AXA-042 - A Novel Systemic TLR2/6 Agonist for Anti-Tumor Therapy.

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INTRODUCTION

• Treatment approaches that engage both the innate and adaptive immune response have the potential to transform anti-cancer therapy, especially in settings of checkpoint inhibitor insensitivity or acquired resistance.
• Toll-like receptors (TLRs) mediate the initial cellular response to external pathogens or endogenous alaramins, activating downstream pro-inflammatory cascades and leading to the activation and recruitment of key innate subsets.
• TLR2 is a cell surface receptor, expressed predominantly on macrophages, dendritic cells (DC), neutrophils and subsets of NK and T cells. TLR2 signaling plays an important role in NK and T cell cytolytic cell functions, as well as DC and macrophage activation.

AXA-042 is a novel synthetic TLR2/6 agonist designed for systemic delivery to re-engage the innate immune response to help overcome tumor immune escape.

MATERIALS AND METHODS

• In vitro potency and selectivity of AXA-042 was assessed across a panel of human and mouse HEX-blue TLR reporter assays.
• AXA-042 activity was profiled relative to other TLR agonists in human PBMC cytokine release assays.
• AXA-042 in vivo efficacy was evaluated in the EMT6 and CT26 syngeneic tumor models.
• The Nanostring nCounter Mouse PanCancer Immune Profiling Panel was used to identify AXA-042 tumor-localized and peripheral response signatures.

RESULTS

• Systemic delivery of AXA-042 was well tolerated in vivo, demonstrated innate response engagement and anti-tumor efficacy as monotherapy and in combination with anti-PD-1 Ab immunotherapy.

• AXA-042 has completed GLP toxicology studies and initiation of Phase 1/1b trial is planned for early 2022.

CONCLUSIONS

Figure 1. AXA-042 is a potent and selective TLR2/6 Agonist

Figure 2. AXA-042 Displays a Distinct PBMC Cytokine Release Profile

Figure 3. Systemic AXA-042 Efficacy in the EMT6 Tumor Model is Associated with Cytokine Release

Figure 4. AXA-042 Enhances anti-PD-1 Ab Response in the CT26 Tumor Model

Figure 5. AXA-042 Induces DC and TAM Activation

Figure 6. AXA-042 CT26 Efficacy is Macrophage and TNFα Dependent

Figure 7. AXA-042 Engages the Innate and Adaptive Immune Response Pathways

Figure 8. AXA-042 Target Engagement Signature Identified in Whole Blood

Non-Responders Display a Distinct Whole Blood DEG Signature

Table 1. TLR EC50 (ng/ml)

<table>
<thead>
<tr>
<th>TLR</th>
<th>EC50 (ng/ml)</th>
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<tr>
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<tr>
<td>TLR2/6</td>
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