Preclinical pharmacokinetic, pharmacodynamic and efficacy relationships of ALG-093702, a liver targeted PD-L1 small molecule inhibitor, in different in vivo models

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INTRODUCTION AND OBJECTIVES

The PD-1/PD-L1 immune checkpoint pathway is an attractive target to reverse immune tolerance in chronic hepatitis B (CHB). However, due to the systemic immune adverse effects associated with antibodies, a lower dose of PD-1/PD-L1 antibodies has been used in CHB vs. the dose used for cancer. ALG-093702 is a liver-targeted PD-L1 small molecule inhibitor that preferentially partitions into the liver and thereby may potentially mitigate extra-hepatic on-target related toxicity. Characterizing the relationship between pharmacokinetics (PK), pharmacodynamics (PD) and the efficacy of ALG-093702 is critical for selecting the dosing strategy of novel liver targeted PD-L1 inhibitor drugs.

METHODS

Biochemical PD-1/PD-L1 interaction was assessed by AlphaLISA®. Cellular activity was measured using a co-culture reporter assay in which NFAT activity of Jurkat T cells was constitutively inhibited by the engagement of PD-L1 by PD-L1-expressing CHO cells. Oral dosing of ALG-093701, a produg of ALG-093702, was used for in vivo PK/PD/efficacy studies. In vivo PK/PD/efficacy were assessed in humanized-PD-L1 MC38 subcutaneous tumors and/or a liver metastasis mouse model. Target engagement was assessed by FACs using MIH1 PD-L1 antibody which competes with PD-L1 antibodies has been used in CHB vs. the dose used for cancer. ALG-093702 is a liver-targeted PD-L1 small molecule inhibitor that preferentially partitions into the liver and thereby may potentially mitigate extra-hepatic on-target related toxicity. Characterizing the relationship between pharmacokinetics (PK), pharmacodynamics (PD) and the efficacy of ALG-093702 is critical for selecting the dosing strategy of novel liver targeted PD-L1 inhibitor drugs.

RESULTS

Discovery of a Highly Potent PD-L1 Small Molecule Inhibitor

Table 1: Biochemical and Cellular activities of Aligos PD-L1 inhibitor vs. FDA-approved antibodies

<table>
<thead>
<tr>
<th>ALG-093702</th>
<th>Intracellular</th>
<th>Durvalumab</th>
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</thead>
<tbody>
<tr>
<td>Biochemical Activity</td>
<td>PD-1/PD-L1 Interaction (EC_{50} (nM))</td>
<td>0.159 ± 0.007 (n=2)</td>
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<tr>
<td>PD-L1 Dimerization (EC_{50} (nM))</td>
<td>not applicable</td>
<td>not applicable</td>
</tr>
<tr>
<td>Cellular Activity</td>
<td>Jurkat PD-1/PD-L1 Blockade</td>
<td>3.3 ± 0.3 (n=2)</td>
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</tbody>
</table>

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CONCLUSIONS

• ALG-093702 is a liver-targeted PD-L1 small molecule inhibitor with similar in vitro potency in vivo PD-L1 target occupancy and tumor growth inhibition as durvalumab.
• Increases in target occupancy were dose dependent, with a correlation provided guidance for the efficacious human dose prediction and dosing strategy for clinical studies of oral liver targeted PD-L1 small molecule inhibitors.

CONTACT INFORMATION

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*Financial disclosure: All authors are current or former employees of Aligos Therapeutics, Inc.

Figure 1: Mean plasma and tissue concentrations of ALG-093702 in C57BL/6 mice

Figure 2: Effect of Aligos PD-L1 inhibitor on target engagement

Figure 3: In vivo anti-tumor activity and PD-L1 Target occupancy of ALG-093702 in humanized-PD-L1 MC38 subcutaneous tumor

Figure 4: In vivo PK/PD relationship of ALG-093702 in MC38 human-PD-L1 subcutaneous model