Antilimab (AK002), an Anti-Siglec-8 Antibody, Inhibits IL-33-mediated Mast Cell Activation and Neutrophilic Inflammation

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**BACKGROUND**

- IL-33 stimulation of mast cells is believed to enhance IgE-mediated degranulation and promote allergic inflammation
- Siglec-8 targeting monoclonal antibodies (mAb) have previously been shown to inhibit IgE-mediated mast cell activation and deplete eosinophils
- However, the effect of a Siglec-8 mAb has not been evaluated in IL-33-driven models of inflammation

- Siglec-8 is an inhibitory receptor selectively expressed on human eosinophils and mast cells, and therefore represents a novel target for the treatment of debilitating allergic, inflammatory, and proliferative diseases such as atopic eosinophilic gastrointestinal disorders (EGIDs), allergic conjunctivitis (AC), and chronic urticaria (CU)
- Antilimab (AK002) is a novel, humanized, non-fucosylated IgG1 monoclonal antibody to Siglec-8
- Engagement of Siglec-8 receptor by antolimab triggers:
  - Antibody dependent cell mediated cytotoxicity (ADCC) against eosinophils (blood)
  - Inhibition of mast cells and apoptosis of tissue eosinophils (tissue)
- Here we evaluate the effect of antilimab (AK002) in IL-33-driven models of inflammation

**METHODS**

- Acute neutrophil infiltration was induced in by intraperitoneal injection of IL-33 in mice
- Immune cells in the peritoneum were analyzed by flow cytometry
- Mast cells were isolated by FACS and subjected to RNA-seq analysis

**RESULTS**

- Antilimab (AK002) globally inhibits IL-33 mediated mast cell activation and neutrophilic inflammation
- Antilimab (AK002) treatment substantially modulates the IL-33-activated mast cell transcriptome
- Antilimab (AK002)-treated IL-33 activated mast cells resemble mast cells from control mice compared to isotype-treated IL-33 activated mast cells

**CONCLUSIONS/DISCUSSION**

- Treatment with antilimab (AK002) decreased acute neutrophilic inflammation by inhibiting IL-33 activation of mast cells
- Targeting Siglec-8 may have the potential to treat diseases associated with mast cells and eosinophils, including those where IL-33 can exacerbate immune responses, such as atopic dermatitis, asthma, and food allergy