Rosnilimab, a Novel PD-1 Agonist Monoclonal Antibody, Reduces T Cell Proliferation, Inflammatory Cytokine Secretion, and PD-1^{high} Expressing CD4 and CD8 T Cells:

Results From a Phase 1 Healthy Volunteer Clinical Trial

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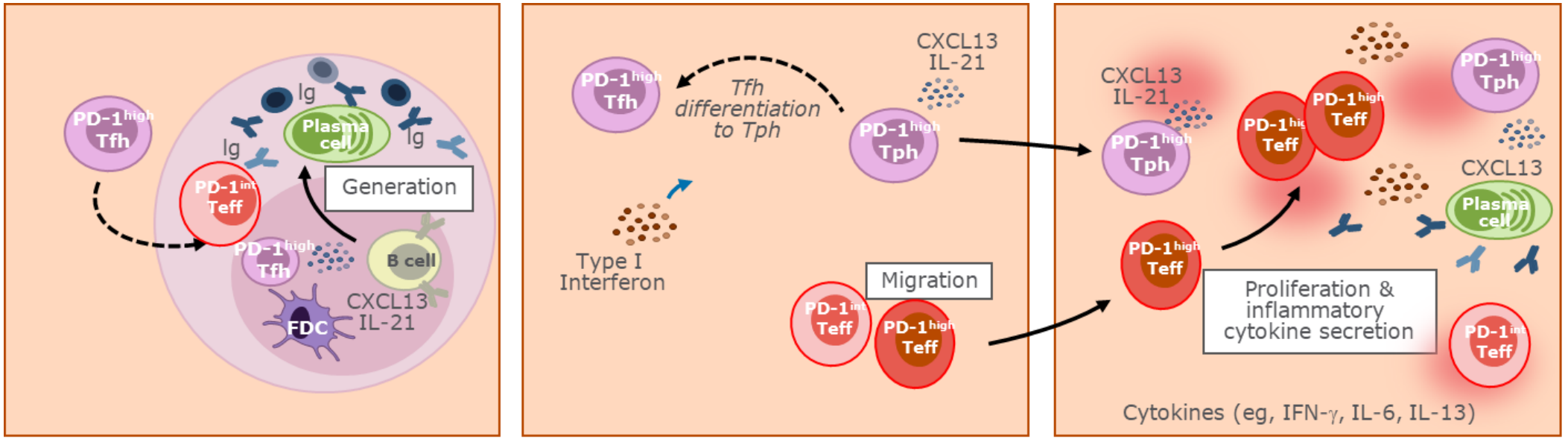
Disclosures

- This research was funded by AnaptysBio
- All authors are employees and stockholders of Anaptys

Programmed Cell Death Protein 1 (PD-1)

- Checkpoint receptor expressed on activated T cells
- Delivers co-inhibitory signal once bound to PD-1 L1 on an opposing cell
- PD-1 pathway mutations increase human susceptibility to multiple autoimmune diseases; insufficient PD-1 signaling can lead to dysregulated T cell responses

PD-1 expressed preferentially on activated Teff and Tfh/Tph cells mediating autoimmune pathology

