ABSTRACT

Background: Inducible T cell co-stimulator (ICOS) is a co-inhibitory molecule expressed primarily on T lymphocytes that is upregulated upon cell activation. Vopratelimab (JTX-2011) is a fully-humanized IgG1 anti-ICOS monoclonal antibody used for the treatment of advanced NSCLC in combination with nivolumab. Gene expression and biological activity of vopratelimab was assessed in the advanced solid tumor setting in the Phase I/II study dose-finding study. Changes to vopratelimab were associated with the emergence of an ICOS hi CD4 T cell population, which was subsequently demonstrated in vivo in activity of vopratelimab and not a PD-1 inhibitor.

Methods: Assessment of expression and function of ICOS hi CD4 T cells was conducted using serial collections of peripheral blood mononuclear cells (PBMCs), whole blood, and tumor samples from a subset of evaluable subjects treated with 0.1mg/kg or 0.3mg/kg vopratelimab (associate with the emergence of ICOS hi CD4 T cell population) and 0.1mg/kg nivolumab alone. Biologic activity was assessed through analysis of T cell clonality, ICOS hi Treg quantification, and PD-L1 expression on T cell subsets.

Results: Four cytometry-based panels were generated; ICOS hi CD4 T Cells as a percentage of total T cells, ICOS hi CD4 T cells as a percentage of total CD4 T cells, ICOS hi CD4 T cells as a percentage of total CD8 T cells, and ICOS lo CD4 T cells as a percentage of total CD4 T cells. Gene expression analysis was performed in the subjects (n=9) that were evaluable for the biological activity.

Conclusion: Increased production of Th1 cytokines (IL-2, IFNγ) and Th2 cytokines (IL-4, IL-13) and downregulation of Th17 cytokines (IL-17A, IL-22) was noted in ICOS hi CD4 T Cells. In combination with nivolumab, vopratelimab increased the expression of ICOS in CD4 T Cells and led to a decrease in the expression of PD-L1, which is co-expressed with ICOS in ICOS hi CD4 T Cells. The increase in ICOS hi CD4 T Cells not only resulted in a decrease in PD-L1 expression, but also led to the induction of ICOS hi CD4 T Cells, which is hypothesized to contribute to biological activity.

SUMMARY

Strong pharmacodynamic evidence of vopratelimab activity has been observed:

- The presence of ICOS hi CD4 T cells tracked with clinical response and disease stability in vopratelimab but not PD-1/PD-L1 inhibition.
- ICOS hi CD4 T cells were pharmacologically distinct from ICOS lo CD4 T cells, delineated by their flow cytometry and functional phenotype.

ICOS hi CD4 T cells are enriched in peripheral blood and tumor samples, with greater expression of tumor-associated clones in subjects displaying ICOS hi CD4 T cell expansion. Vopratelimab treatment results in expansion of de novo T cell clonal populations regardless of ICOS hi CD4 T cell enumeration.

REFERENCES

[1] Logothetis J, Cheah B, Wargo J, Troncoso C, Laheru D, Allison J, et al. NSCLC subject who responded to pembrolizumab shows no induction of ICOS hi CD4 T cells. Histograms are representative of all responders. ImmunoSEQ analysis from anti-PD-1 T cell expansion shows a marked increase in ICOS expression with drug exposure. CTC analysis from anti-PD-1 T cell expansion shows a marked increase in ICOS expression with drug exposure.

[2] Rytlewski J, Logothetis J, Troncoso C, Laheru D, Allison J, et al. NSCLC subject who responded to pembrolizumab shows no induction of ICOS hi CD4 T cells. Histograms are representative of all responders. ImmunoSEQ analysis from anti-PD-1 T cell expansion shows a marked increase in ICOS expression with drug exposure. CTC analysis from anti-PD-1 T cell expansion shows a marked increase in ICOS expression with drug exposure.

[3] Logothetis J, Cheah B, Wargo J, Troncoso C, Laheru D, Allison J, et al. NSCLC subject who responded to pembrolizumab shows no induction of ICOS hi CD4 T cells. Histograms are representative of all responders. ImmunoSEQ analysis from anti-PD-1 T cell expansion shows a marked increase in ICOS expression with drug exposure. CTC analysis from anti-PD-1 T cell expansion shows a marked increase in ICOS expression with drug exposure.

[4] Rytlewski J, Logothetis J, Troncoso C, Laheru D, Allison J, et al. NSCLC subject who responded to pembrolizumab shows no induction of ICOS hi CD4 T cells. Histograms are representative of all responders. ImmunoSEQ analysis from anti-PD-1 T cell expansion shows a marked increase in ICOS expression with drug exposure. CTC analysis from anti-PD-1 T cell expansion shows a marked increase in ICOS expression with drug exposure.

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