A Phase 1, First-in-Human, Open Label, Dose Escalation Study of MGD007, A Humanized gpA33 x CD3 Dual-Affinity Re-Targeting (DART®) Protein in Patients with Relapsed/Refractory Metastatic Colorectal Carcinoma

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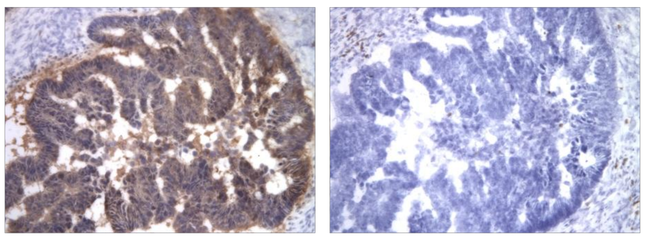
Background

Colorectal Cancer (CRC)

- In 2014, an estimated 136,830 new CRC cases will be diagnosed; CRC is the fourth most common cancer and the third leading cause of cancer death in the United States[1]
- Standard therapies include:
  - 5-Flurouracil, Oxaliplatin, Irinotecan, Bevacizumab, Ziv-Aflibercept, Regorafenib, and Cetuximab or Panitumumab (KRAS Wild-type only)

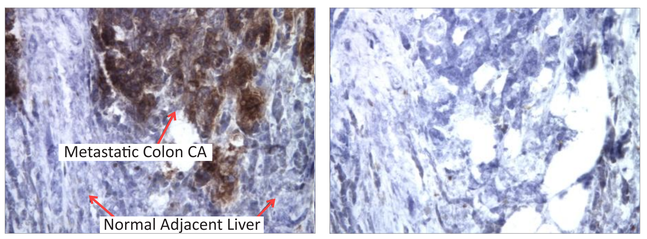
gpA33 Target

- 43 kDa glycoprotein displaying homology to immunoglobulin super-family
- Exhibits restricted expression to normal colonic mucosa and small bowel epithelia
- Overexpressed in 95% of metastatic CRC; strong expression in both primary & metastatic sites
- Putative role in cell-cell recognition and signaling.[2] gpA33 may play a role in relaying information between intestinal epithelial cells and the gut immune system[3]



gpA33 (ch RECA47) Isotype Control

Primary Tumor Adenocarcinoma of Colon

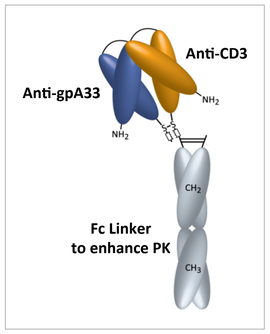


gpA33 (ch RECA47) Isotype Control

Metastatic Colon Tumor to Liver

DART (Dual-Affinity Re-Targeting) Platform

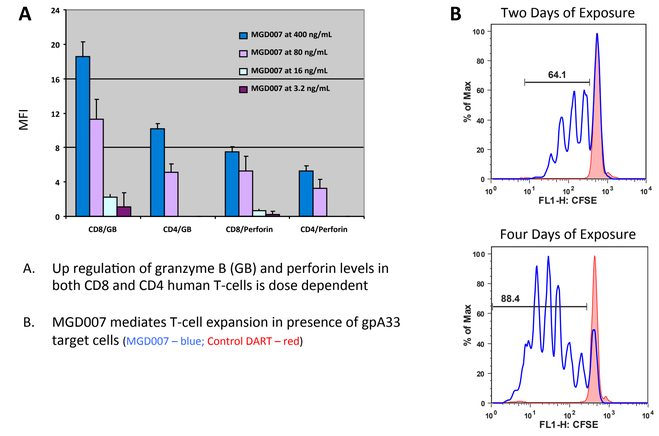
- Flexible platform for generating stable multi-specific molecules
  - >100 DART proteins produced for >40 specificities
- Structural features support:
  - Excellent product stability
  - Optimal heavy & light chain pairing
  - Predictable antigen recognition
- Decreased potential for immunogenicity due to minimal linker size and content
- Expression in mammalian or prokaryotic systems feasible
- Multiple approaches to enhance half-life and avidity
- Biological activity demonstrated in vitro and in vivo