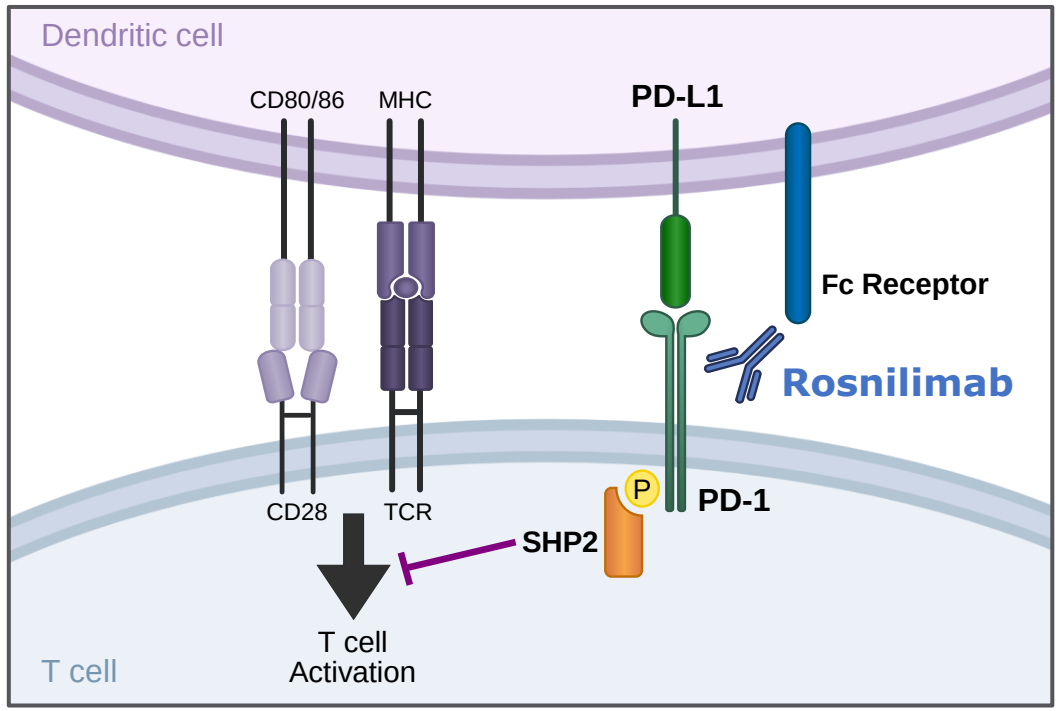


Adapted from Akiyama et al, Ann Rheum Dis, 2023.

Rosnilimab and Ulcerative Colitis

Rosnilimab Mechanism of Action

- PD-1 agonist antibody (IgG1)
- Depletes and agonizes PD-1+ T cells in inflamed tissue and in the periphery
- Potential to restore immune balance in numerous autoimmune and inflammatory indications



UC & PD-1

- Diarrhea and colitis are frequently reported irAEs with PD-1 antagonists[1]
- PD-1+ T cells are prevalent in inflamed lamina propria (>40%) and the periphery[2]
- PD-1 pathway gene expression is dysregulated in UC tissues[3]
- Tfh cells are increased in the germinal center of lymph nodes in UC compared to normal controls
- Mayo clinical score, erythrocyte sedimentation rate, C-reactive protein all positively correlated with frequency of circulating Tfh cells in UC[4]
- Reduction of elevated PD-1^{high} Tph cells in both UC colon and periphery correlates with remission[5,6]

[1]Martins et al, Nat Rev Clin Oncol. 2019:16(9):563-580;
[2]Roosenboom et al, Scand J of Gastro. 2021; 56(6):671-679;
[3]Massimino et al, Nat Comput Sci. 2021:511-515;
[4]Uzzan et al, Nature Med. 2022:28(4): 766–779;
[5]Long et al, Immunology Letters. 2021: 2-10;
[6]Rao et al, Nature. 2017; 542(7639):110-114

Methods

Objective:

- Assess safety and tolerability of single ascending doses (SAD) and multiple ascending doses (MAD) of rosnilimab in a Phase 1 healthy volunteer study

Single-Center Study

- SAD: Intravenous (IV) and subcutaneous (SC) administration assessed in 14 cohorts of 8 participants each (6 active, 2 placebo [PBO])
- MAD: SC administration assessed in 3 cohorts of 8 participants each (6 active, 2 PBO)
- Cohorts enrolled sequentially in each phase
- 144 participants enrolled:
  - SAD cohorts: 90 rosnilimab, 30 PBO
  - MAD cohorts: 18 rosnilimab, 6 PBO

Translational Pharmacodynamics

- FACS and tSNE (PD-1^{high} expressing T cell subset analyses)
- Tetanus toxoid recall (IFN-γ secretion)

