A Phase 1 Study of MGD007, a Humanized gpA33 x CD3 DART® Protein, in Combination with MGA012, an anti-PD-1 Antibody, in Patients with Relapsed/Refractory Metastatic Colorectal Cancer

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Background

MGD007 (gpA33 x CD3) Structural Design

- Anti-gpA33: humanized monoclonal antibody (mAb) selected from colon cancer stem-cell immunization
- Anti-CD3: humanized X232 mAb
- Human Fc: IgG1 with mutations to reduce undesired FcRn binding (alaala) and enhance heterodimerization (knob-into-hole) to retain FcRn binding to enhance half-life

MG007 Can Recruit CD8, CD4 and Suppressive T Cells for Redirected T-cell Killing

- MGD007 Up Regulates PD-L1
- MGD007 Up Regulates PD-1
- MGD007/anti-PD-1 Combination Antitumor Activity

MG007 and MGA012 Leverage Complementary T-cell-Mediated Mechanisms of Action

- MGD007-mediated cytotoxicity against gpA33+ Colo205 colorectal cancer cell line in presence of human T cells (CD3, CD8, or CD4 as indicated; E:T = 3:1; 48 hrs)
- MGV007-mediated enhancement of TCR activation of Jurkat cells under PD-L1/PD-1 mediated inhibition

Anti-PD-1 Enhances MGD007-mediated Antitumor Activity in Preclinical Models

- MGD007-mediated CTL Activity
- MGD007 anti-PD-1 combination antitumor activity

Study Design

Dose Escalation Phase: 3 + 3 + 3 Design
- 3 planned dose levels of MGD007
- MGA012 at fixed dose
- Patients may receive up to 12 cycles in the absence of disease progression, DLT, or other criteria for permanent discontinuation

Cohort Expansion Phase:
- 25 patients treated at MTD/MAD
- 90% of patients will be MSS and 10% MSI-H
- Paired tumor biopsies will be mandatory in 15/25 patients if lesions are accessible with acceptable risk

Key Study Objectives

Primary:
- Characterize safety, tolerability, dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD)/maximum administered dose (MAD) of MGD007 in combination with MGA012

Secondary:
- Characterize pharmacokinetics, pharmacodynamics, and immunogenicity of combination
- Investigate preliminary anti-tumor activity of combination using both RECIST and immune-related RECIST
- Objective response rate, disease control rate, progression-free survival at 16 weeks
- Investigate immune-regulatory activity of combination in vivo

Key Inclusion Criteria

- Histologically proven, relapsed/refractory metastatic colorectal cancer
- Eastern Cooperative Oncology Group performance status 0 or 1
- Measurable disease per RECIST 1.1 criteria
- Participation in the Dose Escalation Phase must have had recurrence, progression or intolerance to standard therapy consisting of at least 2 prior standard regimens (containing a fluoropyrimidine plus a platinum analogue and/or irinotecan) for metastatic disease
- Clinically significant cardiovascular disease: gastrointestinal disorders; pulmonary compromise; viral, bacterial, or systemic fungal infections
- History of positive testing for human immunodeficiency virus or history of acquired immune deficiency syndrome
- 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

Entry Criteria

- History of known or suspected autoimmune disease with certain exceptions
- Major surgery, systemic anti-neoplastic therapy, or investigational therapy within 4 weeks
- Radiation therapy within 2 weeks
- Systemic corticosteroids (≥ 10 mg per day prednisone or equivalent) or other immune suppressive drugs within the 14 days
- History of Grade 3 or greater drug-related diarrhea/cutis during treatment with checkpoint inhibitors including anti-LAG-3, anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibodies
- Clinically significant autoimmune disease: gastrointestinal disorders; pulmonary compromise; viral, bacterial, or systemic fungal infections
- History of positive testing for human immunodeficiency virus or history of acquired immune deficiency syndrome
- 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

Key Exclusion Criteria

- Symptomatic central nervous system (CNS) metastases. No concurrent treatment for the CNS disease; no progression of CNS metastases on MRI or CT for at least 14 days after last day of prior therapy for the CNS metastases; no concurrent leptomeningeal disease or cord compression

The Sponsor thanks the patients and their families for participating in this study.