ASCO 2018
Abstract #TPS2601

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

Alexander Spira[2], James Strauss[3], Liqin Liu[1], Ralph Alderson[1], Ross La-Motte Mohs[1], Tony Wu[1], Syd Johnson[1], Ezio Bonvini[1], Paul Moore[1], Jon Wigginton[1]

[1]MacroGenics Inc., Rockville, MD; [2]Virginia Cancer Specialists, Fairfax, VA; [3]Mary Crowley Cancer Research Center, Dallas, TX

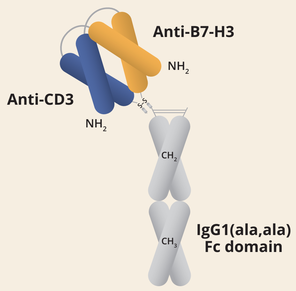
goldbergs@macrogenics.com

NCT03406949

Background

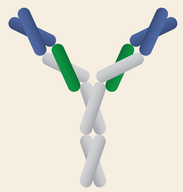
MGD009: B7-H3 x CD3 DART

- 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



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

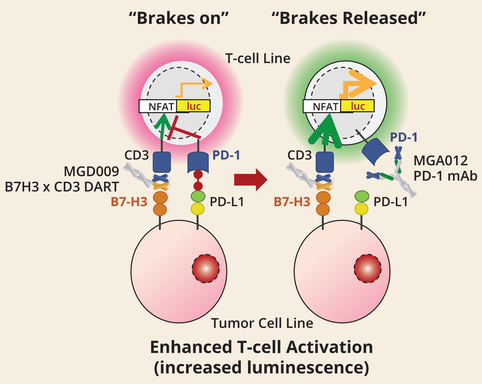


Technical Profile

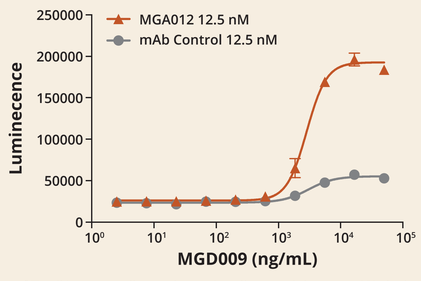
MGA012	Results
Tissue cross-reactivity	No unanticipated findings
Toxicology in cynomolgus monkeys: IV at 10, 40 or 150 mg/kg; QW x 4	Well tolerated at all doses No unanticipated findings NOAEL = 150 mg/kg
Predicted half-life in humans	~18 days

MGA012 Cooperates with MGD009 to Enhance Reporter Cell Activity within a T Cell/Tumor Cell Co-culture Signaling Model System

A. **T-Cell/Tumor Cell Co-culture Signaling Model System**

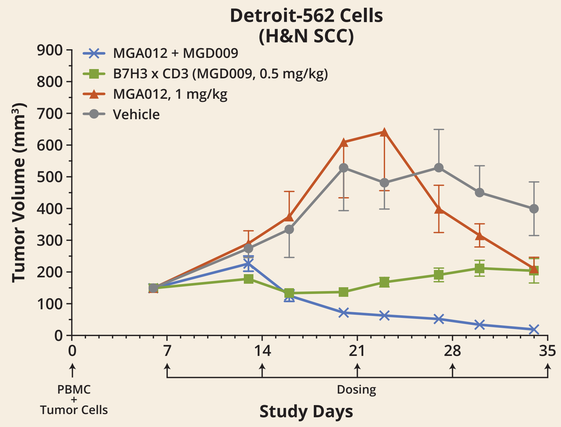


B. **Cooperation Between MGA012 and MGD009**

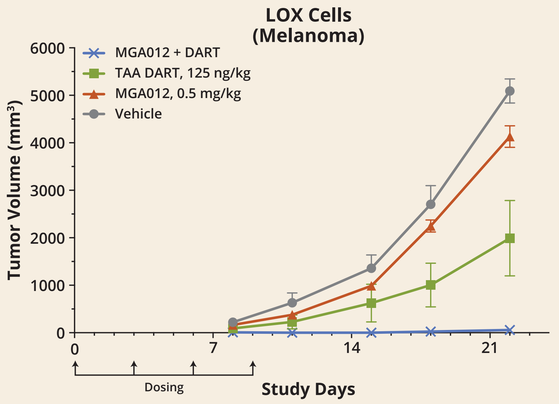


Schematic representation of T cell/ tumor cell co-culture signaling model system **(A)** designed to evaluate the combination activity of MGA012 and MGD009 **(B)**. Model system utilizes CD3 and PD-1 expressing Jurkat reporter cell line co-cultured with triple negative breast cancer tumor cell line MDA-MB-231, 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 MGA012 (brakes released).

MGA012 Enhances DART-mediated T-cell Killing In Vivo



NSG MHC-I$^{-/-}$ mice. Detroit-562, 5x10^6 cells, ID. PBMC, 10^6 cells, IP



NSG mice co-mix model. LOX cells, 2.5x10^6 cells and activated human T cells, 1x10^6 cells, SC

Rationale

- 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 IFNγ inducible upregulation of PD-L1 on tumor cells 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-L1 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

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

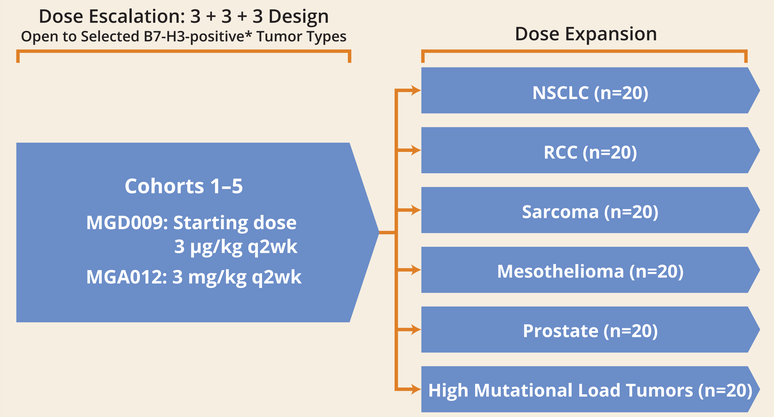
Secondary Objectives:

- 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

Study Design



*B7-H3 positivity defined as > 10% tumor, ≥ 2+ and/or > 25% of vasculature positive.

- MGA012 and MGD009 administered IV every other week
- 8-week tumor assessment cycles; maximum of 14 cycles
- DLT evaluation period through Day 29 of Cycle 1; tumor assessment at Day 56 of each cycle
- 2-year survival follow-up following last dose of study drug
- Dose escalation ongoing

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 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

Presented at the 2018 ASCO Annual Meeting, June 1–5, 2018, Chicago, IL