MGD019, a PD-1 x CTLA-4 Bispecific DART® Molecule, Provides Simultaneous Blockade of PD-1 and CTLA-4 Checkpoint Pathways


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Combinatorial blockade of PD-1 and CTLA-4 has shown clinical benefit beyond that observed with individual mAbs, albeit with increased toxicity. MGD019 is a PD-1 x CTLA-4 tetravalent bispecific molecule with a human IgG4 backbone to limit effector function and designed to engage each target in a bivalent modality. MGD019 demonstrated independent blockade of PD-1/B7 and PD-1/CTLA-4 interactions with a potency comparable to that achieved by replicates of the approved ipilimumab (ipi) and nivolumab (nivo). MGD019 enhanced antigen-driven in vitro T-cell activation to a level comparable to the combinatorial PD-1 plus CTLA-4 blockade. Tumor microenvironment models that recapitulate vascular or stromal compartments confirmed MGD019 induced in vitro immune response profiles comparable to those observed with replicates of ipi plus nivo. Multiple iSH showed enrichment of PD-1/CTLA-4-dual positive cells in tumor-infiltrating lymphocytes (TILs) relative to normal tissues, where distinct populations expressed PD-1 or CTLA-4. MGD019 mediated enhanced blockade of PD-1 x CTLA-4 in cynomolgus monkeys, while demonstrating biological effects of MGD019 in cancer patients.