A Phase 1, First-in-Human, Open-Label, Dose Escalation and Cohort Expansion Study of MGD019, a Bispecific DART® Protein Binding PD-1 and CTLA-4, in Patients with Unresectable or Metastatic Neoplasms

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Background

- Combined blockade of PD-1 and CTLA-4 with 2 checkpoint inhibitors, ipilimumab and nivolumab, increases antitumor activity beyond either single agent alone in patients with metastatic melanoma1.
- Combination of ipilimumab and nivolumab approved in US for patients with microsatellite instability high or mismatch repair deficient metastatic colorectal carcinoma, as well as intermediate or poor-risk advanced renal cell carcinoma.

MGD019: Tetravalent Bispecific PD-1 x CTLA-4 DART Molecule

- MGD019 is a bispecific antibody that reverses both PD-1- and CTLA-4-mediated T-cell suppression in vitro.
- In addition to convenience of single-administration dual checkpoint blockade, bispecific reagents may drive preferential accumulation and enhanced effect on target cells that express both molecules.
- Modeling studies predict that slower dissociation of a bispecific antibody from a dual-target binding complex may increase interaction avidity over that of the combination of single-target bound species.

MGD019 Co-Engages PD-1 and CTLA-4 on Dual-expressing Cells

- MGD019 was well-tolerated in non-human primates.
- MGD019 demonstrates good pharmacokinetics consistent with IgG4 Fc backbone.
- MGD019 receptor occupancy correlates with its serum concentration.

MGD019 Supports Homeostatic Proliferation of T Cells in Monkeys

- MGD019 enhances T-cell activation.

Key Study Objectives

- Primary Objective: Characterize safety, including tolerability, dose limiting toxicities (DLTs), and maximum tolerated dose (MTD) or maximum administered dose (MAD) if no MTD is defined, of MGD019 given intravenously to patients with advanced solid tumors
- Secondary Objectives: Characterize PK and immunogenicity; Describe preliminary evidence of antitumor activity using conventional RECIST v1.1 and immune-related RECIST.
- Exploratory Objectives: Explore relationship between PK, pharmacodynamics, and antitumor activity; immune-regulatory effects of MGD019, including measures of immune cell activation/exhaustion in peripheral blood and/or tumor biopsy specimens; relationships among PD-1, PD-L1, and CTLA-4 expression on tumor cells and immune cell infiltration within biopsy specimens (including CD4+ and CD8+ T cells) and antitumor activity; relationship between gene profiles and antitumor activity; relationship between tumor mutational burden and antitumor activity.

Entry Criteria

- Key Inclusion Criteria:
  - Dose escalation: Patients with histologically proven, unresectable, locally advanced or metastatic solid tumors for whom no approved therapy with demonstrated clinical benefit is available or patients who are intolerant to standard therapy
  - Cohort Expansion Phase: Disease-specific prior therapy requirements to be specified
  - ECOG performance status of 0-1
  - Life expectancy ≥12 weeks
  - Measurable disease as per RECIST 1.1 for the purpose of response assessment must either (a) not reside in a field that has been subjected to prior radiotherapy or (b) have demonstrated clear evidence of radiographic progression since the completion of prior radiotherapy and prior to study enrollment
  - All patients must have an identified formalin-fixed, paraffin-embedded tumor specimen for immunohistochemical evaluation of pharmacodynamic markers of interest
  - Acceptable laboratory parameters and adequate organ reserve

Key Exclusion Criteria:

- In patients who have previously received an immune checkpoint inhibitor, toxicities related to the CPI must have resolved to ≤ Grade 1 or baseline.
- Patients with well controlled immune endocrinopathies secondary to prior checkpoint therapy are eligible
- Patients with symptomatic CNS metastases. Patients with history of CNS metastasis must have been treated and must not have any current treatment for the CNS disease, progression of CNS metastases on MRT or CT for at least 14 days after last day of prior therapy for the CNS metastases, or concurrent leptomeningeal disease or cord compression
- Patients who experienced the following Grade 3 CPI-related AEs are ineligible: ocular AE, changes in liver function tests that met the criteria for Hy's law, neurologic toxicity, colitis, renal toxicity, pneumonitis
- Patients with prior therapy with a combination of monoclonal antibodies against PD-1/PDL1 and CTLA-4 will be excluded in Cohort Expansion
- Patients with any history of known or suspected autoimmune disease with certain exceptions
- History of prior allogeneic bone marrow, stem cell, or solid organ transplantation
- History of trauma, major surgical procedure, systemic neoantigen therapy, or investigational therapy within 4 weeks and treatment with radiation therapy within 2 weeks prior to initiation of study drug administration

References


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