Association of a Predictive RNA Signature (RS) With Emergence of ICOS hi CD4 T Cells and Efficacy Outcomes for the ICOS Agonist Vopratelimab (vopra) and Nivolumab (nivo) in Patients (pts) on the ICONIC Trial

ABSTRACT# 14

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ABSTRACT

Background: ICOS is a costimulatory molecule upregulated on activated T cells. Vopra is an investigational ICOS agonist antibody that results in activation and proliferation of primed CD4 T effector cells. Vopra was assessed in heavily pretreated subjects with advanced solid tumors as monotherapy or in combination with nivolumab (nivo) in the Phase 1/2 ICONIC trial (NCT02904226). Emergence of a distinct ICOS high (hi) population of peripheral CD4 T effector cells, not seen with PD-1 inhibitors alone, was associated with improved ORR, PFS and OS with vopra alone and in combination with nivo.[5] Baseline tumor and blood biomarkers were assessed for ability to predict ICOS hi CD4 T cell emergence and clinical outcomes.

Methods: In ICONIC, fresh pre-treatment tumor biopsies were assessed by a tumor inflammation signature (TIS), previously referred to as RNA Signature (RS), an 18 gene signature describing immune cell infiltration. PD-L1 TPS by IHC was also assessed. Subjects were classified based on varying TIS scores and the threshold was optimized for predicting the emergence of ICOS hi CD4 T cells in the presence of vopra. This selected threshold was then applied to clinical data to assess benefit. Associations between potential predictive biomarkers, ICOS hi CD4 T cell emergence and clinical outcomes were evaluated.

Results: The baseline TIS score coupled with a specific threshold established by Jounce, now referred to as TIS^{vopra}, is significantly higher in subjects with emergence of ICOS hi CD4 T cells. TIS^{vopra} was associated with increased emergence of ICOS hi CD4 T cells, accompanied by improved RECIST response, PFS, and OS. In contrast, no association was noted with PD-L1 IHC (Table 1).

BACKGROUND

Figure 1: Vopra Acts on ICOS hi CD4 T Cells

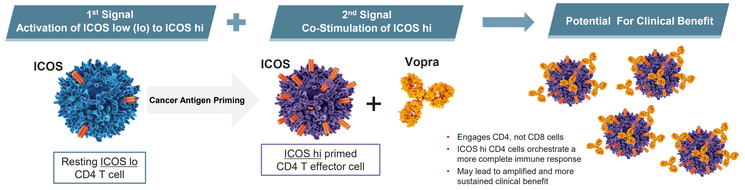
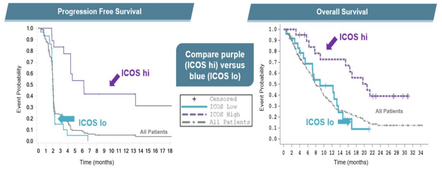


Figure 2: ICOS hi CD4 T Cells are a Vopra Pharmacodynamic Biomarker Linked to Clinical Benefit[1]

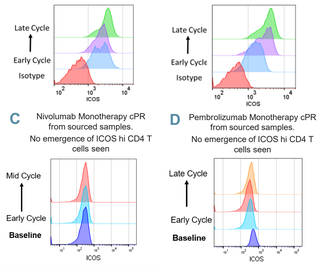
	ICOS hi (n=20)	ICOS lo (n=24)
RECIST 1.1 ORR	4 (20.0%)	0
Median PFS	6.2 months	2.0 months
Median OS	20.7 months	9.0 months



[1]local radiology review for PFS; data cut January 31, 2020

Figure 2: In an ICONIC subset retrospective analysis of 44 subjects with evaluable blood samples, subjects with emergence of ICOS hi CD4 T cells had improved response, PFS, and OS compared to subjects without emergence of this pharmacodynamic biomarker.

