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Phase 1, First-in-Human, Open Label, Dose Escalation Study of MGD009, a Humanized B7-H3 x CD3 Dual-Affinity Re-Targeting (DART®) Protein in Patients with B7-H3-Expressing Neoplasms or B7-H3 expressing Tumor Vasculature

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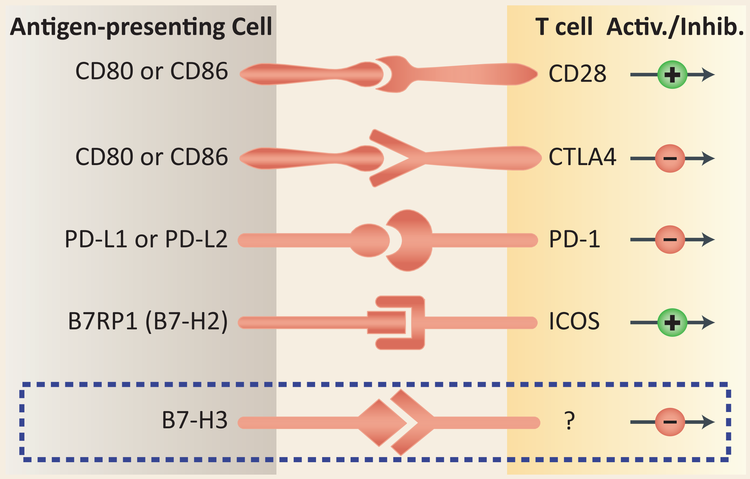
Background

B7-H3: Member of B7 Family of Immune Regulators[1]



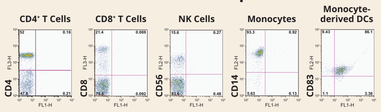
- B7-H3 expressed on broad range of tumors and tumor vessels
- Minimal expression on normal cells
- High expression correlates with advanced disease, metastases, inferior patient survival[2]

Multiple Roles for B7-H3 in Cancer

- **Immunosuppressive role**
  - Expression drives immune escape/invasiveness of glioblastoma in mice[3]
  - Expression on lung cancer and macrophages suppresses T-cell mediated anti-tumor immune response[4]
  - B7-H3-positive myeloid-derived suppressor cells present in tumor microenvironment[5]
- **Metastatic enhancing role**
  - Silencing reduces migration and invasion of melanoma and breast cancer cell lines[6]
  - Enhances metastatic potential of melanoma cells[7]

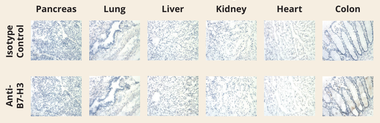
B7-H3 Displays Favorable Tumor/Normal Differential

A. Restricted Immune Cell Expression

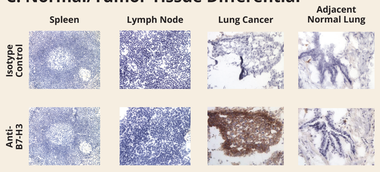


Anti-B7-H3 mAb (BRCA84D)

B. Limited Normal Tissue Expression



C. Normal/Tumor Tissue Differential



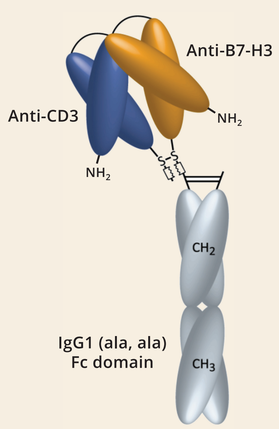
D. High Penetrance of B7-H3 Expression in Broad Set of Solid Tumors by IHC

