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**ABSTRACT**

**Background:** Inducible T cell co-stimulator (ICOS) is a costimulatory molecule expressed primarily on T lymphocytes that is upregulated upon cell activation. Vopratelimab (vop) is a novel investigational ICOS agonist antibody whose primary mechanism of action is the stimulation of primed CD4 T effector cells. Clinical responses in the Phase 1/2 ICONIC trial (NCT03596266) were associated with the emergence of ICOS hi CD4 T cells. In a separate study of PD-1/L1 monotherapy, this phenotype was not observed, suggesting ICOS hi CD4 T cell emergence in ICONIC was due to vop. In this study, stimulation of antigen primed-poly ICOS hi CD4 T cells by vop led to significant downstream activation and induction of a polyclonal cytokine response. Previous studies have shown that sustained ICOS upregulation was associated with clinical benefit in subjects treated with antiCTLA-4 antibodies, with preliminary data confirming a role for ICOS upregulation in enhancing anti-tumor activity. Vop is currently being tested as a sequenced combination with ipilimumab (IP) in the Phase 2 EMEERGE trial (NCT03989362).

**Methods:** Assessment of phenotype and function of ICOS hi CD4 T cells was conducted using serial collections of peripheral blood mononuclear cells (PBMCs) from a subset of evaluable subjects in the ICONIC trial. A mouse syngeneic tumor model was developed to assess the kinetics of ICOS hi emergence as well as determine functionality and transcriptional and flow profiling. PBMCs were isolated from healthy donors and isolated CD4 T cells were stimulated with OKT3 antibody (anti-CD3) and Anti-human ICOS (IP) antibody (anti-ICOS) and 2 hours later stained with fluorescently labeled anti-human CD45RA and CD62L antibodies and analyzed by FACS. Primary CD4 T cell clones were established from a population of ICOS hi CD4 T cells within peripheral blood of ICONIC responders.

**Results:** Phenotypic profiling of ICOS hi CD4 T cells by flow cytometry demonstrated enrichment of subsets including Th1, T central memory phenotype (Tcm), and T follicular helper (Tfh) in vivo and in vitro. These data were then compared with data from IP monotherapy treated subjects. ICOS hi CD4 T cells were enriched in peripheral blood of ICONIC responders following treatment with vop as well as in preclinical experiments using the MC38 mouse model. In vitro stimulation of co-cultured CD4 T cells from healthy donors showed that ICOS hi CD4 T cell clones from ICONIC responders had greater IFN-gamma levels than control ICOS hi CD4 T cell clones from healthy donors. By transcriptional analysis, potent effector molecules, associated with durable responses to PD-1/L1 blockade, were upregulated in ICOS hi CD4 T cell clones from ICONIC responders. These findings were not observed in IP monotherapy treated subjects.

**Conclusion:** ICOS hi CD4 T cell populations have emerged in ICONIC responders following treatment with vop. These cells are enriched in peripheral blood and are associated with durable clinical benefit. Inducible T cell co-stimulator (ICOS) activates ICOS hi CD4 T cells that are induced by TCR stimulation. In a hCTLA-4, nivolumab (NIVO) group subjected to TCM stimulation of antigen primed-poly ICOS hi CD4 T cells by NIVO led to significant downstream activation and induction of a polyclonal cytokine response. Previous studies have shown that sustained ICOS upregulation was associated with clinical benefit in subjects treated with antiCTLA-4 antibodies, with preliminary data confirming a role for ICOS upregulation in enhancing anti-tumor activity. Vop is currently being tested as a sequenced combination with ipilimumab (IP) in the Phase 2 EMEERGE trial (NCT03989362).

**REFERENCES**