

A Phase 1 Study of MGD007, a Humanized gpA33 x CD3 DART® Protein, in Combination with MGA012, an anti-PD-1 Antibody, in Patients with Relapsed/Refractory Metastatic Colorectal Cancer

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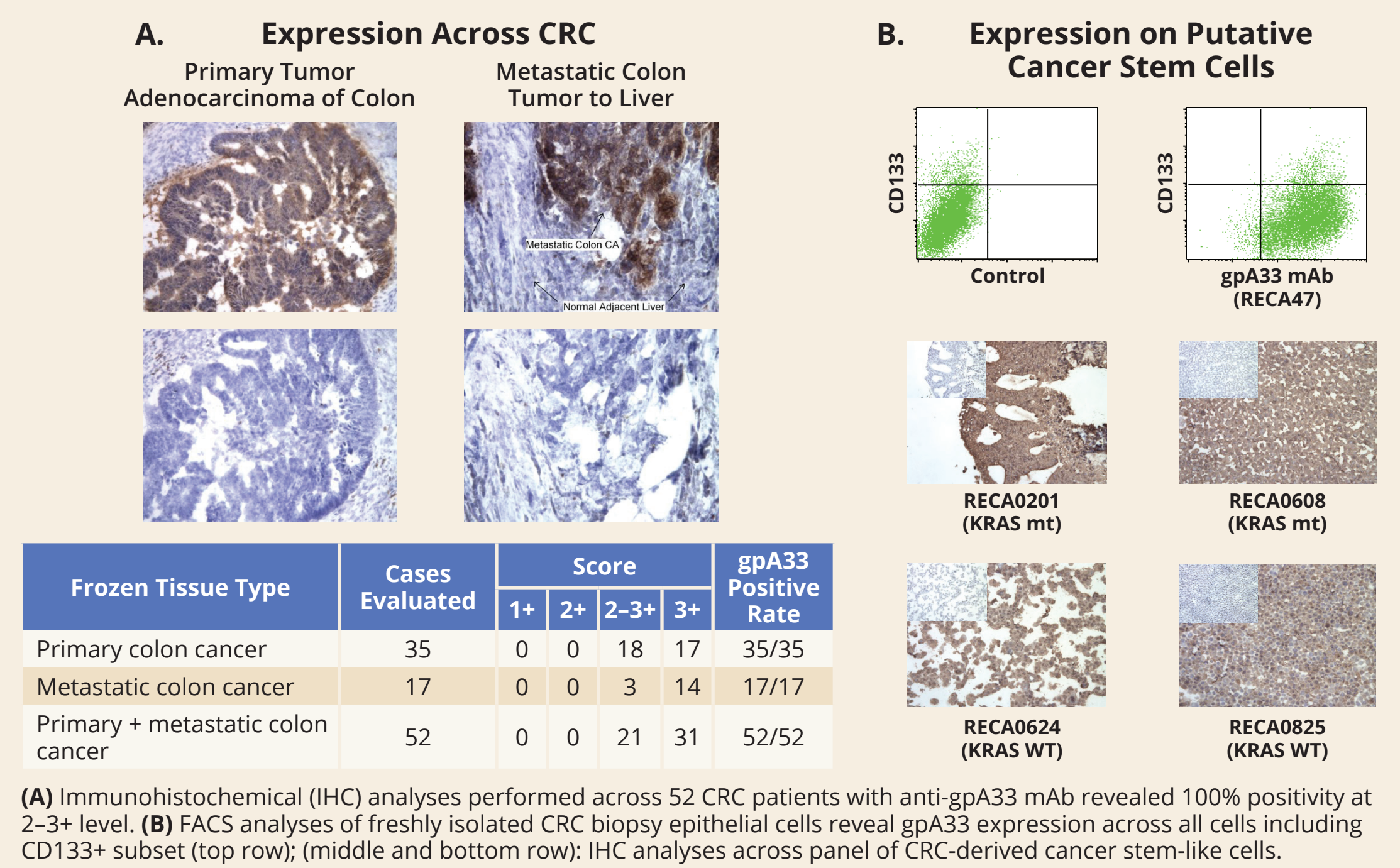