Tumor	B7-H3 Positive		2+ or Above	
Head and Neck	19/19	100%	19/19	100%
Kidney Cancer*	77/78	99%	75/78	96%
Glioblastoma	65/66	98%	63/66	95%
Thyroid Cancer	34/35	97%	33/35	94%
Mesothelioma	90/93	97%	83/93	89%
Melanoma	66/70	94%	32/70	46%
Gastric Cancer	144/155	93%	127/155	82%
Colorectal Cancer	41/45	91%	38/45	84%
Prostate Cancer	88/99	89%	51/99	52%
Pancreatic Cancer	69/78	88%	45/78	58%
Lung Cancer	226/272	83%	211/272	78%
Ovarian Cancer*	59/79	75%	36/79	46%
Breast Cancer	119/164	73%	115/164	70%

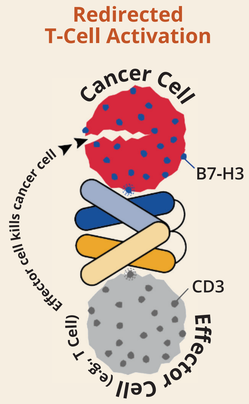
*Also expression in tumor vasculature

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

- 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
- Potential to combine with complimentary immune modulating agents

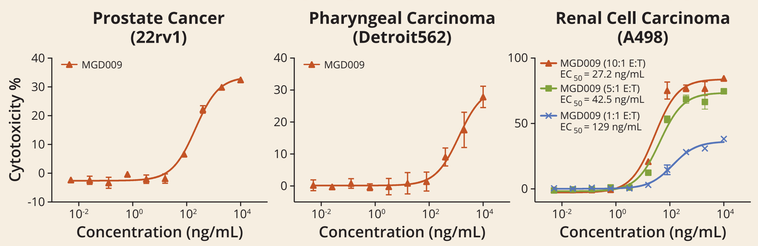


Enabling Effector Cells to Kill Tumors



- 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)
  - gpA33 x CD3 (MGD007)
  - CD19 x CD3 (MGD011)

Potent In Vitro Activity Against Multiple Tumor Types

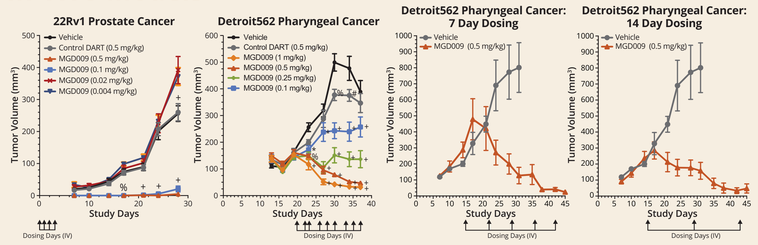


Target Cell Line	Tumor Type	MFI	EC_{50} (ng/mL)
JIMT-1	Breast	65	47
A498	Kidney	150	64
DU145	Prostate	24	84
A375	Melanoma	101	97
U87	Glioblastoma	11	99
BxPC-3	Pancreatic	12	196
22Rv1	Prostate	35	212
SKMES-1	Lung	12	319
Detroit562	Pharyngeal	20	1275
Raji	B-lymphoma	Negative	No activity
CHO	Normal Chinese hamster ovary	Negative	No activity

- Redirected cell killing by MGD009 against B7-H3-positive human cancer target cells.

MGD009 was incubated with purified human T cells and target cells at E:T cell ratio of 5:1 for 24 hours (LDH release assay). MFI: Mean Florescence Intensity. EC 50: Half maximal effective concentration.

