Preclinical profile of STAR-0310, a novel OX40 antagonistic monoclonal antibody

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INTRODUCTION

Atopic dermatitis (AD) is a relapsing, inflammatory skin disease with a prevalence of 2–5% in young adults and up to 20% in children. Skin barrier dysfunction, inflammation, and dysbiosis contribute to AD development and chronicity which has a great impact on the patient’s quality of life, especially due to pruritus. During the acute phases of AD, there is a notable modulation of Th2 and Th2 cytokine responses, with variable Th17 involvement, while the chronic phases include additional Th1 activation.

About STAR-0310

STAR-0310 is a novel, affinity-matured YTE-modified (M252Y/S254T/T256E) monoclonal antibody that inhibits the OX40 receptor. Compared to the parent molecule, telazorlimab (STAR-0305), with previously demonstrated proof of concept in atopic dermatitis, it has increased affinity for OX40 binding and YTE modification in the Fc region. The YTE modification in the Fc region reduces the preclinical profile of STAR-0310, a novel OX40 antagonistic monoclonal antibody

RESULTS

Affinity of STAR-0310 to human OX40

STAR-0310, an affinity-matured, YTE-modified derivative STAR-0305, demonstrates an approximately 8-fold enhancement in binding affinity to human OX40 measured by SPR. Table 1. Comparative analysis reveals that STAR-0310 retains similar binding affinity to human OX40 to STAR-0308, which does not have the YTE modification, suggesting that the YTE modification does not influence the STAR-0310 binding affinity to human OX40.

Table 1. Binding affinity of STAR-0310 to human OX40 measured by SPR

<table>
<thead>
<tr>
<th>Name</th>
<th>EC50 (nM)</th>
<th>Fold diff to STAR-0305</th>
<th>Fold diff to STAR-0308</th>
<th>Fold diff to AMG451</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAR-0310</td>
<td>0.13 ± 0.01</td>
<td>34.87 ± 2.27</td>
<td>5.00 ± 0.28</td>
<td>-----</td>
</tr>
<tr>
<td>STAR-0308</td>
<td>1.73</td>
<td>2.50 ± 0.05</td>
<td>0.34 ± 0.02</td>
<td>-----</td>
</tr>
<tr>
<td>AMG451</td>
<td>1.31</td>
<td>1.00 ± 0.00</td>
<td>1.00 ± 0.00</td>
<td>-----</td>
</tr>
</tbody>
</table>

STAR-0310 potency

Enhanced affinity to OX40 in STAR-0308 results in a dramatic increase in potency in the cytokine release inhibition compared to STAR-0305. The incorporation of the YTE mutation in STAR-0310 does not affect the potency, showing similar EC50 in cytokine release inhibition for both STAR-0310 and STAR-0308. The potency of STAR-0310 in cytokine release inhibition is comparable to rocatinlimab (AMG451) (Figure 3).

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Figure 3. Potency of STAR-0310 assessed in cytokine release inhibition assay

STAR-0310 ADCC

STAR-0310 showed less activated T cell depletion compared to rocatinlimab, which demonstrated a 5-fold greater killing capacity. STAR-0310 showed ~75% less maximal killing on activated T cells relative to rocatinlimab (Figure 4).

Figure 4. ADCC on activated T cells

CONCLUSIONS

- STAR-0310 is a high affinity anti-OX40 antibody, demonstrating an ~8 fold increase in binding affinity to human OX40 compared to telazorlimab.
- Enhanced affinity of STAR-0310 results in a significant inhibition of cytokine release, as demonstrated in T cell proliferation assay. STAR-0310 has comparable potency to rocatinlimab.
- There is significantly less ADCC potential with STAR-0310 compared to rocatinlimab which is related to specific ADCC engineering, including the YTE modification and lack of disulfide formation. Less ADCC in the context of robust potency has the potential to improve safety profile of this OX40 antagonist without impacting potential efficacy. Compared to rocatinlimab, STAR-0310 has 5-fold less depletion of activated T cells, while it shows 46-fold less elimination of regulatory T cells through ADCC.
- Impact of YTE modification on pharmacokinetics of STAR-0310 is under investigation.
- These preclinical data support further development of STAR-0310 for the treatment of moderate-to-severe AD and other immunologic diseases.

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REFERENCES


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