ASCO 2016
Abstract 165517

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

John Powderly[1], Herbert Hurwitz[2], David P. Ryan[3], Daniel Laheru[4], Naimish Pandya[5], Joanna Lohr[5], Paul Moore[5], Ezio Bonvini[5], Jon Wigginton[5], Todd Crocenzi[6]

pandyan@macrogenics.com

[1]Carolina BioOncology Institute, Huntersville, NC; [2]Duke University, Durham, NC; [3]Massachusetts General Hospital, Boston, MA; [4]Johns-Hopkins University, Baltimore, MD; [5]MacroGenics, Inc., Rockville, MD; [6]Providence Portland Medical Center, Portland, OR

NCT02248805

Background

Colorectal Cancer

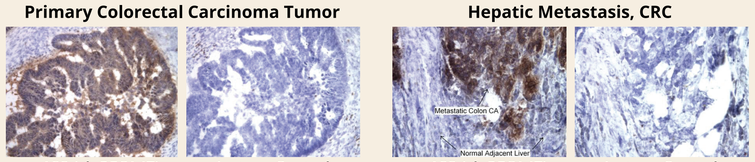
- In 2016, an estimated 134,490 new CRC cases will be diagnosed
- CRC is third most common cancer and third leading cause of cancer death in the United States[1]
- Standard therapies include:
  - 5-flurouracil, oxaliplatin, irinotecan, bevacizumab, ziv-aflibercept, regorafenib, and cetuximab or panitumumab (KRAS Wild-type only)

DART® (Dual-Affinity Re-Targeting)

- A flexible platform for generating stable multi-specific molecules
- 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
- Multiple approaches to enhance half-life and avidity

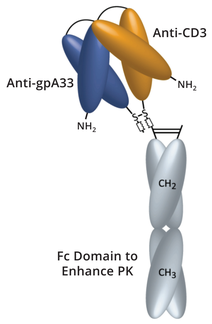
gpA33

- 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]

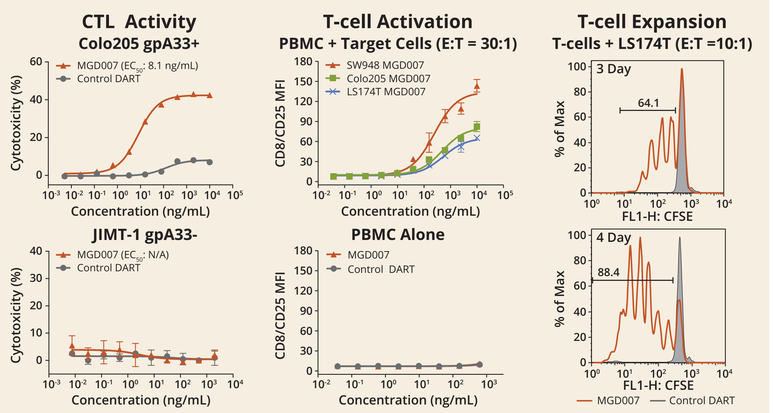


MGD007 DART: gpA33 x CD3

- Humanized gpA33 x CD3 Fc-bearing DART (extended PK)
- gpA33 mAb selected from panel of mAbs identified from mouse immunization with cell line model of colorectal cancer stem cells
- 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 & activation
- Activity strictly dependent on co-engagement of MGD007 with gpA33-expressing target cells

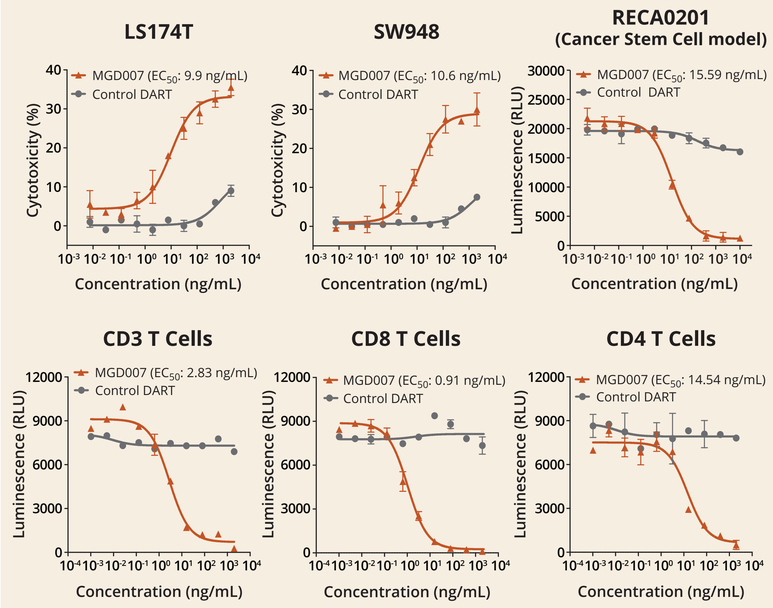


MGD007-Mediated T-Cell Activity Dependent on gpA33 Co-engagement[4]