MGD009 Mediates Antitumor Activity in Multiple In Vivo Models



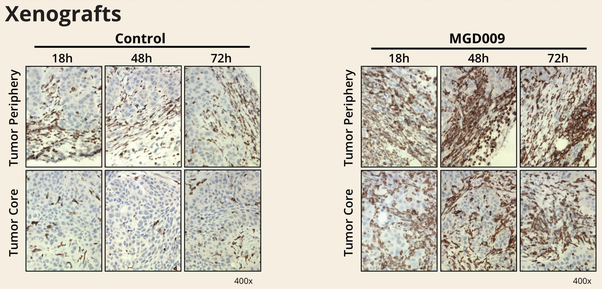
Co-mix mouse xenograft model:
- NOD/SCID mice (n = 8/group)
- Co-mix: activated human T cells and tumor cells implanted subcutaneously (SC) at E:T cell ratio of 1:5 (Day 0)

Established tumor model in human T-cell reconstituted mice:
- NSG β2m$^{-/-}$ mice (n = 7-8/group)
- Reconstitution: 1 x 10^7 human PBMCs intraperitoneally (Day -1)
- Tumor implantation: 5 x 10^6 tumor cells intradermally (Day 0)

Established tumor model in human T-cell reconstituted mice:
- MHC1$^{-/-}$ mice (n = 5-7/group)
- Reconstitution: 1 x 10^7 human PBMCs intraperitoneally (Day 0)
- Tumor implantation: 5 x 10^6 tumor cells intradermally (Day 0)

Mean ± SEM; two-way ANOVA with Bonferroni post-test: * p <0.05; # p <0.01; % p <0.001; + p <0.0001

Treatment with MGD009 is Associated with T-cell Recruitment to Tumor Xenografts



IHC staining of CD3-positive T cells in NSG/β2m$^{-/-}$ mice engrafted SC with Detroit562 cancer cells, reconstituted with human PBMCs, and treated IV with MGD009 (0.5 mg/kg) or vehicle control.

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

Key Study Objectives

Primary Objective

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

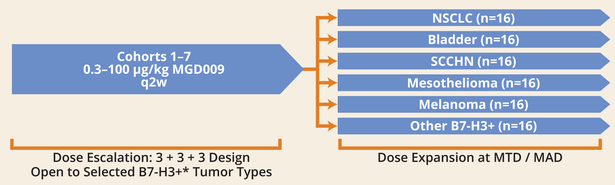
Secondary Objectives

- 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 using both conventional RECIST 1.1 and immune-related response criteria (irRC)

Exploratory Objectives

- To explore relationships between PK, PD, patient safety, and antitumor activity of MGD009
- To investigate the immune-regulatory activity of MGD009 in vivo, including various measures of T-cell activation in peripheral blood and/or tumor biopsy specimens
- To determine relationships between B7-H3 expression in tumor membrane and/or tumor-associated vasculature (based on screening IHC testing), immune cell infiltration within biopsy specimens (including CD4+ and CD8+ T-Cells) and anti-tumor activity

Study Design



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

- Multi-center Phase 1, open-label, 3+3+3 design dose escalation and cohort expansion study
- Expansion segment includes cohorts of MESO, bladder cancer, SCCHN, NSCLC, melanoma, and other B7-H3-expressing cancer
- MGD009 administered at escalating doses of 0.3, 1, 3, 10, 30, 50, and 100 µg/kg IV every 2 weeks for 6 weeks (Cycle 1) and every 8 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 MAD
- Patient management according to IR principles and may receive up to 14 cycles of MGD009

Entry Criteria

Key Inclusion 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

1. Pardoll D, et al., Nature Reviews Cancer 2012; 12 (4): 252-264. **2.** Loos M, BMC Cancer 2009; Yamato I, Br J Cancer 2009. **3.** Lemke D, et al., Clin Cancer Res 2012; 18(1): 105-117. **4.** Chen C, et al., Exp Cell Res 2013; 19(1): 96-102. **5.** Zhang G, et al., Oncoimmunology 2015; 4(2): e977164. **6.** Chen YW, et al., Cur Cancer Drug Targets 2008; 8(5): 404-413. **7.** Tekle C, et al., Int J Cancer 2012; 130 (10): 2282-2290. **8.** Suh WK, et al., Nat Immunol. 2003 Sep;4(9):899-906, Leitner J, et al., Eur J Immunol. 2009 Jul;39(7):1754-64.