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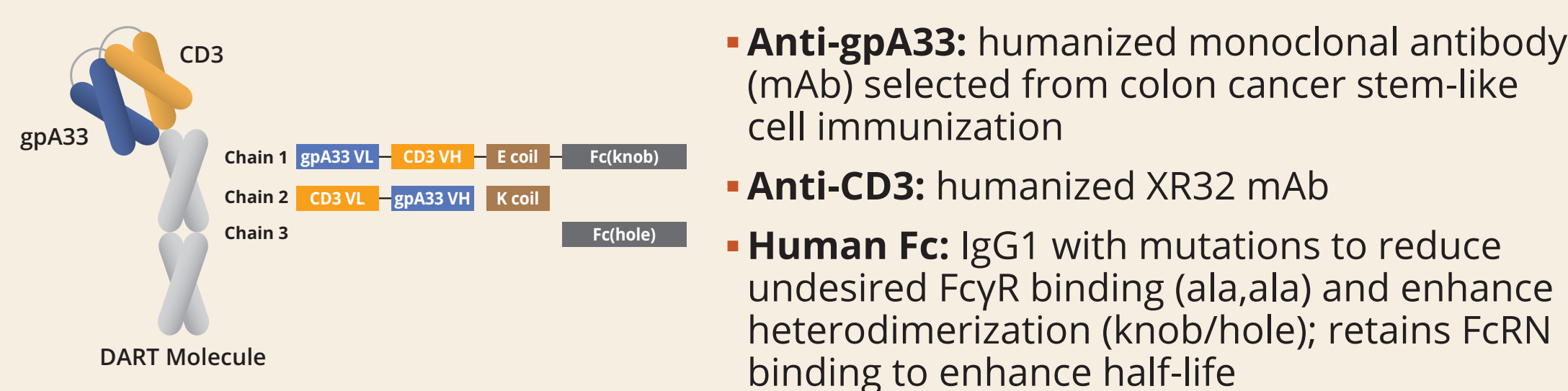
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Background

gpA33 is Broadly Expressed in Colorectal Cancer (CRC)



MGD007 (gpA33 x CD3) Structural Design



MGA012: Anti-PD-1 Monoclonal Antibody*

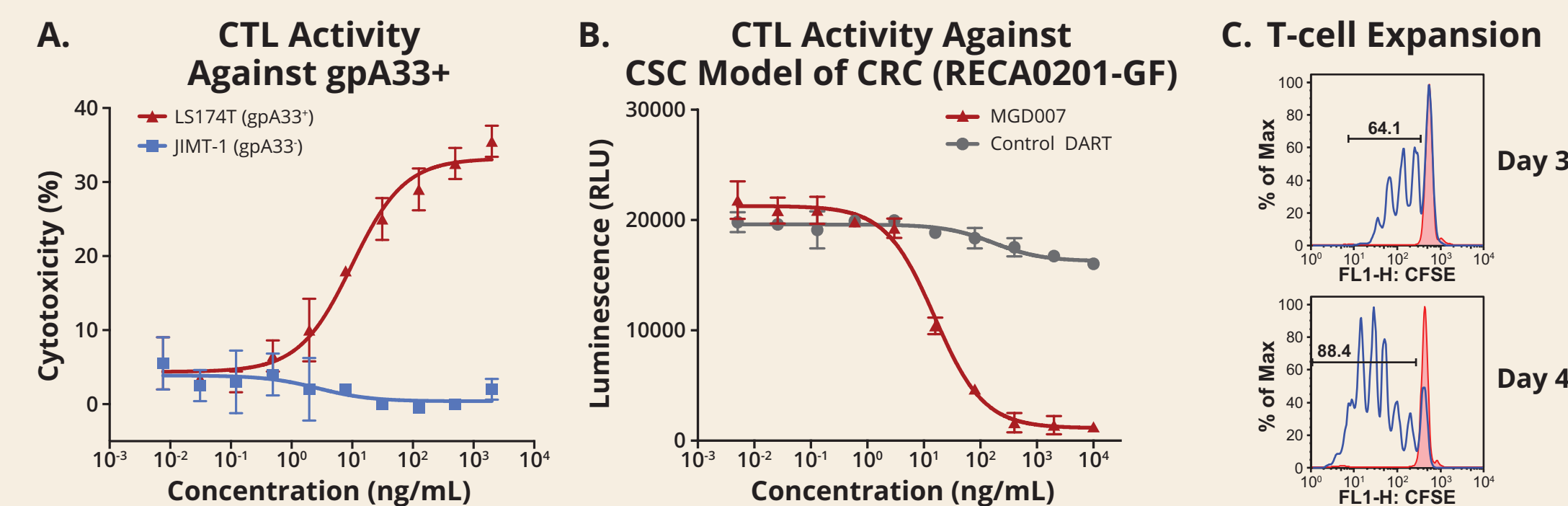
- Humanized proprietary anti-PD-1 mAb
 - Hinge stabilized humanized IgG4
 - Blocks PD-L1 and PD-L2 ligand binding to PD-1 and mediates enhanced T-cell responses
- Anti-PD-1 becoming mainstay of cancer immunotherapy
- Basis for combination immunotherapy

