Rosnilimab, a Novel PD-1 Agonist Monoclonal Antibody, Demonstrated Modulation of Peripheral T cell Activity and Reduction of Circulating PD-1 high Expressing CD4 and CD8 T cells in a Phase 1 Healthy Volunteer Clinical Trial

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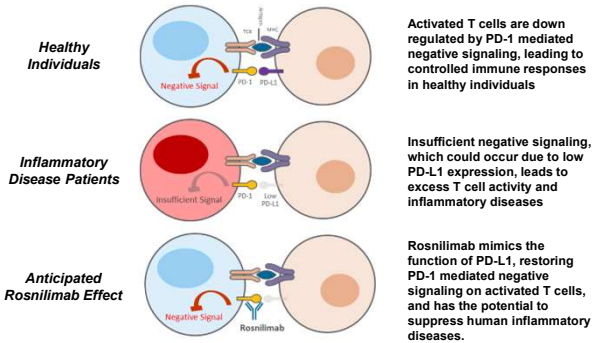
Abstract

Genetic studies have demonstrated that PD-1 pathway mutations increase human susceptibility to multiple autoimmune diseases and insufficient PD-1 signaling can lead to dysregulated T cell responses. Rosnilimab is a PD-1 agonist antibody designed to modulate activated T cells for the treatment of inflammatory diseases.

Rosnilimab's pharmacodynamic activity resulted in rapid and sustained reduction in the quantity and functional activity of PD-1+ T cells, which are known to be pathogenic drivers of inflammatory diseases. Conventional T (Tcon) cells expressing PD-1 were reduced, on average through Day 30 in single ascending dose cohorts where full receptor occupancy was sustained following rosnilimab treatment, by approximately 50%, including in both CD4+ and CD8+ subsets, in a dose-dependent manner and in correlation with receptor occupancy. This reduction was maximized on high PD-1 expressing Tcon cells, with approximately 90% reduction relative to baseline. Rosnilimab did not modulate total T cells, total Tcon cells, or total regulatory T (Treg) cells, resulting in a favorable shift in the ratio of PD-1+ Tcon cells to total Treg cells post-treatment. No effect was observed on any of the aforementioned cell types in placebo-dosed subjects. In addition, an antigen-specific functional T cell assay measuring ex vivo interferon-gamma released in response to antigen challenge, was inhibited to a maximum of approximately 90% relative to baseline within 30 days following single rosnilimab dose, while placebo administration had no effect. Based upon these data, we believe rosnilimab's in vivo mechanism has the potential to treat T-cell driven human inflammatory diseases.

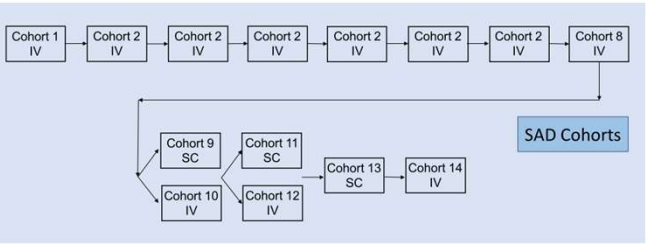
Introduction

Rosnilimab: PD-1 Agonist Antibody



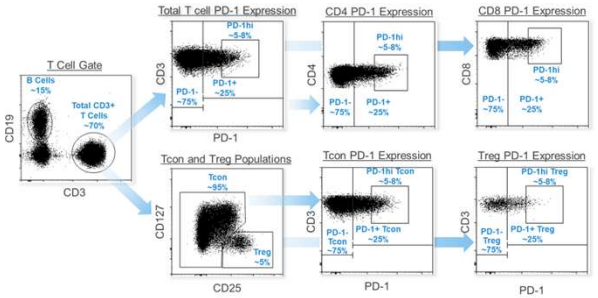
Programmed cell death protein 1 (PD-1) is an integral membrane protein expressed primarily on the surface of activated T cells. Upon engagement with one of its ligands, PD-L1 or PD-L2 on antigen presenting cells, PD-1 signals to turn off T cell activation by recruiting one or more tyrosine phosphatases to its phosphorylated cytoplasmic domain. PD-1 is one of the major immune checkpoint molecules used by the immune system to naturally down regulate immune responses. Functional antagonist antibodies to PD-1 are approved as therapeutic agents for cancer immunotherapy. These antibodies enhance pre-existing immune responses by blocking PD-L1 and PD-L2 binding.
Anti-PD-1 antibodies with T cell inhibitory, or agonist activity are being tested as potential therapeutic agents for autoimmune and inflammatory diseases to down regulate immune cells.

Phase 1 Study Design



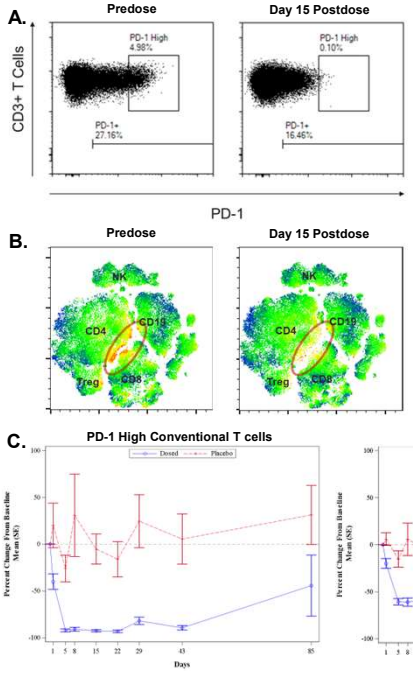
A total of 144 subjects were enrolled in the randomized, double-blind, placebo-controlled healthy volunteer Phase 1 trial, where single ascending dose (SAD) cohorts were administered single subcutaneous or intravenous doses of rosnilimab ranging between 0.02mg to 600mg or placebo, while multiple ascending dose (MAD) cohorts (data not shown) received four weekly subcutaneous doses of rosnilimab ranging between 60mg and 400mg or placebo. Dose escalation was conducted subsequent to data safety monitoring board review of safety and tolerability parameters following each single and multiple ascending dose level.

