progression-Free and Overall Survival (PFS/OS) in Patients (pts) with Emergence of JTX-2011 (vopratelimab) Associated Biomarker (ICOS high CD4 T cells) on the ICONIC Trial

ABSTRACT# CT189

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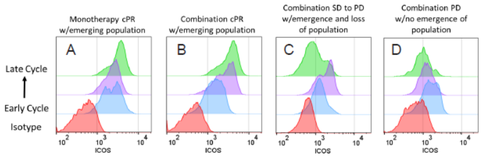
ABSTRACT

Background: ICOS is a costimulatory molecule upregulated on activated T cells. JTX-2011 (vopratelimab) is an ICOS agonist antibody intended to stimulate primed CD4 T effector cells. Vopratelimab was assessed in pts with advanced solid tumors as monotherapy (mono) and combination (combo) with nivolumab (nivo) in the Phase 1/2 ICONIC trial (NCT02904226). Peripheral T cell phenotyping in ICONIC demonstrated emergence of an ICOS high (hi) subset of CD4 T cells associated with tumor reductions in mono and combo pts. Emergence of this peripheral ICOS hi CD4 T cell population is associated with best percent change in target lesion. PD-1/L1 inhibitor monotherapy does not induce this T cell population.

Methods: Ad hoc flow cytometry phenotyping on PBMCs from a subset of pts with evaluable samples (n=50) was initiated retrospectively in early 2018 in ongoing pts, then prospectively on newly enrolled pts. Clinical characteristics and outcomes were analyzed, including unadjusted p-values for post-hoc statistical analyses. Phenotyping was also done on samples from pts treated with PD-1/L1 inhibitor (PD-1/L1i) mono collected outside of ICONIC. Microsatellite instability (MSI), tumor mutation burden (TMB), and mutations to oncogenic driver genes were assessed by targeted next generation sequencing of archival tumor biopsy samples (Foundation Medicine, Cambridge, MA) or data curation from similar assay previously ordered by treating oncologist.

Results: Available samples from 50 subjects were analyzed longitudinally for the presence of a treatment emergent ICOS hi T cell population. Clinical characteristics and outcomes of the patients assessed are presented in Table 1. Emergence of ICOS hi CD4 T effector cells (all FoxP3-, subset Tbet+ Ki67+) was observed in all pts with ≥30% target lesion tumor reduction by investigator assessment on mono and combo therapy (n=7). Emergence was seen in pts with stable target lesions (n=11/23) including subsequent loss of these cells with disease progression. ICOS hi cells were not seen in ICONIC pts with target lesion increase ≥20% (n=14), or in pts treated with PD-1/L1i mono, including responders. Emergence of ICOS hi CD4 T cells appears to correlate with improved PFS and OS.

Figure 1: Emergence and Persistence of ICOS hi CD4 T Cells Correlates with Clinical Response in Subjects Treated with Vopratelimab



Emergence of a peripheral ICOShi CD4 T cell population is associated with target lesion response

See Abstract # 4053: Genetic and molecular profiling of ICOS hi CD4 T effector cells following vopratelimab (JTX-2011) treatment in subjects with solid tumors

RESULTS

Figure 2: ICOS hi CD4 T Cells Emerge Due to Vopratelimab, not an Anti-PD-1/L1

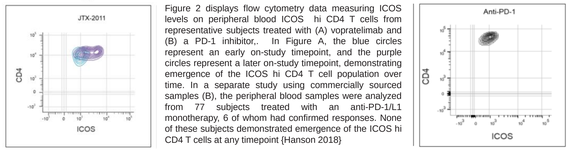
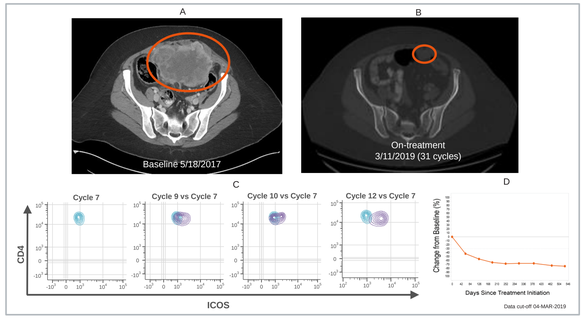


Figure 2 displays flow cytometry data measuring ICOS levels on peripheral blood ICOS hi CD4 T cells from representative subjects treated with (A) vopratelimab and (B) a PD-1 inhibitor,. In Figure A, the blue circles represent an early on-study timepoint, and the purple circles represent a later on-study timepoint, demonstrating emergence of the ICOS hi CD4 T cell population over time. In a separate study using commercially sourced samples (B), the peripheral blood samples were analyzed from 77 subjects treated with an anti-PD-1/L1 monotherapy, 6 of whom had confirmed responses. None of these subjects demonstrated emergence of the ICOS hi CD4 T cells at any timepoint {Hanson 2018}

