A PD-1 x CTLA-4 Bispecific DART® Protein with Optimal Dual Checkpoint Blockade and Favorable Tolerability in Nonhuman Primates


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Abstract

PD-1 x CTLA-4 DART Molecule In Vitro:

MGD019, the PD-1 x CTLA-4 DART molecule, demonstrated binding to immobilized programmed cell death protein 1 (PD-1) and PD-1-expressing cells lines, inhibition of PD-1 interaction with PD-L1 or PD-L2, as well as reversal of PD-1-mediated T-cell signal inhibition in gene-reporter assays comparable to that supported by a replica of nivolumab. Similarly, binding, ligand blocking and rescue of CTLA-4-mediated T-cell suppression was comparable to that supported by a replica of ipilimumab. MGD019 demonstrated activation properties comparable to the combination of the replicas of nivolumab and ipilimumab in a variety of human primary T-cell assays and showed enhanced B7-ligand binding blockade over that mediated by the ipilimumab replica on PD-1/CTLA-4 double-positive cells.

PD-1 x CTLA-4 DART Molecule In Vivo:

In cynomolgus monkeys, MGD019 exhibited a PK profile consistent with that of an IgG4 and was well tolerated with no mortality or significant adverse findings up to 75 mg/kg QWx3, the highest dose tested. T-cell expansion in the peripheral blood and lymphoid organs was observed, which was attributable to the CTLA-4 blocking arm, since no such finding was observed with similar or higher doses of the anti-PD-1 constituent of the bispecific molecule.

Significance:

The favorable safety and tolerability profile of the MGD019 combined with its enhanced activity on PD-1/CTLA-4 double-positive cells suggests a potential for an improved therapeutic window for PD-1/CTLA-4 co-blockade strategies, with the administration of a single molecule providing dosing convenience and ease of incorporation into additional therapeutic regimens.

Introduction

Rationale for PD-1 x CTLA-4 Dual Checkpoint Targeting Strategy

PD-1 x CTLA-4 DART

MGD019 is designed to block both PD1 and CTLA4 checkpoint inhibition pathways with enhanced activity on PD1/CTLA4 double-positive cells.

MGD019 Co-engages PD-1 and CTLA-4

Molecules were evaluated using enzyme fragment complementation assay employing PathHunter® U2OS PD-1/CTLA-4 dimerization cell line (DiscoverX).

MGD019 Is Equipotent to Nivolumab + Ipilimumab Combination In Vitro

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MGD019 Displays Prolonged Exposure and T-cell Occupancy in Cynomolgus Monkeys

MGD019 Expands Memory T Cells In Vivo

Conclusions

- MGD019 binds to and blocks its targets with increased activity on dual PD-1/CTLA-4-expressing cells.
- MGD019 enhances T-cell responses in vitro to the level achieved by a combination of replicas of nivolumab and ipilimumab.
- MGD019 was well tolerated in cynomolgus monkeys with a safety profile similar to that observed with PD-1 blockade alone while demonstrating biological effects of CTLA-4 antagonism.