Results

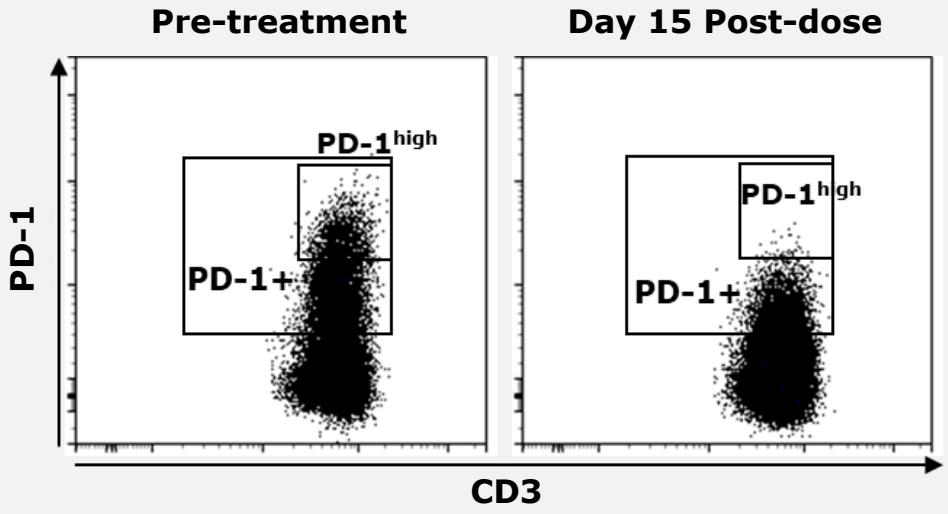
Safety, Tolerability, and PK

- Rosnilimab was well tolerated and there were no dose-limiting toxicities
  - 2 SAEs in SAD cohorts deemed unrelated to treatment; no SAEs in MAD cohorts
- No carcinogenic events observed; no increased risk of infections
- Favorable PK with 2 wk half-life and nearly dose-proportional exposure in IV and SC

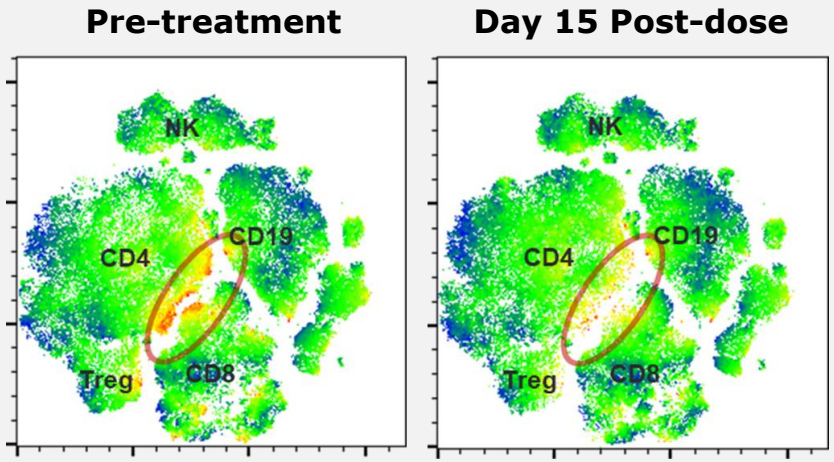
Translational Pharmacodynamics

- Receptor occupancy increased in a dose-dependent manner and consistent with PK

PD-1^{high} expressing T cells were reduced by >90% at Day 15 following rosnilimab administration