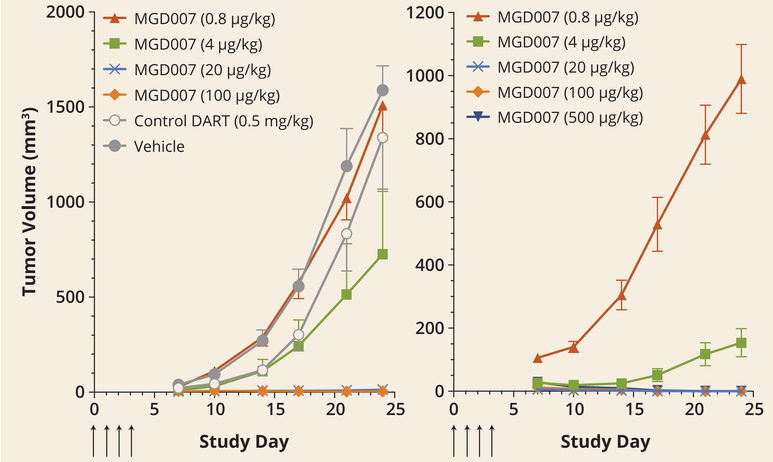
- MGD007 mediates lysis of gpA33 expressing colorectal cancer cells (e.g., Colo205) in presence of human T-cells (E:T = 10:1) but not gpA33-ve cell lines (eg JIMT-1 breast cancer cell line)
- MGD007 mediates T-cell activation in presence of gpA33+ve colorectal cancer cells and human PBMC but displys no T-cell activation in PBMC alone
- MGD007 mediates T-cell expansion in presence of gpA33+ve LS174T target cells following 3 days (right upper panel) or 4 days (right bottom panel) exposure at E:T cell ratio = 10:1 (MGD007 = brown; Control DART = gray). Proliferation of CFSE-labeled T-cells was monitored by levels of CFSE dilution over time by flow cytometry

MGD007-Mediated CTL Activity Against CRC Cell Lines



- Top Panel: Potent CTL activity against gpA33+ve CRC cell lines including model cancer stem cell line (RECA0201-luciferase labelled)
- Bottom Panel: Recruitment of both CD4 and CD8 T-cells effectively lyses (luciferase labelled)

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

Key Study Objectives

Primary Objective

- To characterize safety, tolerability, dose-limiting toxicities (DLT) and maximum tolerated dose (MTD) of MGD007

Secondary Objectives

- To characterize PK, pharmacodynamics activity and immunogenicity of MGD007
- To investigate preliminary anti-tumor activity of MGD007 in patients with relapsed/refractory metastatic colorectal carcinoma, using both conventional RECIST 1.1 and immune-related response criteria (irRC)

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 gpA33 immunohistochemical staining to assess gpA33 expression in tumor specimens

Rationale

- 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

Study Design

- Open-label, Phase 1 study, enrolling metastatic relapsed/refractory CRC patients
- The study will be conducted in two parts:
  - Dose-escalation
    - 3 + 3 + 3 design
    - Q3 Week dosing x 2 per cycle (6-week cycle)
  - Dose-expansion
    - Using single MTD dose from dose escalation phase
- Response assessment
  - Response will be assessed by 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 to 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
- Safety assessments
  - Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03
  - To be assessed continuously during the study and for 30 days after the last treatment

Entry Criteria

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
- Identification of archival tumor sample for gpA33 analysis
- ECOG Performance Status 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; prior Grave's disease, now euthyroid
- Prior immunotherapy treatment w/<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 10 mg/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

References

1. American Cancer Society. Cancer Facts & Figures 2016. Atlanta: American Cancer Society; 2016. **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

Thank you to the patients and their families for participating in this study.