Preclinical Characterization of MGA012, A Novel Clinical-stage PD-1 Monoclonal Antibody

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Abstract

Background: Monoclonal antibodies (mAbs) that target immune checkpoint pathways, such as the cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and the programmed cell death protein-1 (PD-1) pathways, have demonstrated broad clinical efficacy across a variety of malignancies as monotherapy or in a combination. MGA012 is a novel anti-PD-1 mAb developed to disrupt the PD-1 interaction with PD-L1/PD-L2 to restore or improve T-cell function as stand-alone therapy or in combination with other immune approaches.

Methods: Murine PD-1 mAbs were generated and benchmarked against replicas of the approved mAbs, nivolumab, and pembrolizumab. Several mAbs with favorable characteristics were further chimerized or humanized. MGA012, a humanized, hinge-stabilized IgG4k mAb, was selected based on binding and biophysical properties as well as a functional characterization inclusive of enhanced T-cell activation following superantigen restimulation.

Results: MGA012 bound human PD-1 with an affinity equal to or exceeding those of replicates of nivolumab or pembrolizumab. MGA012 bound PD-1-expressing cell lines and chronically-activated T cells, blocked PD-1 interactions with PD-L1/PD-L2, resulting in inhibition of PD-1 signaling, and enhanced antigen-driven cytokine secretion to levels comparable to those observed with nivolumab or pembrolizumab replicates. Furthermore, characterization of MGA012 in ex vivo tumor microenvironment immune models showed activation profiles recapitulating the benchmark PD-1 mAbs. MGA012 showed combinatorial activity in vitro when added to anti-CTLA-4 or anti-LAG-3 lymphocyte-activation gene 3 (LAG-3) mAbs and enhanced the activity of a T-cell redirecting molecule in a mouse tumor model. MGA012 showed no unexpected cross-reactivity in human tissues, with staining observed primarily in lymphocytes and lymphoid organs. In a repeat-dose (10–150 mg/kg QWx4) study in cynomolgus monkeys, pharmacokinetics (PK) was linear with a beta half-life of 11.2 days (4.6 SD) and full PD-1 occupancy on circulating T cells at all doses tested. Occupancy of ~80%, persisting for ~7–8 weeks, was also observed in monkeys receiving a single 10 mg/kg dose. MGA012 was well tolerated in cynomolgus monkeys and demonstrated a favorable safety profile with a no-observed-adverse-effect level (NOAEL) of 150 mg/kg.

Conclusion: MGA012 is a novel anti-PD-1 mAb with favorable preclinical characteristics, including PD-1 binding and biophysical properties, PD-1 pathway blockade, the ability to enhance T-cell responses in vitro and in vivo, and a favorable PK and safety profile in cynomolgus monkeys. Clinical trials are ongoing (NCT03059823) or in planning stage to ascertain the safety and preliminary activity of MGA012 alone or in combination with other immune oncology agents, including T-cell redirecting bispecific DART® molecules.

Introduction and Strategy


title

MGA012 Binding Characteristics Compares favorably to benchmarks

A. Soluble Human PD-1 Anti-PD-1 mAbs

<table>
<thead>
<tr>
<th>MGA012</th>
<th>Nivo†</th>
<th>Pembrolizumab†</th>
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<tbody>
<tr>
<td>Kd (nM)</td>
<td>4.3 x 10⁵</td>
<td>2.4 x 10⁴</td>
</tr>
<tr>
<td>Kd (nM)</td>
<td>3.1</td>
<td>1.0</td>
</tr>
<tr>
<td>Kd (nM)</td>
<td>4.3 x 10⁴</td>
<td>2.4 x 10³</td>
</tr>
</tbody>
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B. Binding to PD-1-NSG Cells

Inhibition of PD-1 Ligand Binding

MGA012 blocks PD-L1 and PD-L2 binding to NSG-PD-1 cells in the presence of titrating concentrations of the indicated PD-1 mAbs.

Signal Blockade & Functional Activity

MGA012 reverses PD-1 signal inhibition

A. Inhibition of SHP-2 Activation

B. Release of NFAT Blockade

C. Enhanced IFN-γ Secretion

Concomitant Activity

CTLA-4 or LAG-3 blockade enhances MGA012-driven T-cell response

Combination activity with CTLA-4 or LAG-3 blockade can enhance MGA012-driven T-cell response.

MGA012 Enhances Antitumor Activity in Vivo

Combination activity with CD3-based DART molecules

MGA012 Evaluation in Cynomolgus Monkeys

Linear PK and full T-cell occupancy at all doses tested

Immune Activation in the Tumor Microenvironment

MGA012 induces immune changes consistent with other PD-1 mAbs

A mouse anti-PD-1 mAb panel was subjected to performance-based selection and benchmarked against replicates of nivolumab* and pembrolizumab:*

- Binding characteristics
- Ligand-binding and inhibitory signaling binding
- Immune response enhancement (cytokine release)
- Cynomolgus monkey cross-reactivity
- Lead mAbs were humanized and engineered as a hinge-stabilized IgG4k mAb for further testing

*Replicas of nivolumab and pembrolizumab were generated by MacroGenics based on published sequences.

Conclusions

- MGA012 blocks PD-1/PD-L1 and PD-L2 interactions, interrupts PD-1 signaling and enhances antigen-induced IFN-γ release with potency comparable to replicates of nivolumab or pembrolizumab.
- MGA012 shows combinatorial activity with LAG-3 or CTLA-4 in antigen-driven T-cell stimulation assays (see also Poster 337, 10 Nov 17 and Poster 308, 11 Nov 17).
- MGA012 enhances antitumor activity in combination with CD3-based DART molecules.
- MGA012 is well-tolerated and demonstrates favorable PK with full receptor occupancy at doses ≥ 10 mg/kg in cynomolgus monkeys.
- A Phase 1 study (NCT03059823) evaluating the safety, tolerability, and PK of MGA012 in patients with advanced solid tumors is ongoing (see Poster 249, 10 Nov 17).