Preclinical Characterization of MGD013, a PD-1 x LAG-3 Bispecific DART® Molecule


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NCT03219268

Abstract

Background: Monoclonal antibodies (mAbs) that target the immune checkpoint antibodies (PD-1/LAG-3) are currently in clinical development. Combination of checkpoint inhibitors may offer synergistic antitumor effects. MGD013, a humanized IgG4 tetravalent bispecific DART molecule, is a mAb1 VH + mAb2 VH DART that co-engages PD-1 and LAG-3. Its design and preclinical characterization are described.

Methods: A panel of tumor cell lines expressing PD-1, LAG-3, both or neither and their isotype controls was tested for MGD013 binding in an ELISA format and for IFN-γ induction in combination with other drugs. The specificity of MGD013 binding to human PD-1 and LAG-3 was determined. MGD013 and its components were tested for cytokine, proliferative, and expression assays. A Phase 1 clinical trial was conducted.

Results: MGD013 binds to tumor cells expressing PD-1 and LAG-3, and to the PD-1+LAG-3+ tumor cell line Daudi. MGD013 enhanced IFN-γ secretion in response to antigen stimulation in a PD-1 dependent manner. Following the Phase 1 clinical trial, MGD013 is currently in Phase 2 trials combining MGD013 with other immune checkpoint inhibitors.

Conclusion: MGD013 is a promising PD-1/LAG-3 bispecific DART molecule that has shown promising preclinical and early clinical activity.

Introduction

Rationale

PD-1 and LAG-3 are two inhibitory molecules that deliver negative signals upon interaction with ligands expressed on tumor cells and/or antigen presenting cells (PD-L1, PD-L2, or MHC-II).

PD-1 and LAG-3 are Expressed on TILs

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>PD-1</th>
<th>LAG-3</th>
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<tbody>
<tr>
<td>Lung Adenocarcinoma</td>
<td>*</td>
<td>+</td>
</tr>
<tr>
<td>Lung Squamous Cell Carcinoma</td>
<td>*</td>
<td>+</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Other Tumor Types</td>
<td>+</td>
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Combination mAb blockade of PD-1 and LAG-3 in animal models resulted in enhanced antitumor immunity than either mAb alone and is actively being tested clinically.

MGD013 is a checkpoint inhibitor DART molecule currently under clinical evaluation that has been designed to restore T-cell effector function and enhance antitumor activity by simultaneously targeting PD-1 and LAG-3.

MGD013 Binds PD-1 and LAG-3 and Blocks Ligand Interactions

MGD013 Co-engages PD-1 & LAG-3

Indicated molecules were evaluated using enzyme fragment complementation assay employing PathHunter® U2OS PD-1/LAG-3 dimerization cell line (DiscoverX).

MGD013 Disrupts PD1- & LAG3- Mediated T-cell Inhibitory Signaling

MGD013 Enhances Antigen-driven T-cell Cytokine Function In Vitro

Enhancement of T-cell response following SEB stimulation

MGD013 Enhances Immune Responses in TME Models

Well Tolerated in Cynomolgus Monkeys

Conclusions

MGD013 was engineered as a tetravalent bispecific DART molecule in a human hinge-stabilized IgG4 backbone.

MGD013 is capable of simultaneously binding PD-1 and LAG-3.

MGD013 blocks PD-1/PD-L1/PD-L2 and LAG-3/MHC-Class II interactions and resultant inhibitory signal with potency comparable to MGA012 (anti-PD-1), and replicas of nivolumab or 25F7 (anti-LAG-3).

MGD013 enhances T-cell responses compared to individual mAbs or combination mAb blockade.

MGD013 was well-tolerated and demonstrates favorable pharmacokinetics in cynomolgus monkeys.

Clinical testing of MGD013 in several cancer indications is ongoing [NCT03219268].