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

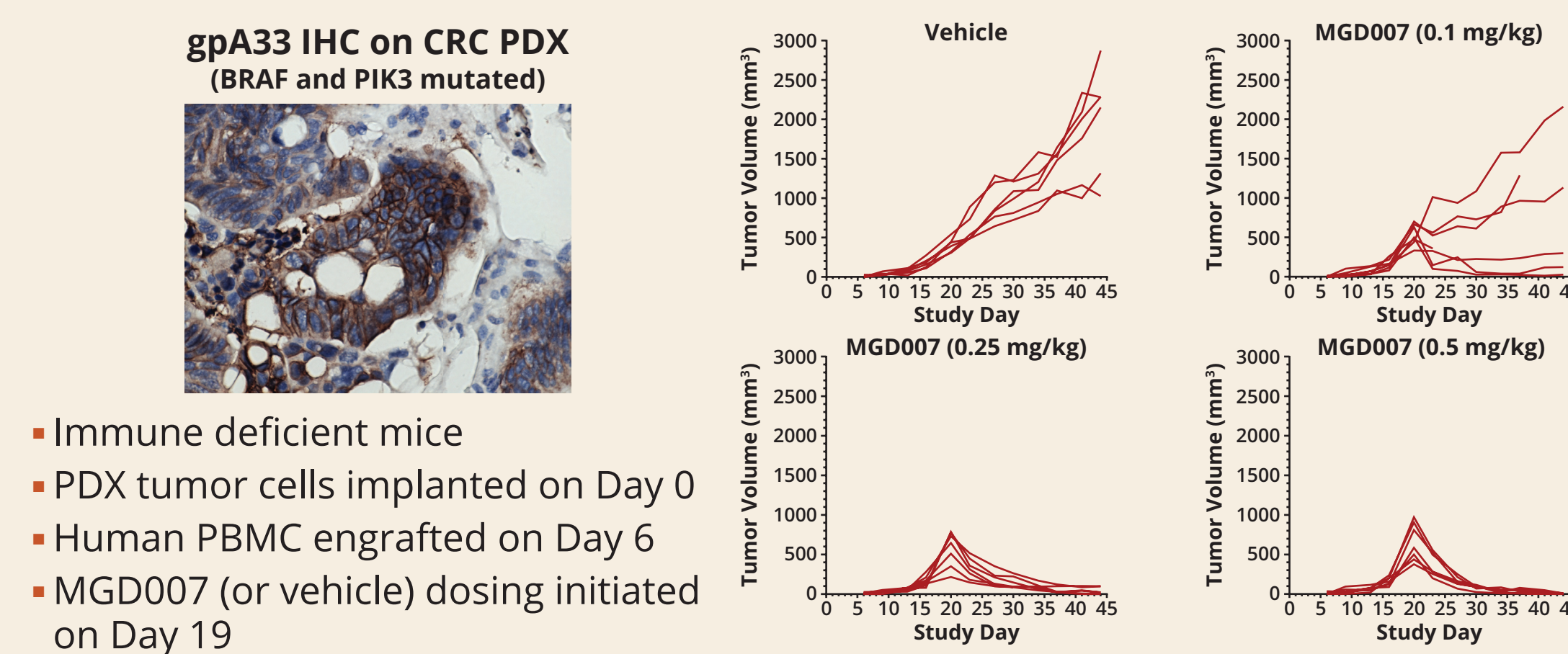
*Also known as INCMGA00012; licensed to Incyte 2017.