Figure 3: Gastric Cancer Patient, 21 months+*



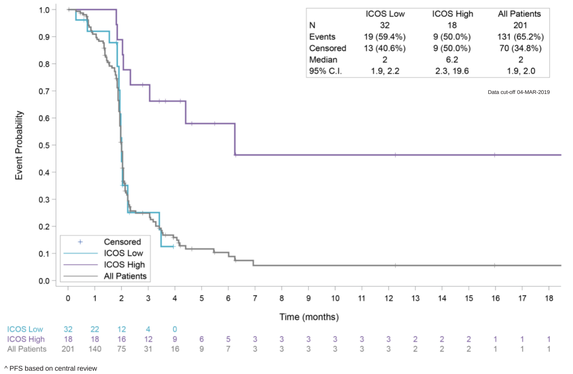
43yo female diagnosed with MSS gastric adenocarcinoma in December 2013, s/p 6 prior lines of therapy (immunotherapy naïve), prior to starting treatment with vopratelimab 0.1mg/kg + nivolumab 240mg q3 weeks in May 2017. -74% RECIST PR 21+ months as of 11-MAR-2019. ICOS hi CD4 T cell emergence noted at Cycle 9, associated with target lesion response. A) Baseline tumor measurement B) On-treatment tumor measurement 662 days later C) Flow cytometry demonstrating emergence of ICOS hi CD4 T cells D) Spider plot showing target lesion response as assessed by the site. * Treatment ongoing as of 11-MAR-2019

Table 1: Baseline Characteristics in ICONIC patients with Emergence of ICOS hi vs Persistent ICOS lo CD4 T Cells

ICONIC Patient Characteristics	ICOS hi (N=18)	ICOS lo (N=32)
Age, median yrs (range)	63.1 (42.9 – 80.0)	63.3 (31.2 – 74.3)
Sex, n (%) Male Female	 8 (44.4) 10 (55.6)	 14 (43.8) 18 (56.3)
Race, n (%) Caucasian Non-Caucasian Not Reported	 12 (66.7) 2 (11.1) 4 (22.2)	 23 (71.9) 6 (18.8) 3 (9.4)
≥3 prior therapies, n (%)	13 (72.2)	18 (56.3)
Prior immunotherapy, n (%)	6 (33.3)	15 (46.9)
Refractory to prior immunotherapy (best overall response of progressive disease), n (%)	1 (16.7)	6 (40.0)
Tumor type, n (%)	Gastric n=9 (50) NSCLC n=3 (16.7) TNBC n=2 (11.1) Other n=4 (22.2)	Gastric n=8 (25) NSCLC n=6 (18.8) TNBC n=4 (12.5) Other n=14 (43.8)
Monotherapy vs Combination with nivolumab, n (%)	Mono n=2 (11.1) Combo n=16 (88.9)	Mono n=11 (34.4) Combo n=21 (65.6)
G3-4 treatment-related adverse events, n (%)	1 (5.6)	2 (6.3)
Immune-related treatment emergent adverse events, n (%)	2 (11.1)	6 (18.8)

Data cut-off 04-MAR-2019

Figure 4: Six Month Median PFS^ for Patients with ICOS hi T Cell Emergence

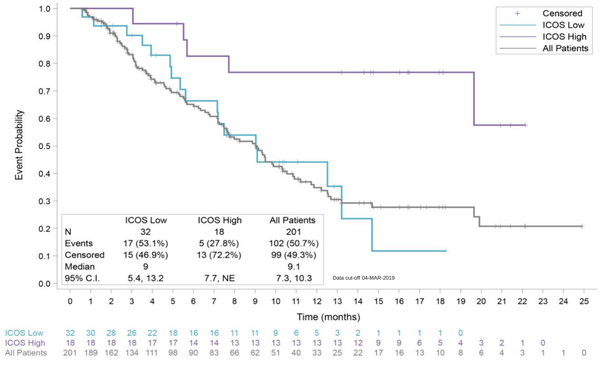


	ICOS Low	ICOS High	All Patients
N	32	18	201
Events	19 (59.4%)	9 (50.0%)	131 (65.2%)
Censored	13 (40.6%)	9 (50.0%)	70 (34.8%)
Median	2	6.2	2
95% C.I.	1.9, 2.2	2.3, 19.6	1.9, 2.0

