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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ABSTRACT

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• Acute neutrophil recruitment was induced in Siglec-8-Transgenic (TG) mice by intratracheal injection of IL-33 (3) (Figure 3)

- Peripheral lavage was collected and analyzed 3 hours later

- Experimental COPD was induced by exposing TG mice to chronic 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 3. Mouse Model of IL-33-Induced Neutrophil Infiltration

BACKGROUND

- IL-33 stimulation of mast cells is believed to play a role in driving acute and chronic inflammatory diseases including, asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis (AD), and inflammatory bowel disease (IBD) (Figure 1)

- Siglec-8 monoclonal antibodies (mAbs) 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

• Antolimab (AK002), an Anti-Siglec-8 monoclonal antibody, was tested in a 16-week mouse model of cigarette smoke-induced chronic obstructive pulmonary disease (COPD), atopic dermatitis (AD), and inflammatory bowel disease (IBD) (Figure 1)

• Figure 4. Antolimab Reduces IL-33-driven Inflammation

RESULTS

- Eosinophil stimulation of mast cells is believed to play a role in driving inflammatory and proliferative diseases

- Inhibition of mast cells

- Antibody dependent cell mediated cytotoxicity (ADCC) against blood eosinophils

- Activation of neutrophils

- Inhibition of mast cell

- Neutrophils

- Monocytes

- Mast Cells

- 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 5. Antolimab Globally Inhibits IL-33 Activated Mast Cells

CONCLUSIONS

- Antolimab reduces acute IL-33-driven non-allergic inflammation by inhibiting non-IgE-mediated mast cell activation

- Consistent with IL-33-mediated mast cell inhibition, antolimab downregulated genes associated with TNFα, mTOR, 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 7. Antolimab Reduces Chronic Inflammation and Improves Lung Function in Cigarette-Smoke-Induced Experimental COPD

REFERENCE