MGD007 Mediates T-cell Lysis of gpA33+ CRC Accompanied with T-cell Expansion

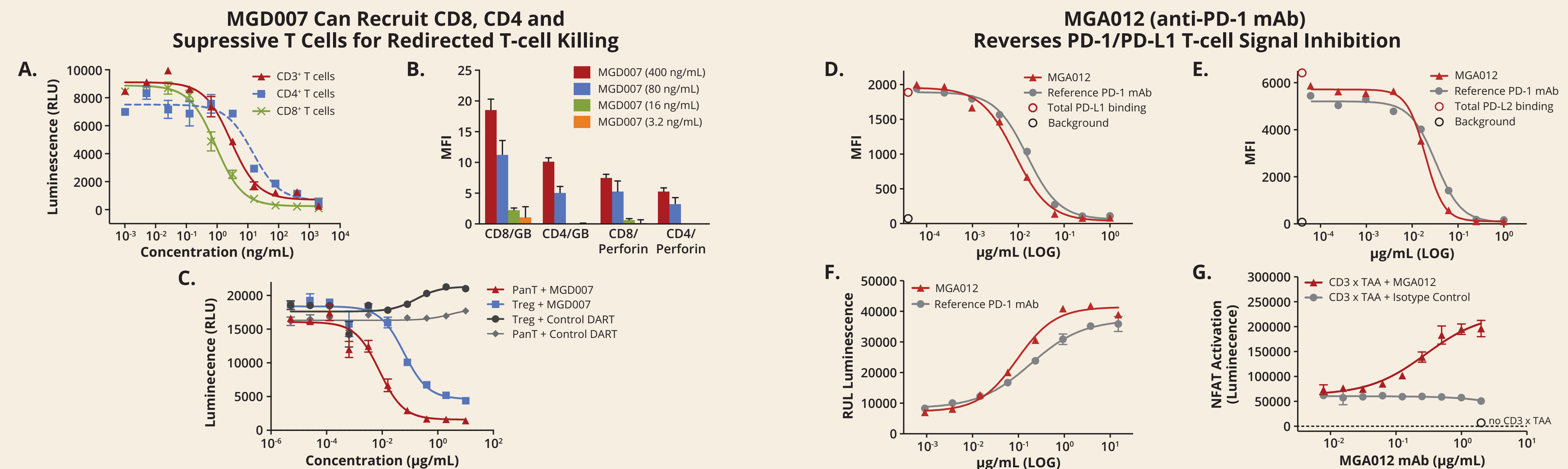


(A) MGD007-mediated cytotoxicity against gpA33⁺ LS174T colorectal cancer cell in presence of freshly isolated human PBMC (E:T = 30:1; 24h). (B) MGD007 mediated lysis of gpA33 luciferase-transduced RECA020108-GF colorectal Cancer Stem-Like Cells in presence of freshly isolated human T cells (E:T = 10:1; 48 h). (C) Proliferation of T-cells monitored by CFSE dilution in presence of MGD007 (blue) or control DART (red) incubated with gpA33⁺ LS174T (E:T = 10:1).

