Phase 2 Multicenter Trial of ICOS Agonist Vopratelimab and a CTLA-4 Inhibitor in PD-1/PD-L1 Inhibitor Experienced Adult Subjects with Non-small Cell Lung Cancer or Urothelial Cancer (EMERGE)

ABSTRACT# P438

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Background

ICOS is a costimulatory molecule upregulated on activated T cells. Vopratelimab (JTX-2011) is an IgG1 ICOS agonist monoclonal antibody that leads to activation and proliferation of primed CD4 T effector cells. In the Phase 1/2 ICONIC trial (NCT02904226), vopratelimab was found to be safe and well tolerated as monotherapy and in combination with nivolumab in subjects with advanced solid tumors (Yap 2018). Emergence of peripheral blood ICOS High (hi) CD4 T effector cells following treatment with vopratelimab +/- nivolumab was associated with improved response rate, PFS, and OS (Figure 1). The ICOS hi CD4 T cells from responding subjects have been shown to be Tbet+, cycling, express perforin and granzyme, and show clonal expansion of TCR found in matched archival tumors (Harvey 2019). Emergence of these ICOS hi cells has not been observed with PD-1/PD-L1 inhibitors (Hanson 2018). Ipilimumab, on the other hand, has been demonstrated to induce ICOS hi CD4 T cells, with sustained levels associated with improved outcomes (Carthon 2010).

Ex vivo antigen recall studies (Hanson 2018) showed that soluble vopratelimab stimulated a polyfunctional cytokine response only in CD4 T cells that were ICOS hi, further supporting the hypothesis that vopratelimab induces activation and proliferation of CD4 T effector cells only after an initial priming event induces an ICOS hi CD4 T cell phenotype (Figure 2). Additionally, vopratelimab does not cause the depletion of any T cell subsets from subjects (Hanson 2018).

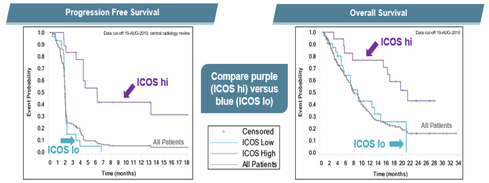
The study drugs in the EMERGE trial are sequenced: ipilimumab is administered first to lower the threshold for priming and induce ICOS hi CD4 T cells, followed by vopratelimab to proliferate, expand and maintain ICOS hi CD4 T cells. This may lead to an increased clinical benefit by a mechanism independent of PD1-L1 inhibition.

Additionally, administering vopratelimab in a pulsatile manner at a lower dose with longer dosing interval may improve clinical benefit.

Study Rationale

Figure 1: ICONIC Trial: Survival Benefit for Subjects who Develop ICOS hi CD4 T Cell Populations*

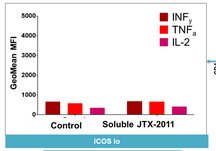
	ICOS hi (n=18)	ICOS lo (n=32)
RECIST 1.1 ORR	4 (22.2%)	0
Median PFS	6.2 months	2 months
Median OS	21.4 months	9 months



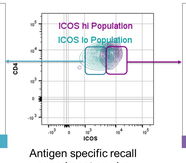
*Subset of 50 subjects with evaluable blood samples and tumor measurements; central radiology review for PFS, local radiology review for OS; data cut August 19, 2019

Figure 1: In an ICONIC subset retrospective analysis of 50 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.

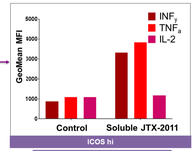
Figure 2: Vopratelimab Leads to Activation and Proliferation of Induced ICOS hi CD4 T Cells in Vitro



ICOS lo CD4 T cells show no response to soluble vopratelimab



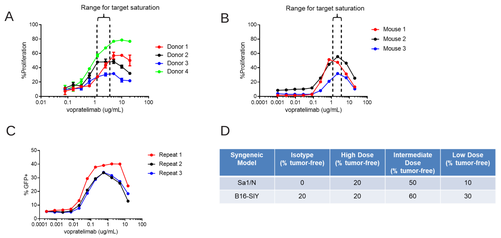
Antigen specific recall experiment *ex vivo*



ICOS hi CD4 T cells produce IFNγ and TNFα in response to soluble vopratelimab

Figure 3. PBMCs from healthy donors were stimulated to induce an ICOS hi CD4 population using tetanus toxoid as a model recall antigen (representative plot in inset). Following 24hr of stimulation, cells were washed to remove stimulus and rest the CD4 T cells. Following washing, soluble vopratelimab was added, and intracellular cytokine production was assessed by flow cytometry following 6hr incubation in the presence of brefeldin A. (*Hanson, 2018*)

Figure 3: In Preclinical Models, Continuous Saturation of ICOS Results in Reduced Activity



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Syngeneic Model	Isotype (% tumor-free)	High Dose (% tumor-free)	Intermediate Dose (% tumor-free)	Low Dose (% tumor-free)
Sa1/N	0	20	50	10
B16-SIY	20	20	60	30

Figure 3. A-B) Ability of vopratelimab to induce proliferation of CD4 T cells was assessed in vitro on isolated CD4 T cells from four healthy donors (A) or naive B6 mice (B). Isolated CD4 T cells were labeled with CFSE and stimulated with suboptimal anti-CD3 and vopratelimab for 72 hours. Following the incubation, degree of proliferation was assessed by flow cytometry. Data are mean +/- SD at each concentration tested. A hook effect, signaling loss of activity at high concentrations was demonstrated. Vertical dashed lines indicate concentration range above which target saturation was observed. C) Ability of vopratelimab to induce activation of Jurkat-ICOS reporter cells was assessed. D) Monotherapy dose-response assessment of mouse version of vopratelimab was performed in the SA1/N or B16-SIY tumor models. The frequency of tumor free mice is indicated out of a total 10 mice per group.

