A Phase 1, Open Label, Dose Escalation Study of MGD009, a Humanized B7-H3 x CD3 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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MGD009: B7-H3 x CD3 DART
- Humanized Fc-bearing B7-H3 x CD3 DART designed to redirect T cells to eliminate B7-H3-expressing target cells through co-engagement of B7-H3 on target cell and CD3 on T cell
- 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, proliferation and cytokine production by T cells, and enhances expression of mediators of T-cell killing, including granzyme B and perforin
- Currently enrolling a Phase 1 study of MGD009 in patients with advanced B7-H3-positive solid tumors

MGD009: B7-H3 x CD3 DART
- Humanized proprietary anti-PD-1 mAb – Hinge stabilized humanized IgG4 – Benchmark against replicas of approved anti-PD-1 mAbs – Anti-PD-1 becoming mainstay of cancer immunotherapy – Basis for combination immunotherapy

MGD009: B7-H3 x CD3 DART
- Tumor Volume (mm³)
- MGA012: 3 mg/kg q2wk
- MGA012 + DART: 125 mg/kg
- MGA012: 0.5 mg/kg
- Vehicle

MGD009: B7-H3 x CD3 DART
- Primary Objective: Investigate immune-regulatory activity of combination in vivo, including measures of T-cell activation in peripheral blood and/or PBMC
- Secondary Objectives: Explore relationships between PK, PD, and patient safety as well as antitumor activity
- Exploratory Objectives: Determine relationship between B7-H3 and PD-L1 expression in tumor, immune cell infiltration, and antitumor activity

MGD009: B7-H3 x CD3 DART
- Tumor Volume (mm³)
- MGA012: 12.5 mg/kg
- mAb Control 12.5 mg/kg

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MGD009: B7-H3 x CD3 DART
- B7-H3 is over-expressed on wide range of malignant neoplasms, with minimal 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 tumor expression correlates with advanced disease, metastases, and poorer survival
- B7-H3 tumor expression level is negatively correlated with T-cell infiltrate
- Upregulation of PD-1 on T-cells and IFNy inducible upregulation of PD-L1 on T-cell may be associated with mechanism of action of MGD009, suggesting that antitumor activity of MGD009 could be further enhanced by coordinate blockade of PD-1/PD-1 pathway
- Inhibition of PD-1/PD-L1 axis with MGA012 could enhance antitumor activity of MGD009 in patients, a hypothesis supported by various preclinical studies demonstrating enhanced MGD009-mediated activity in presence of B7-H3-expressing tumor cells when combined with MGA012 as compared to MGD009 or MGA012 alone

Rationale

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 ≤ 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 thyroid-replacement hormones

Key Exclusion Criteria
- Patients with history of prior central nervous system (CNS) metastasis must have been treated, be asymptomatic, and must not have concurrent treatment; progression of CNS metastases ≥ 14 days after last day of prior therapy for CNS metastases; concurrent 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 systemic fungal 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

Key Study Objectives
- Primary Objective: Characterize safety, tolerability, dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD); or maximum administered dose (MAD) of MGD009 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

Entry Criteria

Study Design

Dose Escalation: 3 + 3 + 3 Design
Open to Selected B7-H3-positive Tumor Types

Cohorts 1–5
MGD009: Starting dose 1 µg/kg q2wk
MGA012: 3 mg/kg q2wk

High Mutational Load Tumors (n=20)
- NSCLC (n=20)
- RCC (n=20)
- Sarcoma (n=20)
- Mesothelioma (n=20)
- Prostate (n=20)

MGA012: Anti-PD-1 Monoclonal Antibody (mAb)
- Humanized proprietary anti-PD-1 mAb – Hinge stabilized humanized IgG4 – Benchmarks against replicas of approved anti-PD-1 mAbs – Anti-PD-1 becoming mainstay of cancer immunotherapy – Basis for combination immunotherapy

Technical Profile

<table>
<thead>
<tr>
<th>MGA012</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue cross-reactivity</td>
<td>No unanticipated findings</td>
</tr>
<tr>
<td>Toxicology in cynomolgus monkeys: IV at 10, 40 or 150 mg/kg; QW x 4</td>
<td>Well tolerated at all doses No unanticipated findings NOAEL = 150 mg/kg</td>
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<tr>
<td>Predicted half-life in humans</td>
<td>~18 days</td>
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MGD009: B7-H3 x CD3 DART
- T-Cell/Tumor Cell Co-culture Signaling Model System
- “Brakes on” “Brakes Released”

MGD009: B7-H3 x CD3 DART
- Cooperation Between MGA012 and MGD009

Schematic representation of T cell/Tumor cell co-culture signaling model system (A) designed to evaluate the combination activity of MGA012 and MGD009 (B). Model system utilizes CD2 and PD-1 expressing Jurkat reporter cell line co-cultured with triple negative breast cancer tumor cell line MDA-MB-231, which expresses both B7-H3 and PD-L1. In presence of MGD009, a basal level luciferase activity under control of TCR-mediated NFAT signaling is observed, but limited due to interaction between PD-1 and PD-L1 (brakes on). Release of PD-1/PD-L1 mediated inhibition is measured by an increased luminescence under control of TCR-mediated NFAT signaling in presence of MGD009 (brakes released).

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