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

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Background

Colorectal Cancer
- In 2016, an estimated 134,490 new CRC cases will be diagnosed
- CRC is the third most common cancer and third leading cause of cancer death in the United States
- Standard therapies include:
  - 5-fluorouracil, oxaplatin, irinotecan, bevacizumab, ziv-albiflucerase, 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 superfamily
    - 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 system3

Rationale

- It is hypothesized that, in patients with metastatic colorectal carcinoma, administration of MGD007 will lead to binding of gpA33 to T-cells expressing 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
  - No prior immunotherapy treatment w/5 half-lives from last dose
  - Grade 3 diarrhea/colitis during immunotherapy treatments
  - No corticosteroid use (≥ Prednisone 10 mg/day) 2 weeks from Rx
  - Uncontrolled or clinically significant GI disorders
  - Vaccination with live virus vaccine 4 weeks from initiation
  - Uncontrolled or clinically significant GI disorders
- 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

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 (irREC)
- 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

References


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