ICOS Low	32	22	12	4	0														
ICOS High	18	18	16	12	9	6	5	3	3	3	3	3	2	2	2	1	1	1	
All Patients	201	140	75	31	16	9	7	3	3	3	3	3	2	2	2	1	1	1	

^ PFS based on central review

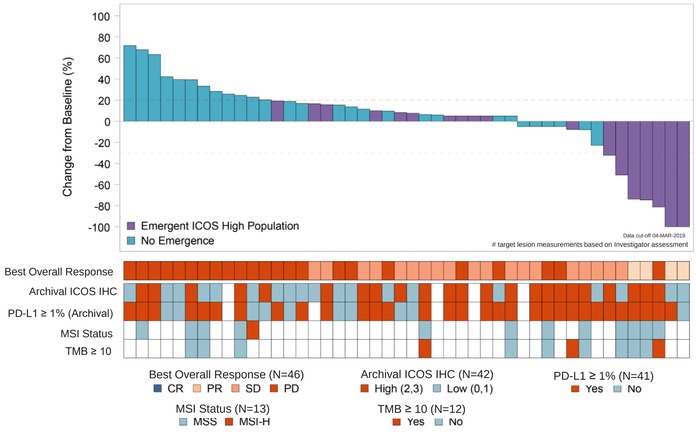
Figure 5: Median OS for Patients with ICOS hi T Cell Emergence Not Yet Reached



	ICOS Low	ICOS High	All Patients
N	32	18	201
Events	17 (53.1%)	5 (27.8%)	102 (50.7%)
Censored	15 (46.9%)	13 (72.2%)	99 (49.3%)
Median	9		9.1
95% C.I.	5.4, 13.2	7.7, NE	7.3, 10.3

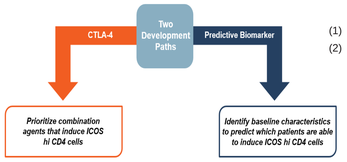
ICOS Low	32	30	28	26	22	18	16	16	11	11	9	6	5	3	2	1	1	1	1	0					
ICOS High	18	18	18	18	17	17	14	14	13	13	13	13	13	13	12	9	9	6	5	4	3	2	1	0	
All Patients	201	189	162	134	111	98	90	83	66	62	51	40	33	25	22	17	16	13	10	8	6	4	3	1	1	0

Figure 6: Target Lesion Response# is Associated with Emergence of an ICOS hi CD4 T Cell Population in the Peripheral Blood; No Apparent Trend with Common Predictive Markers



CONCLUSION

- Emergence of a distinct and persistent population of ICOS hi peripheral CD4 T cells is associated with improved survival with vopratelimab mono and combo therapy, with improved PFS (median 6.2mo for patients with ICOS hi CD4 T cells vs 2mo for both patients with only ICOS lo CD4 T cells and all patients on study, including those for whom ICOS hi T cell emergence were not analyzed) and OS (median not yet reached for patients with ICOS hi CD4 T cells vs 9mo for patients with only ICOS lo CD4 T cells and 9.3mo for all ICONIC patients)
- The emergence and persistence of ICOS hi CD4 cells is attributed to vopratelimab and not PD-1/L1 inhibitors
- Within the 50 patient subset analyzed for ICOS hi vs ICOS lo CD4 T cells, emergence of these T cells does not appear to trend with archival PD-L1 IHC, archival ICOS IHC, MSI status or TMB, suggesting the emergence of ICOS hi CD4 T cells is not associated with these markers
- Two vopratelimab development paths are planned:



(1) combo with agents that induce ICOS hi CD4 T cells;

(2) use of potential putative biomarkers predictive of emergence of this T cell population and vopratelimab response based on analysis of baseline blood and tumor samples from subjects who had emergence of ICOS hi CD4 T cells vs those who did not.

References

A. Hanson, S. M. Lacey, C. Hart, T. McClure, E. Hooper, E. G. Trehu, D. Law, and C. Harvey, *Emergence of an ICOShi CD4 T cell subset correlates with tumor reductions in subjects treated with the ICOS agonist antibody JTX-2011.* SITC Meeting Abstract #P52, 2018.

C. Harvey, A. Hanson, M. Fan, L McGrath, D. Felitsky, C. Johnson, S. Lacey, H. Hirsch, E. Hooper, T. McClure, E. Trehu, D. Law and H. Laken. *Genetic and molecular profiling of ICOS hi CD4 T cells demonstrates clonal expansion of Th1 effector cells following JTx-2011 treatment in subjects with solid tumors.* AACR Meeting Abstract #4053, 2019

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