MGD007 DART: gpA33 x CD3 DART

- Humanized gpA33 x CD3 Fc-bearing DART (extended PK; mean half-life of ~8 days)
- gpA33 mAb selected from panel of mAbs identified from colon cancer model cell line immunization
- Redirected T-cell killing against colorectal cancer cells mediated by both CD8 and CD4 T-cells
- Mechanism of action associated with up-regulation of granzyme B/perforin; T-cell expansion and activation
- Activity strictly dependent on co-engagement of MGD007 with gpA33-expressing target cells

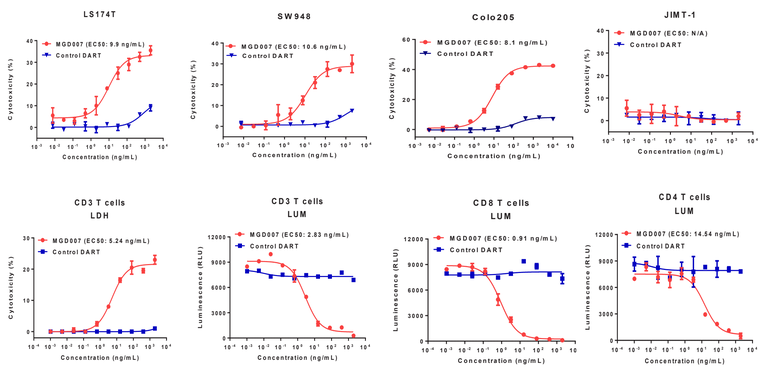
MGD007-Mediated Cytolytic Activity of T Cells[4]



A. Up regulation of granzyme B (GB) and perforin levels in both CD8 and CD4 human T-cells is dose dependent

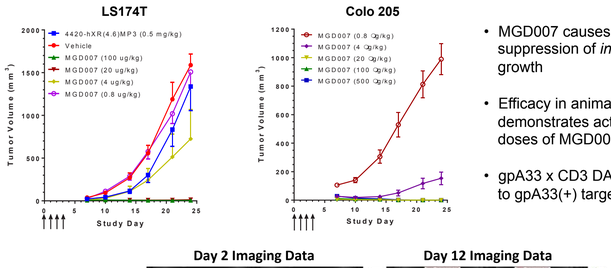
B. MGD007 mediates T-cell expansion in presence of gpA33 target cells (MGD007 – blue; Control DART – red)

MGD007-Mediated CTL Activity Against gpA33 Target Cells[4]

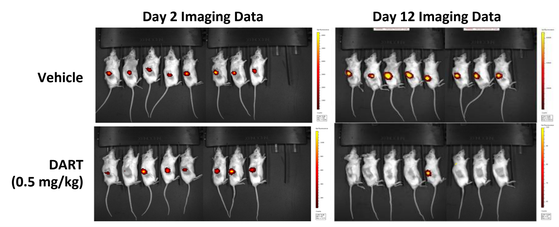


- Concurrent gpA33 and CD3 target engagement is required for MGD007-mediated T-cell killing
- No T-cell activation in absence of gpA33 target

MGD007 Mediated Anti-Tumor Activity[4]



- MGD007 causes significant suppression of *in vivo* tumor growth
- Efficacy in animal models demonstrates activity at low doses of MGD007 (4 µg/kg)
- gpA33 x CD3 DART localizes to gpA33(+) target cells *in vivo*



Study Rationale

- Glycoprotein A33 antigen is a transmembrane glycoprotein expressed almost exclusively in the intestinal epithelium and is present in > 95% of primary and metastatic colorectal cancer
- It is hypothesized that, in patients with metastatic colorectal carcinoma, administration of MGD007 will lead to binding of MGD007 to gpA33 expressed on surface of colorectal cancer tumor cells and to CD3 expressed on surface of tumor-infiltrating T-cells resulting in redirected, T-cell mediated killing of those cancer cells and leading to tumor regression
- It is further hypothesized that administration of MGD007 will be sufficiently well tolerated to permit further study subsequent to completion of this Phase 1 study

Key Study Objectives

Primary Objective

To characterize safety, tolerability, dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) of MGD007 when administered intravenously (IV) on weekly or every three week schedules in patients with relapsed/refractory metastatic colorectal carcinoma

