Optimizing PD-1 Agonist Signaling with Membrane-Proximal Binding of Rosnilimab, a Clinical Stage PD-1 Agonist IgG1 Antibody

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ABSTRACT

Rosnilimab binds to a membrane-proximal epitope of PD-1, distinct from the binding epitope of PD-L1 and the membrane-distal binding epitope of reference 1.

BACKGROUND/PURPOSE

- Programmed cell death protein 1 (PD-1), a T cell checkpoint receptor, functions to downregulate active T cells by inducing a negative signaling pathway when engaged with its ligand (L1).
- PD-1 expressing T cells are elevated in the synovium and in the periphery, and PD-1+ T cells represent persistent unmet needs in the treatment of autoimmune diseases, including rheumatoid arthritis (RA), where unmet needs persist despite available therapies.
- Rosnilimab is a PD-1 agonist, IgG1 isotype monoclonal antibody, mimics the function of PD-1 agonist molecules.
- It is currently in clinical development for RA and other inflammatory conditions.
- For the treatment of autoimmune diseases, including RA, where unmet needs persist despite available therapies.

RESULTS

- Rosnilimab optimizes PD-1+ T cell inhibitory signaling by enabling tight immune synapse formation between an immune cell and an antigen presenting cell.
- To demonstrate the membrane-bound PD-1 agonist properties of Rosnilimab, the T cell proliferation and antigen-dependent cellular cytotoxicity (ADCC) in vitro assays were used to compare rosnilimab to a reference PD-1 agonist antibody (reference 1) with a more membrane-distal binding epitope.

CONCLUSIONS

- Rosnilimab binds to a membrane-proximal region of PD-1 while reference 1 binds to a more membrane-distal region.
- Optimization of rosnilimab's binding characteristics results in more potent agonism and deeper depletion of PD-1+ expressing T cells compared to reference 1.
- These results are consistent with published studies that demonstrate membrane-proximal binding of PD-1 antibodies improves PD-1 agonistic activity and enhances target cell depletion.

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REFERENCES