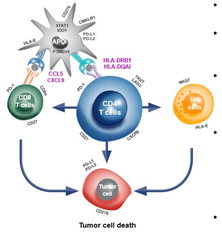
Figure 3: ICOS hi CD4 T Cells are not Associated with PD-1 Inhibition



RESULTS

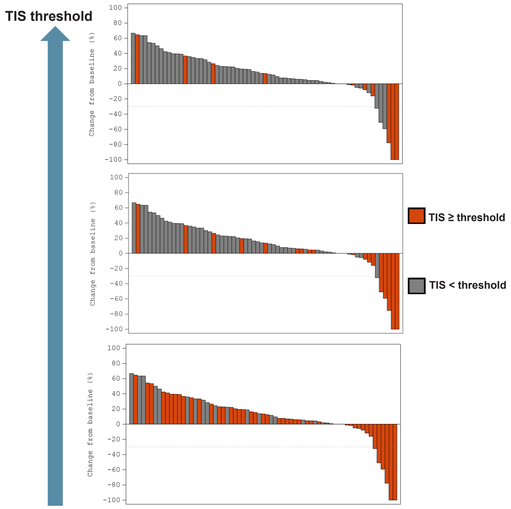
TIS^{vopra} Predicts Vopra Associated ICOS hi CD4 T Cell Emergence and Clinical Benefit

Figure 4: RS, Also Known as Tumor Inflammation Signature (TIS), is an 18 Gene RNA Signature Containing Elements of CD4 T Cell Biology



- A variant of TIS was originally identified as a predictive biomarker of response to PD-1 inhibitors[2]
- The genes included in the TIS signature are associated with antigen presentation, lymphocyte and monocyte abundance and immune cell activity, including activation of CD4 T cells[3]
- Genes associated with successful APC and T cell recruitment (CCL5 and CXCL9) as well as antigen presentation (HLA-DRB1 and HLA-DQA1) are integral elements of CD4 T cell activation that may contribute to a more comprehensive immune response
- **TIS^{vopra} is the gene signature TIS with a specific threshold that was established by Jounce and identified as a biomarker predictive of ICOS hi CD4 T cell emergence. TIS^{vopra} positive subjects treated with vopra alone or in combination with nivo also had improved clinical benefit as compared with TIS^{vopra} negative subjects**
- Subjects with positive baseline TIS^{vopra} are most likely to demonstrate activation of CD4 T cells, priming them for co-stimulation with vopra

Figure 5: Different TIS Thresholds Provide Varying Degrees of Sensitivity and Specificity for Predicting Tumor Regression



[1]Subset of 67 subjects with evaluable TIS samples and tumor measurements; local radiology review; data cut December 10, 2019

Figure 5: Waterfall plots showing percent change in tumor size in subjects who were evaluated for TIS. Bars are colored based on whether tumors have a TIS score greater than or equal to the TIS threshold (orange) or less than the TIS threshold (gray). Data is presented for high (top), medium (middle) and low (bottom) TIS thresholds.

Figure 6: TIS^{vopra} Optimizes Prediction of ICOS hi CD4 T Cell Emergence Better than PD-L1 IHC

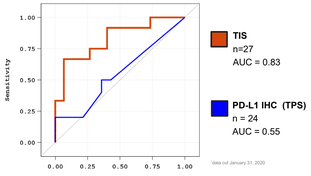


Figure 6: Receiver operating characteristic (ROC) curves were created to evaluate sensitivity and specificity of different biomarkers, using matched RNA signatures and ICOS hi T cell emergence data (red) or matched PD-L1 IHC and ICOS hi T cell emergence data (blue) from ICONIC. The Youden index was calculated, optimizing the sensitivity and specificity for predicting the vopra-driven pharmacodynamic response. The optimal threshold at the Youden index is what is used as the threshold in TIS^{vopra}. Using this threshold the positive predictive value (PPV) is 89% and the negative predictive value (NPV) is 78%. PD-L1 IHC does not predict ICOS hi CD4 T cell emergence.

Figure 7: Positive TIS^{vopra} Score and ICOS hi CD4 T Cell Emergence are Associated With Longer Duration on Study

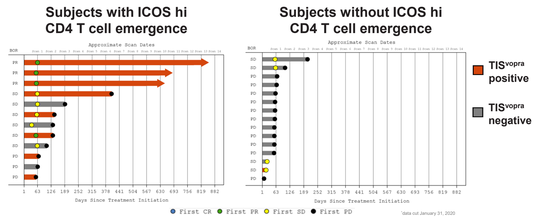


Figure 7: Swimmers plots showing time on treatment for subjects who were evaluated for ICOS hi emergence and TIS. Subjects with ICOS hi CD4 T cell emergence are grouped on the left; subjects without ICOS hi emergence are grouped on the right. Subjects that were TIS^{vopra} positive are shown in orange; those were TIS^{vopra} negative are shown in gray.