Secondary Objectives

- To characterize PK, pharmacodynamic activity and immunogenicity of MGD007 administered on weekly and every three week schedules
- To investigate preliminary anti-tumor activity of MGD007 in patients with relapsed/ refractory metastatic colorectal carcinoma, including patients with K-ras wild-type and K-ras mutant tumors using both conventional RECIST 1.1 and immune-related response criteria (irRC)

Key Exploratory Objectives

- To explore relationships between PK, pharmacodynamics and MGD007 dose/schedule, patient safety and anti-tumor activity
- To explore impact of MGD007 on progression-free survival (PFS), immune-related PFS (irPFS) and overall survival (OS) in patients with metastatic relapsed/refractory colorectal carcinoma
- To investigate immuno-regulatory activity of MGD007 in vivo, including various measures of T-cell function in peripheral blood and/or tumor biopsy specimens
- To gain initial experience with the gpA33 immunohistochemical diagnostic test via exploration of gpA33 expression in tumor biopsy specimens

Study Design

- Open-label, Phase 1 study
- Enroll patients with metastatic relapsed/refractory colorectal carcinoma
- The study will be conducted in two parts:

Dose-escalation

- 3 + 3 + 3 design, exploring two doing schedules
- Arm A: Weekly dosing x 6 per cycle (6-week cycle)
- Arm B: Q3 Week dosing x 2 per cycle (6-week cycle)
  - Arm B to be triggered by occurrence of any ≥ Grade 3 drug-related adverse event (AE) in Arm A
  - Arm B will begin dosing one dose level below Arm A

Dose-expansion

- Using single MTD dose and schedule from dose escalation phase
- Two dose expansion cohorts: K-ras Mutant and K-ras Wild-Type

Safety Assessments

- Adverse event will be graded according to the Common Terminology Criteria for Adverse Events, version 4.03
- To be assessed continuously during the study and for 30 days after last treatment

Response Assessments

- Response will be assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines and by immune-related RECIST guidelines
  - Treatment decisions on study determined by immune-related RECIST guidelines
- Assessments will be performed at baseline and every 6 weeks for first 4 cycles and then every 12 weeks thereafter until confirmed progression disease, completion of follow-up, or patient withdrawal

References

1. **Siegel R, et al.**, "Colorectal cancer statistics, 2014", CA Cancer J Clin. 2014 Mar-Apr;64(2):104-17
2. **Heath JK, et al.**, "The human A33 is a transmembrane glycoprotein and a novel member of the immunoglobulin superfamily," Proc Natl Acad Sci. 1997; 94(2):469-474
3. **Lee JW, et al.**, "Peripheral antigen display by lymph node stroma promotes T-cell tolerance to intestinal self," Nat Immunol. 2007; 8(2): 181-190
4. **Moore PA, et al.**, "Development of MGD007, a gpA33 x CD3 bi-specific DART for T-cell immunotherapy of metastatic colorectal cancer", American Association of Cancer Research (AACR) Annual Meeting, 2014; Abstract 669

Acknowledgements

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Key Inclusion Criteria

- Histologically-proven relapsed / refractory metastatic colorectal adenocarcinoma
  - Dose Escalation: at least 2 prior lines of therapy
  - Dose Expansion: at least 1 prior line of therapy
- Measurable disease as per Recist 1.1 criteria
- K-*ras* status documentation
- Identification of archival tumor sample for gpA33 analysis
- ECOG 0 or 1
- Life expectancy ≥ 12 weeks
- Men and women ≥ 18 years of age
- Adequate organ function
- Signed Informed Consent

Key Exclusion Criteria

- Known brain metastasis
- History of known or suspected autoimmune disease
  - Exceptions: Vitiligo, Atopic Dermatitis, Grave's disease now euthyroid
- Prior immunotherapy treatment with < 5 half-lives from last dose
  - List not all inclusive: anti-CTLA4, anti-PD-1, anti-PD-L1, anti-LAG3
- ≥ Grade 3 Diarrhea / Colitis during immunotherapy treatments
- No corticosteroid use (≥ Prednisone 10mg/day) 2 weeks from Rx
- Uncontrolled or clinically significant cardiovascular disease
- Uncontrolled or clinically significant GI disorders
- Vaccination with live virus vaccine 4 weeks from initiation
- Positive for hepatitis B or C or HIV
- Second primary malignancy not in remission > 3 years
- Any anti-cancer therapy or GCSF, GMCSF, or Epo within 4 weeks from study initiation

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