Antolimab (AK002), an Anti-Siglec-8 Antibody, Suppresses Acute IL-33-induced Neutrophil Infiltration and Attenuates Tissue Damage in a Chronic Experimental COPD Model Through Mast Cell Inhibition

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Background

- IL-33 stimulation of mast cells is believed to play a role in driving acute and chronic inflammation in many diseases including, asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis (AD), and inflammatory bowel disease (IBD) (Figure 1)
- Siglec-8 monoclonal antibodies (mAb) have been previously been shown to inhibit mast cell activation and selectively deplete eosinophils
- However, the effect of an anti-Siglec-8 antibody has not been evaluated in non-allergic models of inflammation

Figure 1. Mast Cells and Eosinophils are Key Drivers of Acute and Chronic Inflammation

Methods

- Acute neutrophil recruitment was induced in Siglec-8-Transgenic (TG) mice by intraperitoneal injection of IL-33 (Figure 3)
- Peritoneal lavage was collected and analyzed 3 hours later
- Experimental COPD was induced by exposing TG mice to cigarette smoke (CS) for 12 weeks followed by analysis of lung function and inflammation. Mice were dosed therapeutically on week 8 with antolimab or isotype control mAb

Figure 2. Antolimab (AK002) Mechanism of Action

Results

- IL-33 directly activates mast cells and antolimab treatment substantially modulates the mast cell transcriptome
- These data demonstrate that antolimab directly inhibits non-IgE mediated mast cell activation in vivo

Figure 3. Mouse Model of IL-33-Induced Neutrophil Infiltration

Conclusions

- Antolimab reduces acute IL-33-dependent non-IgE allergic inflammation by inhibiting non-IgE-mediated mast cell activation
- Consistent with IL-33-mediated mast cell inhibition, antolimab downregulated genes associated with TNFα, mTNF, and PI3K signaling
- Antolimab also suppressed chronic non-allergic inflammation, suggesting anti-Siglec-8 mAbs can be effective in both allergic and non-allergic disease settings

Figure 4: Antolimab Reduces IL-33-driven Inflammation

Figure 5: Antolimab Globally Inhibits IL-33 Activated Mast Cells

Figure 6: Antolimab Inhibits Downstream Signaling Pathways of IL-33 Activation

Figure 7: Antolimab Reduces Chronic Inflammation and Improves Lung Function in Cigarette-Smoke-Induced Experimental COPD


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