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 Carcinoma (EMERGE)

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ICOS is a cell-surface molecule upregulated on activated T cells. Vopratelimab (JTX-2011) is an IgG1 ICOS agonist monoclonal antibody that leads to activation and proliferation of PD-1+ T effector cells. In the Phase 1b ICOS model (NCT02584265), vopratelimab was found to be safe and well tolerated as monotherapy and in combination with rituximab in subjects with advanced solid tumors (Hanson 2018). Emergence of peripheral blood ICOS hi (hi) CD4 T effector cells following treatment with vopratelimab + rituximab was associated with improved response rate, PFS, and OS (Figure 1). The ICOS hi CD4 T cells have not been previously shown to be Th1, Th2, Th17, suppressor, or granzyme+B effector cells. The results from this study support the hypothesis that vopratelimab induces activation and proliferation of CD4 T effector cells only after an initial priming event induced by an ICOS+/PD-L1 agonistic interaction (Figure 2). Vopratelimab does not cause the depletion of any T cell subsets from subjects (Hanson 2018).

The study design in the EMERGE trial is similar to the ICOS model. Vopratelimab is administered intravenously to the threshold for priming and induce ICOS hi T cells, followed by vopratelimab to promote, expand and maintain ICOS hi T cells. This may lead to an increased clinical benefit by a mechanism independent of PD-L1 inhibition. Additionally, administering vopratelimab in a pulsatile manner at a lower dose with longer dosing intervals may preserve ICOS T cell function.

**Key Objectives**

**Primary Objective**
- Evaluate the efficacy, as measured by overall response rate (ORR), following treatment with vopratelimab + nivolumab.
- Evaluate the emergence of anti-ICOS and neutralizing antibodies against vopratelimab and nivolumab.
- Evaluate the safety and tolerability of vopratelimab in sequence with anti-T, anti-ICOS, and a PD-L1 inhibitor.
- Evaluate and differentiate the clinical effects of different vopratelimab dosing regimens.

**Secondary Objectives**
- Evaluate the safety and tolerability of vopratelimab in sequence with PD-1/PD-L1 inhibitors.
- Evaluate the level of anti-ICOS and neutralizing antibodies against vopratelimab and nivolumab.
- Evaluate the safety and tolerability of vopratelimab in sequence with PD-1/PD-L1 inhibitors.
- Evaluate and differentiate the clinical effects of different vopratelimab dosing regimens.

**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 or a platinum-based sequence 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-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 timelines specified below, or ongoing toxicity from prior therapy:
    - Grade 1: PD-L1 within 21 days prior to C1D1
    - Grade 2 within 21 days prior to C1D1
    - Any grade anti-ICOS therapy at any time
  - No prior anti-CTLA-4 therapy at any time

**Summary**

- Vopratelimab demonstrated a survival benefit in the ICOS model in subjects with ICOS hi PD-1 T cell phenotype, which can be induced by PD-L1 blockade.
- Vopratelimab leads to activation and proliferation of ICOS hi PD-1 T cells.
- The EMERGE dosing sequence is designed to prime new T cells with up to 2 staggered doses of rituximab to generate ICOS hi PD-1 T cells. Vopratelimab is then sequenced into the regimen to bind, expand, and sustain ICOS hi PD-1 T cell populations.
- The pulsed dose and schedule of vopratelimab are designed to optimize antigen antibody activity.
- Continuous exposure to concentrations at or above receptor saturation have been demonstrated to result in reduced agonist activity in preclinical models.
- 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 saturation signaling, allowing T cells to recover.
- This may be best achieved with lower doses of vopratelimab administered at a longer dosing interval to allow time for the ICOS hi T cells to be reprimed and refractory T cells to escape vopratelimab binding.
- The study designs of vopratelimab are being explored in the EMERGE study to evaluate the impact of duration of saturation and rest period.

**References**