Figure 8: TIS^{vopra} Predicts Clinical Benefit

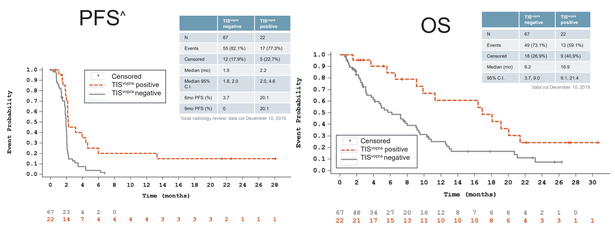


Figure 8: Subjects who are TIS^{vopra} positive had a higher 6 month PFS (20.1% vs 3.7%) and significantly higher median OS (16.9 months vs. 6.2 months; p-value 0.0062) than those who were TIS^{vopra} negative. PD-L1 and ICOS IHC are not predictors of clinical benefit with vopra alone or in combination with nivo (data not shown).[5]

Table 1: TIS^{vopra} Positivity and not PD-L1 ≥ 1% is Associated With ICOS hi CD4 T Cell Emergence and Improved Clinical Benefit in Heavily Pre-Treated PD-1i Experienced and PD-1i Naïve Subjects

	All (N=201)	TIS^{vopra} positive (n= 22/89)	PD-L1 ≥ 1% (n= 54/96)
Subjects evaluated for vopra associated ICOS hi CD4 emergence	44/201	9/22	11/54
Subjects with ICOS hi emergence (%)	20/44 (45)	8/9 (89)	5/11 (45)

data cut January 31, 2020

Outcomes	All (N=201)	TIS^{vopra} positive (n= 22)	PD-L1 ≥ 1% (n= 54)
ORR, n (%)	4 (2.0)	3 (13.6)	1 (1.9)
DCR, n (%)	52 (25.9)	10 (45.5)	16 (29.6)
Median PFS, mo	2	2.2	1.9
6mo PFS (%)	**8.6**	**20.1**	**7.8**
9mo PFS (%)	**5.3**	**20.1**	**5.2**
Median OS, mo	**7.9**	**16.9**	**9.9**

[1]data cut December 10, 2019

Table 1: In this retrospective subset analysis, a positive TIS^{vopra} score in baseline tumor biopsies was predictive of emergence of an ICOS hi CD4 T cell population and improved RECIST response, landmark PFS, and OS in subjects treated with vopra alone and in combination with nivo as compared with a negative TIS^{vopra} score. PD-L1 was not predictive of ICOS hi CD4 T cell emergence or clinical benefit (association analysis of PD-L1 data not shown). **In the subset of subjects who were PD-1 inhibitor naïve and evaluated for TIS (n=59), 12 (20%) are TIS^{vopra} positive, for which the ORR is 3 (25%).**

SUMMARY

- TIS^{vopra} is the gene signature TIS with a specific threshold that was identified by Jounce as a biomarker predictive of ICOS hi CD4 T cell emergence. TIS^{vopra} positive subjects treated with vopra alone or in combination with nivo also had improved clinical benefit (response rate, 6mo and 9mo landmark PFS and OS) as compared with TIS^{vopra} negative subjects
- The TIS^{vopra} threshold was chosen to optimize prediction of ICOS hi CD4 T cell emergence and was more predictive of clinical benefit than PD-L1 IHC in ICONIC
- The emergence of ICOS hi CD4 T cells is a vopra, but not a PD-1 inhibitor, pharmacodynamic biomarker linked to clinical benefit in the ICONIC study
- ICOS hi CD4 T cells display central memory characteristics, expansion of T cell receptors associated with matched archival tumor and express cytolytic mediators[4]
- In the upcoming SELECT study, TIS^{vopra} will be used to select subjects for treatment with vopra + JTX-4014, a PD-1 inhibitor

REFERENCES

1 Hanson et al., SITC Annual Meeting (2018) #P52
2 Ayers et al., The Journal of Clinical Investigation (2017) 127(8) 2930:2940
3 Danaher et al., Journal for ImmunoTherapy of Cancer (2018) 6:63
4 Harvey et al, AACR Annual Meeting (2019) #4053
5 Yap et al., AACR Annual Meeting (2019) #CT189

SCAN ME