MGD007 Mediates Antitumor Activity in a CRC PDX Model

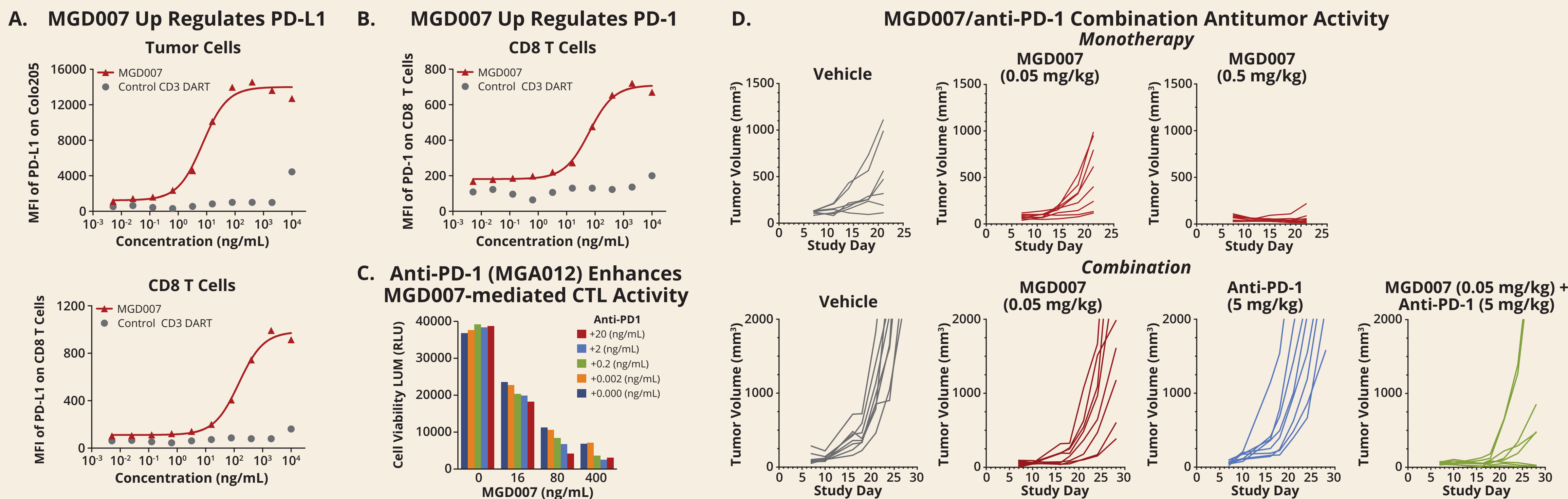


MGD007 and MGA012 Leverage Complementary T-cell-Mediated Mechanisms of Action



(A) MGD007-mediated cytotoxicity against gpA33⁺ Colo205-luc colorectal cancer cell line in presence of human T cells (CD3, CD8, or CD4 as indicated; E:T = 10:1). (B) Dose-dependent up-regulation of granzyme B (GB) and perforin levels following incubation of MGD007 with Colo205 and purified T cells (E:T = 10:1). (C) Tregs expanded in vitro for 15 days support MGD007 mediated cytotoxicity against gpA33⁺ Colo205. (D-E) MGA012 blockade of soluble PD-L1 or PD-L2 binding to NSO cells engineered to express cell surface PD-1. (F) MGA012 mediated enhancement of TCR activation of Jurkat cells under PD-L1/PD-1 mediated inhibition. (G) MGA012 mediated enhancement of CD3 based bispecific DART* activation of Jurkat cells under PD-L1/PD-1 mediated inhibition.

Anti-PD-1 Enhances MGD007-mediated Antitumor Activity in Preclinical Models



Cell surface expression of (A) PD-L1 on Colo205 (top), and CD8 T-cells (lower) and (B) PD-1 on CD8 T-cells in presence of MGD007 (E:T = 5:1; 24 hrs). (C) Redirected T-cell killing of Colo205 by MGA012 enhanced by addition of anti-PD1 mAb in presence of T cells (E:T = 3:1; 48 hrs). (D) MC38/hgpA33 colonic adenocarcinoma tumor growth in hCD3KI-Tg mice administered MGD007 alone (upper panels) or MGD007 ± anti-mouse PD-1 (lower panel). MGD007 dosed every 3-4 days; anti-PD-1 dosed on Days 0, 3 and 6.

Key Study Objectives

Primary:

- Characterize safety, tolerability, dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD)/maximum administered dose (MAD) of MGD007 in combination with MGA012

Secondary:

- Characterize pharmacokinetics, pharmacodynamics, and immunogenicity of combination
- Investigate preliminary anti-tumor activity of combination using both RECIST and immune-related RECIST
 - Objective response rate, disease control rate, progression-free survival at 16 weeks

Exploratory:

- Investigate immune-regulatory activity of combination in vivo

Entry Criteria

Key Inclusion Criteria

- Histologically proven, relapsed/refractory metastatic colorectal cancer
- Eastern Cooperative Oncology Group performance status 0 or 1
- Measurable disease per RECIST 1.1 criteria
- Participants in the Dose Escalation Phase must have had recurrence, progression or intolerance to standard therapy consisting of at least 2 prior standard regimens (containing a fluoropyrimidine plus a platinum analogue and/or irinotecan) for metastatic disease. Participants in the Cohort Expansion Phase will be allowed to participate after 1 prior standard regimen. Those who are inappropriate candidates for or have refused treatment with these regimens are also eligible. No more than 5 prior therapies are permitted
- Availability of sufficient tumor specimens to enable retrospective determination of gpA33, CD3, PD-1, and PD-L1 expression

Key Exclusion Criteria

- Symptomatic central nervous system (CNS) metastases. No concurrent treatment for the CNS disease; no progression of CNS metastases on MRI or CT for at least 14 days after last day of prior therapy for the CNS metastases; no concurrent leptomeningeal disease or cord compression

Study Design

Dose Escalation Phase: 3 + 3 + 3 Design

- 3 planned dose levels of MGD007
- MGA012 at fixed dose
- Patients may receive up to 12 cycles in the absence of disease progression, DLT, or other criteria for permanent discontinuation

Cohort Expansion Phase:

- 25 patients treated at MTD/MAD
- 90% of patients will be MSS and 10% MSI-H
- Paired tumor biopsies will be mandatory in 15/25 patients if lesions are accessible with acceptable risk

- History of known or suspected autoimmune disease with certain exceptions
- Major surgery, systemic anti-neoplastic therapy, or investigational therapy within 4 weeks
- Radiation therapy within 2 weeks
- Systemic corticosteroids (≥10 mg per day prednisone or equivalent) or other immune suppressive drugs within the 14 days
- History of Grade 3 or greater drug-related diarrhea/colitis during treatment with checkpoint inhibitors including anti-LAG-3, anti-PD-1, anti PD-L1, or anti-CTLA-4 antibodies
- Clinically significant cardiovascular disease; gastrointestinal disorders; pulmonary compromise; viral, bacterial, or systemic fungal infections
- History of positive testing for human immunodeficiency virus or history of acquired immune deficiency syndrome
- 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

The Sponsor thanks the patients and their families for participating in this study.