Toripalimab, an Anti-PD-1 Antibody Demonstrating Potent T-Cell Activation and Enhanced Clinical Efficacy Irrespective of PD-L1 Status

Tumor Cell Cytotoxicity of Activated PBMC Cultured with Toripalimab, an Anti-PD-1 Antibody

Tori is currently under clinical development (JUPITER-02 [NPC], JUPITER-06 [ESCC], and CHOICE-01 [NSCLC]) and thus function. Toripalimab is a PD-1-targeting humanized IgG4 antibody, which has demonstrated significant efficacy in several cancer indications. Tori positively modulates genes associated with IFN-γ production, which is distinct from other anti-PD-1/PD-L1 agents. Tori induces an elevated IFN-γ response gene signature in NSCLC tumor cells derived from treatment-naive patients with different kinetics and intensity compared to pembrolizumab. In comparison to pembrolizumab, Tori induces a 1.9-fold higher binding affinity for PD-1 compared to pembrolizumab. Tori recruits lower levels of SIFH4 or SHP2, the negative regulators of T-cell activation, compared to pembrolizumab in Zukert-PD1 cells. (A) Schematic of the experimental system. (B) Oste response curve for S.H.F. and SHP2 recruitment. (C) IL-10 and IL-17 values calculated from dose response curves.

**Background**

Immune checkpoint inhibitors targeting PD-1 have revolutionized cancer treatment, resulting in clinical benefits to a broad range of cancer patients. PD-1 is an inhibitory cell surface receptor that is upregulated upon T-cell activation, leading to immune suppression. Toripalimab (Tori) is a humanized IgG4 antibody designed to bind the Fc region of PD-1, thereby blocking the interaction of PD-1 to its ligands.

In clinical trials, toripalimab (Tori), in combination with chemotherapy, demonstrated significant efficacy in several cancer indications. Tori is more potent than pembrolizumab in enhancing IFN-γ production and SHP1 and SHP2 recruitment. Demonstration of unique binding epitopes—higher affinity to PD-1 and PD-L1 molecules—enabled enhanced activation of several unique genes in IFN-γ producing PBMC, compared to pembrolizumab treatment.

**T.R.I.C.K.S.**

- Tori exhibits a 2.5-fold higher binding affinity for PD-1 compared to pembrolizumab. Global gene expression of PD-1 binding to IFN-γ-expressing PBMC in Jurkat PD-1 cells.
- Tori positively modulates genes associated with IFN-γ production. PBMC from treatment-naive patients with different kinetics and intensity compared to pembrolizumab.
- Tori induces an elevated IFN-γ response gene signature in NSCLC tumor cells derived from treatment-naive patients.
- Tori is a unique epitope binding antibody, which enhances IFN-γ production.

**Conclusions**

Tori is currently under clinical development (JUPITER-02 [NPC], JUPITER-06 [ESCC], and CHOICE-01 [NSCLC]) and thus function. Toripalimab is a PD-1-targeting humanized IgG4 antibody, which has demonstrated significant efficacy in several cancer indications. Tori positively modulates genes associated with IFN-γ production, which is distinct from other anti-PD-1/PD-L1 agents. Tori induces an elevated IFN-γ response gene signature in NSCLC tumor cells derived from treatment-naive patients with different kinetics and intensity compared to pembrolizumab. In comparison to pembrolizumab, Tori induces a 1.9-fold higher binding affinity for PD-1 compared to pembrolizumab. Tori recruits lower levels of SIFH4 or SHP2, the negative regulators of T-cell activation, compared to pembrolizumab in Zukert-PD1 cells. (A) Schematic of the experimental system. (B) Oste response curve for S.H.F. and SHP2 recruitment. (C) IL-10 and IL-17 values calculated from dose response curves.

**Data demonstrate toripalimab as a next-generation anti-PD-1 checkpoint inhibitor that warrants future multicenter clinical trials to evaluate its efficacy in combination with chemotherapy and other combination treatments in multiple cancer types.**