PD-1 Expression on Peripheral T cells



- **PD-1 high expression among T cell subset is ~5-8%**

Pharmacodynamics: PD-1 High Reduction Following Dosing



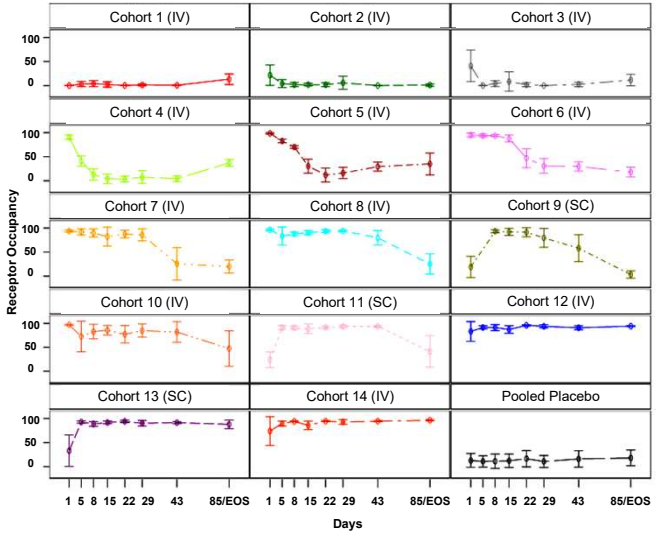
A. PD-1 high expressing T cells reduced > 90% at Day 15 following rosnilimab administration in cohort 11. B. Data from all dosed subjects from cohort 11 concatenated into one tSNE plot showing PD-1 high cells from the CD4 and CD8 T cells reduced (red circle) at day 15 postdose compared to predose, while not modulating the distribution of the other lymphocyte subsets. C. Near complete reduction of high-expressing PD-1 cells following rosnilimab administration persisted for > 30 days, with 50% reduction as soon as day 1, and >90% reduced at day 5 and after. Conventional T cells expressing PD-1 reduced 50% and persisted for > 30 days following rosnilimab administration.

Change in T Cells PD-1 Expression Following Rosnilimab Dosing

T Cell Population	Surface Markers	Average Change From Baseline
Total T (Tcon and Treg) cells	CD3+	<5% change
Conventional T (Tcon) cells	CD3+, CD25low	<5% change
PD-1 expressing Tcon cells	CD3+, CD25low, PD-1+	50% reduction
High PD-1 expressing Tcon cells	CD3+, CD25low, PD-1high	90% reduction
Total regulatory T (Treg) cells	CD3+, CD4+, CD25bright, CD127-	<5% change

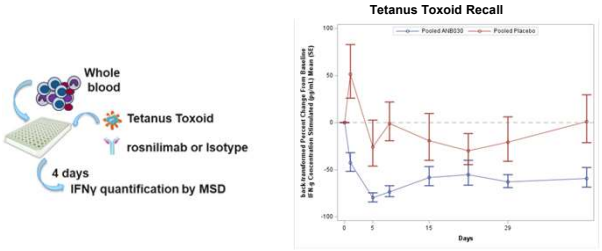
- **Average change in T cell populations relative to baseline in SAD cohorts achieving full receptor occupancy between Day 5 and Day 29 following rosnilimab treatment.**

Rosnilimab Receptor Occupancy



- **Receptor occupancy (RO) increased in a dose-dependent manner and consistent with PK**
- **Transient full RO at doses starting in cohort 4 (IV) and cohort 9 (SC).**
- **Onset of full RO starts as early as Day 1 for IV and Day 5 for SC.**
- **Sustained full RO for at least 30 days at doses starting in cohort 7 (IV) and cohort 11 (SC).**
- **Full RO lasted for 1 month or longer at doses for cohort 10 (IV) or cohort 11 (SC) supporting monthly dosing.**

Pharmacodynamics: Tetanus Toxoid Recall (TT Recall)



- **Subject derived whole blood ex vivo assay for IFNγ released in response to tetanus toxoid challenge**
- **Rosnilimab significantly reduced IFNγ secretion relative to Placebo**
- **Mean reduction up to -92% of INFγ in an *ex vivo* antigen-specific T cell recall response assay consistent with reduction of PD-1+ T cells**
- **Response lasted for more than 30 days**

Conclusions

- **Rosnilimab's pharmacodynamic activity resulted in rapid and sustained reduction in the quantity and functional activity of PD-1+ T cells.**
- **Conventional T (Tcon) cells (CD3+, CD25 low) expressing PD-1 were reduced by 50%, including in both CD4+ and CD8+ subsets, in a dose-dependent manner and in correlation with receptor occupancy.**
- **PD-1 high expressing Tcon cells, which represented approximately 5% of peripheral T cells have a 90% reduction relative to baseline.**
- **An antigen-specific functional T cell recall response, measured as ex vivo IFNγ released in response to tetanus toxoid challenge, was inhibited in a receptor occupancy dependent manner and was consistent with the observed reduction of PD-1+ Tcon cells, to a maximum of approximately 90% relative to baseline within 30 days following single rosnilimab dose.**
- **Based upon these data, we believe rosnilimab's in vivo mechanism has the potential to treat T-cell driven human inflammatory diseases.**