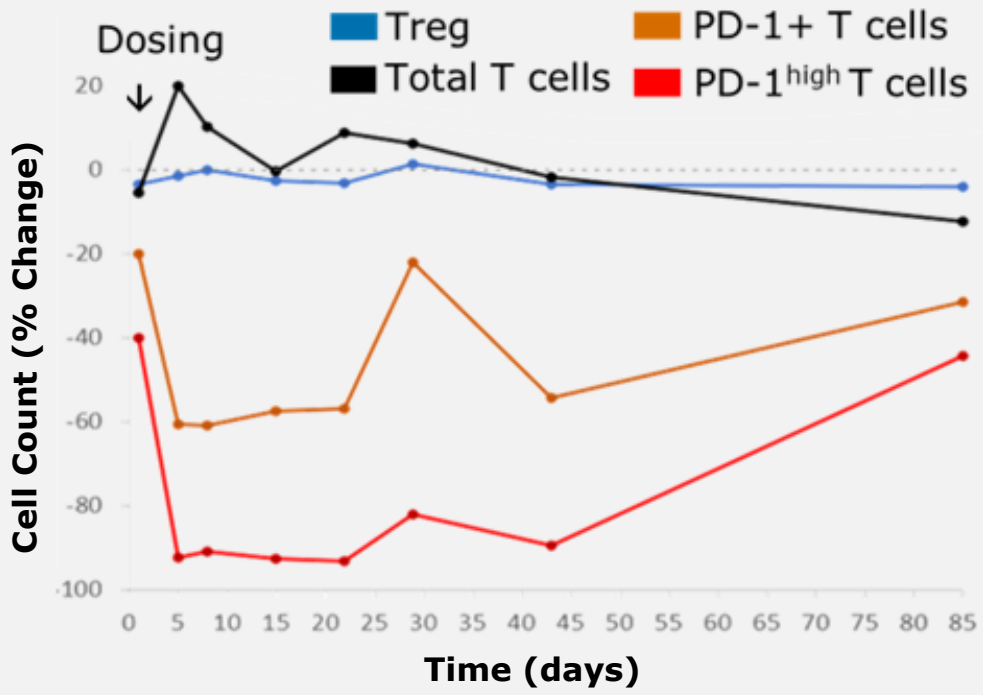


PD-1^{high} cells from the CD4+ and CD8+ T cells were reduced at Day 15 following rosnilimab administration



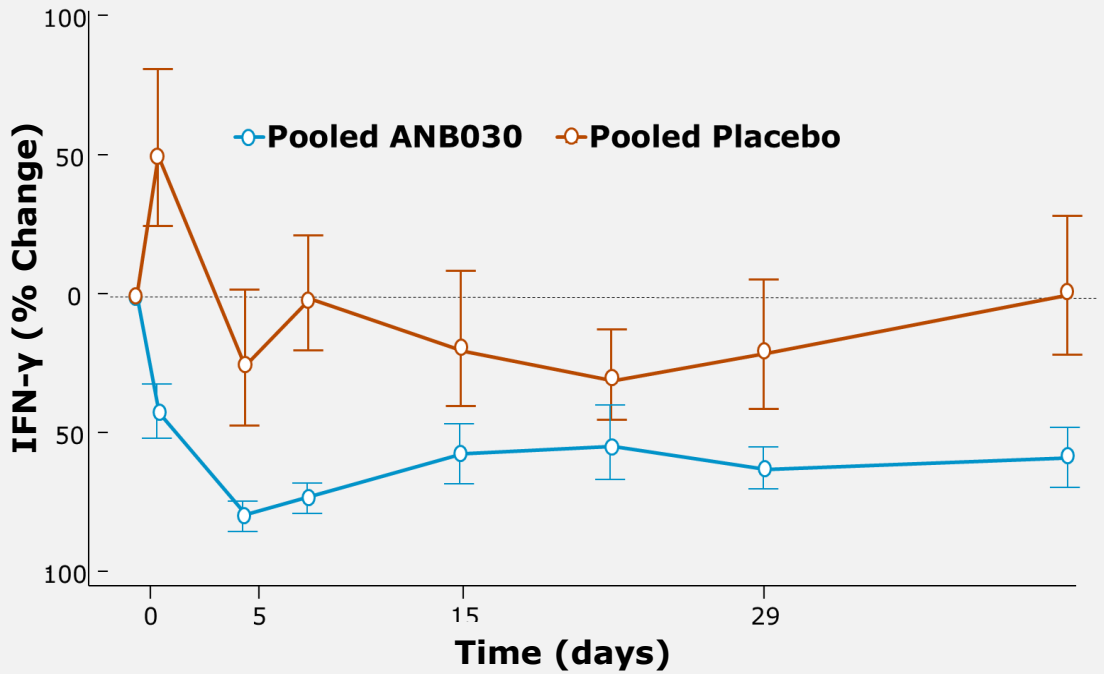
Translational Pharmacodynamics

Near complete reduction of PD-1^{high} expressing T cells persisted for over 30 days after a single 400mg dose



- Over 90% reduction of PD-1^{high} T cells and >50% reduction of PD-1+ T cells at Day 5
- PD-1^{high} T cells represent only 5-8% of T cells
- Overall T cell composition restored to a less activated state

Antigen-specific functional T cell assay of subject-derived whole blood



- Mean reduction up to -92% of IFNγ lasted for over 30 days

Conclusion

- In this first-in-human Phase 1 healthy volunteer study, rosnilimab was well tolerated with no clinically significant safety signals and a favorable PK profile
- Receptor occupancy increased in a dose-dependent manner consistent with PK and sustained for >30 days
- Pharmacodynamic activity resulted in rapid and sustained reduction in the quantity and functional activity of PD-1+ T cells for >30 days
- These data, combined with preclinical data demonstrating a prominent role for PD-1 in the pathogenesis of UC, support the rationale for evaluating rosnilimab in UC in an ongoing Phase 2 study (NCT06127043)