B7-H3: Member of B7 Family of Immune Regulators

- B7-H3 expressed on broad range of tumors and tumor vessels
- Minimal expression on normal cells
- High expression correlates with advanced disease, metastases, inferior patient survival

Multiple Roles for B7-H3 in Cancer

- Immunosuppressive role
  - Expression drives immune escape/invasiveness of glioblastoma in mice
  - Expression on lung cancer and macrophages suppresses T-cell mediated anti-tumor immune response
- B7-H3-positive myeloid-derived suppressor cells present in tumor microenvironment
- Metastatic enhancing role
  - Silencing reduces migration and invasion of melanoma and breast cancer cell lines
  - Enhances metastatic potential of melanoma cells

B7-H3 Displays Favorable Tumor/Normal Differential

- Restricted Immune Cell Expression
- Limited Normal Tissue Expression
- Normal/Tumor Tissue Differential

MGD009 Dual-Affinity Re-Targeting (DART®) Protein

- Humanized Fc-bearing B7-H3 x CD3 Dual-Affinity Re-Targeting (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
- Potential to combine with complimentary immune modulating agents

Enabling Effector Cells to Kill Tumors

- Co-engagement of T-cells (CD3) with B7-H3 expressed on tumor cells
- Monovalent binding to CD3 to avoid target independent T-cell activation
- Strict dependence on co-engagement of both targets for T-cell activation
- T-cell receptor & MHC-independent tumor-cell recognition: virtually any T cell can kill cancer cells
- Ongoing clinical trials with DART® proteins targeting solid and hematologic malignancies:
  - CD123 x CD3 (MGD006)
  - gp100 x CD3 (MGD007)
  - CD19 x CD3 (MGD011)

Potent In Vitro Activity Against Multiple Tumor Types

- Target Cell Line
- Tumor Type
- MFI
- EC50 (ng/mL)

MGD009 Mediates Antitumor Activity in Multiple In Vivo Models

- Treatment with MGD009 is Associated with T-cell Recruitment to Tumor Xenografts
- MGD009 recapitulates clinical outcome in preclinical models

Rationale

- B7-H3 is widely expressed on melanoma, squamous cell carcinoma of the head & neck (SCCHN), mesothelioma (MESO), non-small cell lung cancer (NSCLC) urothelial cancer, NSCLC and other solid tumors, with minimal expression on normal tissue
- Increased B7-H3 tumor expression correlates to more advanced disease, development of metastases and poorer clinical outcomes such as survival
- B7-H3 tumor expression level is negatively correlated with T-cell infiltration
- There remains a high level of unmet need in a broad range of tumors that also over-express B7-H3
- It is hypothesized that MGD009 will induce potent redirected T-cell killing and tumor regression, with an acceptable safety profile

Primary Objective

- To characterize safety, tolerability, dose-limiting toxicity (DLT), and maximum tolerated dose (MTD) of MGD009 when administered IV every 2 weeks to patients with B7-H3 expressing, unresectable locally-advanced or metastatic cancer

Secondary Objectives

- To characterize pharmacokinetics (PK), pharmacodynamic (PD) activity and immunogenicity of MGD009 administered on an every 2-week schedule
- To investigate the preliminary anti-tumor activity of MGD009 in patients with B7-H3 expressing neoplasms utilizing both conventional RECIST 1.1 and immune-related response criteria (irRECIST)

Key Study Objectives

- Multi-center Phase 1, open-label, 3+3 design dose escalation and cohort expansion study
- Expansion segment includes cohorts of MESSO, bladder cancer, SCCHN, NSCLC, melanoma, and other B7-H3-expressing cancers
- MGD009 administered at escalating doses of 0.1, 0.3, 1, 3, 10, 30, 50, and 100 µg/kg IV every 2 weeks for 5 weeks (Cycle 1) and every 4 weeks thereafter
- MTD: Dose at which <33% of patients experience a drug-related DLT during Cycle 1. If no MTD is defined, highest dose level will be designated as MTD
- Patient management according to IR principles and may receive up to 14 cycles of MGD009

Entry Criteria

- Histologically and/or cytologically proven unresectable locally advanced or metastatic tumors that express B7-H3 on the membrane or vasculature.
- The requirement for previous systemic therapy may be waived if a person was intolerant of standard front-line therapy
- At least one prior systemic therapy and up to 2–5 prior therapies depending upon tumor type
- Clinically significant history of autoimmune disease with certain exceptions
- Measurable disease per RECIST 1.1 criteria
- Easter Cooperative Oncology Group (ECOG) performance status 0 or 1

Key Exclusion Criteria

- Patients with symptomatic central nervous system metastases must have been treated and be asymptomatic, with certain exceptions
- Clinically significant pulmonary compromise
- History of allogeneic bone marrow, stem cell, or solid organ transplant
- Treatment with systemic cancer therapy within 4 weeks; radiation within 2 weeks; corticosteroids (greater than or equal to 10 mg prednisone or equivalent per day) or other immune suppressive drugs within 2 weeks

References