A Phase 1, Open Label, Dose Escalation Study of MGD009 (Orlotamab), A Humanized B7-H3 x CD3 Bispecific DART® Molecule, in Combination with MGA012, An Anti-PD-1 Antibody, in Patients with Relapsed or Refractory B7-H3-Expressing Tumors

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Background

Orlotamab: B7-H3 x CD3 Bispecific DART Molecule
- Humanized Fc-bearing B7-H3 x CD3 DART molecule designed to redirect T cells to eliminate B7-H3-expressing target cells through co-engagement of B7-H3 on target cells and CD3 on T cells
- Human IgG1 Fc domain mutated to reduce/eliminate effector function via binding to FcγRs and complement
- Retains binding to neonatal Fc receptor, enabling use of IgG salvage pathway to prolong circulating half-life
- Enhances activation and proliferation as well as production of cytokines and mediators (granulocyte/monocyte) of T-cell cytolytic activity
- Currently enrolling a Phase 1 study of orlotamab in patients with advanced B7-H3-positive solid tumors

MGA012: Anti-PD-1 Monoclonal Antibody (mAb)*
- Humanized proprietary anti-PD-1 mAb
  - Hinge stabilized humanized IgG4
  - Blocks PD-L1 and PD-L2 ligand binding to PD-1 and mediates enhanced T-cell responses

MGA012 Cooperates with Orlotamab to Enhance Reporter Cell Activity in a T Cell/Tumor Cell Co-culture Signaling Model System

MG012 Enhances Orlotamab-Mediated T-cell Killing

In Vitro

A. CTL Activity
B. PD-L1 Expression
C. PD-1 Expression
D. PD-L1 Expression
E. IFNγ
F. Cell Viability
G. Orlotamab CTL Potency

Rationale

- B7-H3 is over-expressed on wide range of malignant neoplasms, with minimal protein expression on normal tissue; CD3 is expressed almost exclusively by T cells and is present in all stages of T-cell development
- Increased B7-H3 expression may correlate with various adverse clinical features, including advanced disease, metastasis and poorer survival
- B7-H3 tumor expression level inversely correlates with T-cell infiltrate
- Upregulation of PD-1 on T cells and IFNγ-inducible upregulation of PD-L1 on tumor cells may be associated with the mechanism of action of orlotamab, suggesting that the antitumor activity of orlotamab could be further enhanced by coordinate blockade of PD-1/PD-L1 pathway
- Inhibition of PD-1/PD-L1 axis with MGA012 could enhance the antitumor activity of orlotamab in patients, a hypothesis supported by various preclinical studies demonstrating enhanced orlotamab-mediated activity in the presence of B7-H3-expressing tumor cells when combined with MGA012 as compared to orlotamab alone

Key Study Objectives

Primary Objective:
- Characterize safety, tolerability, dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) of orlotamab in combination with MGA012

Secondary Objectives:
- Characterize pharmacokinetics (PK) and immunogenicity of combination
- Investigate preliminary anti-tumor activity of combination using both RECIST and immune-related response criteria (irRECIST)

Exploratory Objectives:
- Explore relationships between PK, PD, and patient safety as well as antitumor activity
- Investigate immune-regulatory activity of combination in vivo, including measures of T-cell activation in peripheral blood and/or biopsy specimens
- Determine relationship between B7-H3 and PD-L1 expression in tumor, immune cell infiltration, and antitumor activity
- Characterize transcript profiles and T-cell repertoire

Study Design

Dose Escalation: 3 + 3 + 3 Design
- Open to Selected B7-H3-positive* Tumor Types
- Dose Expansion
  - Cohorts 1-5
  - Orlotamab: Starting dose 3 mg/kg q2w
  - MGA012: 3 mg/kg q2w

Entry Criteria

Key Inclusion Criteria
- Patients with selected B7-H3-positive tumors for whom no approved therapy with demonstrated clinical benefit is available. Requirement for previous systemic therapy may be waived if patient was intolerant of or refused standard first-line therapy
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Measurable disease per RECIST 1.1, with the exception of prostate cancer
- Tissue specimen available for B7-H3 and PD-L1 expression testing
- Life expectancy ≥12 weeks
- Acceptable laboratory parameters
- Toxicities related to prior checkpoint inhibitors must be resolved to ≤ Grade 1 or baseline. Patients who experienced previous hypothyroidism toxicity on checkpoint inhibitor are eligible regardless of Grade resolution as long as patient is well controlled on replacement therapy

Key Exclusion Criteria
- Patients with history of prior central nervous system (CNS) metastasis must have been treated, be asymptomatic, and must not have the following at the time of enrollment: concurrent treatment; progression of CNS metastases ≥14 days after last day of prior therapy for CNS metastases; leptomeningeal disease or cord compression
- Patients with any history of known or suspected autoimmune disease, with certain exceptions
- Treatment with any investigational therapy within 4 weeks, systemic chemotherapy within 3 weeks, radiation therapy within 2 weeks, and systemic corticosteroids or other immune suppressive drugs within 2 weeks prior to study drug administration
- Clinically significant cardiovascular or pulmonary disease
- Evidence of active viral, bacterial, or fungal systemic infection requiring parenteral treatment within 7 days prior to initiation of study drug
- Known history of positive testing for human immunodeficiency virus or history of acquired immune deficiency syndrome
- Known history of hepatitis B or hepatitis C infection or known positive test for hepatitis B surface antigen, hepatitis B core antigen, or hepatitis C polymerase chain reaction

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