Figure 4: Vopratelimab Dosing is Being Optimized to Result in Pulsed Periods of Target Engagement, Which May Enhance Agonist Activity

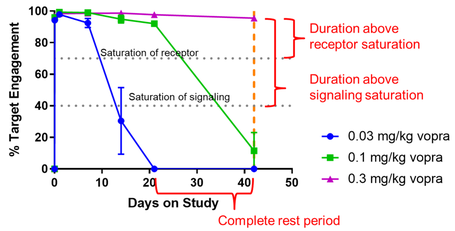

Figure 4. Target engagement was measured on peripheral blood CD4 T cells following administration of vopratelimab to subjects at three different dose levels given q6w. Data shown are mean ± SD. Saturation of signaling was determined by assessing the vopratelimab dose-response relationship with AKT phosphorylation

Study Design

Key Objectives

Primary Objective
- Evaluate the efficacy, as measured by overall response rate (ORR), following treatment with vopratelimab administered in sequence with ipilimumab in subjects with NSCLC or urothelial cancer

Secondary Objectives
- Evaluate the safety and tolerability of vopratelimab in sequence with ipilimumab
- Evaluate the PK of vopratelimab and ipilimumab
- Evaluate the emergence of anti-drug antibodies and neutralizing antibodies against vopratelimab and ipilimumab
- Evaluate the efficacy, as measured by tumor reduction in target lesion(s), duration of response, disease control rate, landmark PFS rates, PFS, and OS, following treatment with vopratelimab and ipilimumab
- Evaluate and differentiate the clinical effects of different vopratelimab dose regimens

PD-1i Experienced NSCLC

PD-1i Experienced Bladder

Key Eligibility Criteria

- Prior treatment with standard of care in the metastatic setting, including:
  - a PD-1/PD-L1 inhibitor for at least 3 months
  - either concurrent with a platinum-based regimen or in sequence with a platinum-based regimen;
  - no other therapy if platinum ineligible;
- No history of immune-related adverse events (irAEs) leading to treatment discontinuation on prior PD-1/L1 inhibitor
- No major surgery within 4 weeks prior to C1D1
- No brain metastases, leptomeningeal disease, or spinal cord compression not definitively treated with surgery or radiation
- No prior whole brain radiation
- No prior anticancer therapies within the timeframes specified below, or ongoing toxicity from prior therapy > Grade 1:
  - PD-1/PD-L1i within 21 days prior to C1D1
  - Chemotherapy within 21 days prior to C1D1
  - Anti-CTLA-4 or anti-ICOS therapy at any time
  - CAR T-cell therapy at any time
  - Organ transplantation, including allogeneic or autologous stem-cell transplantation, at any time
- Any active disease, including primary or acquired immunodeficiency (with exceptions allowed upon discussion with the medical monitor), requiring systemic immunosuppressive therapy

Figure 5: EMERGE Study Sequences Therapies at Two Different Dose Levels of Vopratelimab to Maximize ICOS Induction of ICOS hi CD4 T Effector Cells

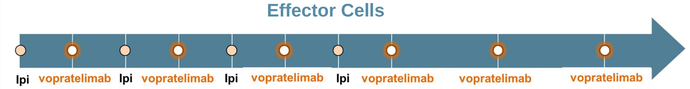

Figure 5: Vopratelimab will be administered in sequence with ipilimumab. Up to 4 doses of ipilimumab are allowed on study, as tolerated. Ipilimumab is administered on C1D1 to induce ICOS hi CD4 T cells followed by vopratelimab to bind to, expand, and sustain ICOS hi CD4 T cell population(s). Vopratelimab doses and interval are intended to achieve pulsatile dosing.

Summary

- Vopratelimab demonstrated a survival benefit the ICONIC study in subjects with ICOS hi CD4 T cells, a T cell phenotype that can be induced by ipilimumab
- Vopratelimab leads to activation and proliferation of ICOS hi CD4 T cells
- The EMERGE dosing sequence is designed to prime new T cells with up to 4 staggered doses of ipilimumab to generate ICOS hi CD4 T cells. Vopratelimab is then sequenced into the regimen to bind to, expand, and sustain the ICOS hi T cell population(s).
- The pulsed dose and schedule of vopratelimab are designed to optimize agonist antibody activity:
  - Continuous exposure to concentrations at or above receptor saturation have been demonstrated to result in reduced agonist activity in preclinical models (in vitro and in vivo)
  - Continuous saturation in subjects was observed throughout the dose cycle at 0.3 mg/kg dose level and may result in suboptimal T cell activity
  - Pulsed dosing will allow for a period of receptor saturation followed by a period of time in which the receptors become available and receptor occupancy falls below the level of signaling saturation, allowing T cells to recover.
  - This may be best achieved with lower doses of vopratelimab administered at a longer dosing interval than was used in the ICONIC study. Two doses of vopratelimab are being explored in the EMERGE study to evaluate the impact of duration of saturation and rest period.

References

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