Abstract #264851

A Phase 1, First-in-Human, Open-Label, Dose Escalation and Cohort Expansion Study of MGD019, a Bispecific DART® Protein Binding PD-1 and CTLA-4, in Patients with Unresectable or Metastatic Neoplasms

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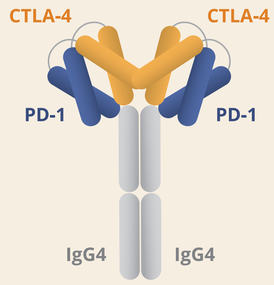
NCT03761017

Background

- Combined blockade of PD-1 and CTLA-4 with 2 checkpoint inhibitors, ipilimumab and nivolumab, increases antitumor activity beyond either single agent alone in patients with metastatic melanoma[1, 2]
- Combination of ipilimumab and nivolumab approved in US for patients with microsatellite instability high or mismatch repair deficient metastatic colorectal carcinoma, as well as intermediate- or poor-risk advanced renal cell carcinoma[3]

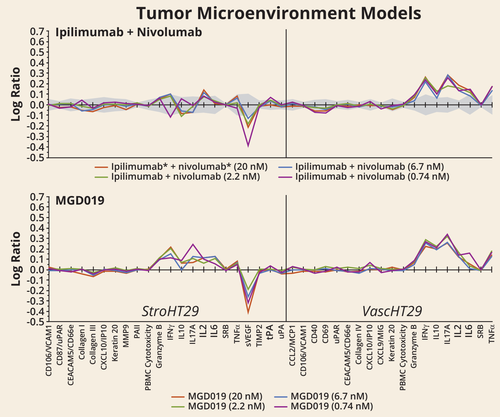
MGD019: Tetravalent Bispecific PD-1 x CTLA-4 DART Molecule

- MGD019 is a bispecific inhibitor that reverses both PD-1- and CTLA-4-mediated T-cell suppression in vitro
- In addition to convenience of single-administration dual checkpoint blockade, bispecific reagents may drive preferential accumulation and enhanced effect on target cells that express both molecules[4]
- Modeling studies predict that slower dissociation of a bispecific antibody from a dual-target binding complex may increase interaction avidity over that of the combination of single target-bound species[5]



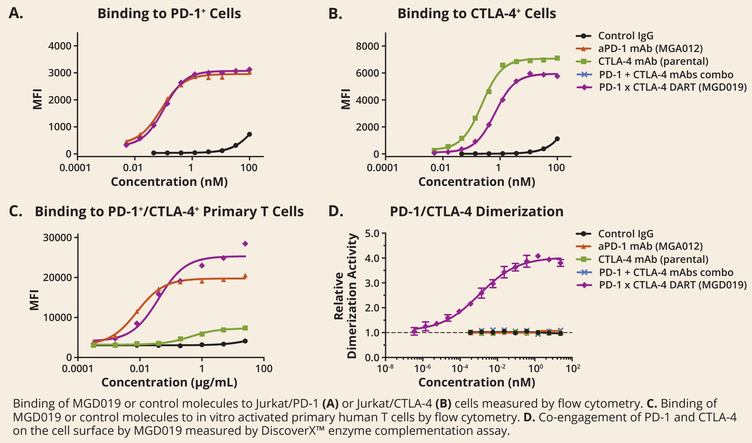
- Dual checkpoint inhibitor
- Hinge stabilized, tetravalent IgG4

MGD019 Induces Activation Profiles Similar to the Combination of Ipilimumab & Nivolumab



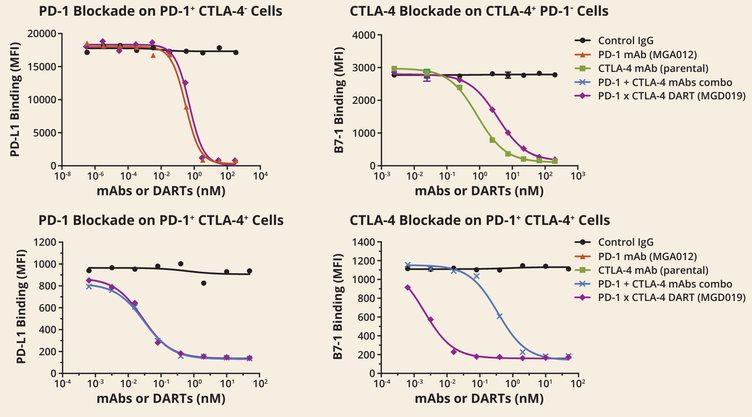
DiscoverX StroHT29 and VascHT29 TME models: HT-29 colorectal cells were cultured with stromal cells and PBMCs to recapitulate a tumor microenviroment (DiscoverX). Protein expression was measured following treatment with mAbs or MGD019.
*Replicas of nivolumab and ipilimumab were constructed on the basis of the published sequences.

MGD019 Co-Engages PD-1 and CTLA-4 on Dual-expressing Cells

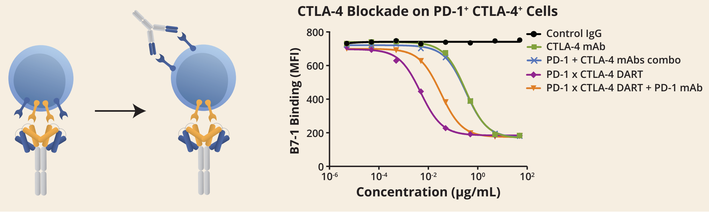


Binding of MGD019 or control molecules to Jurkat/PD-1 **(A)** or Jurkat/CTLA-4 **(B)** cells measured by flow cytometry. **C.** Binding of MGD019 or control molecules to in vitro activated primary human T cells by flow cytometry. **D.** Co-engagement of PD-1 and CTLA-4 on the cell surface by MGD019 measured by DiscoverX™ enzyme complementation assay.

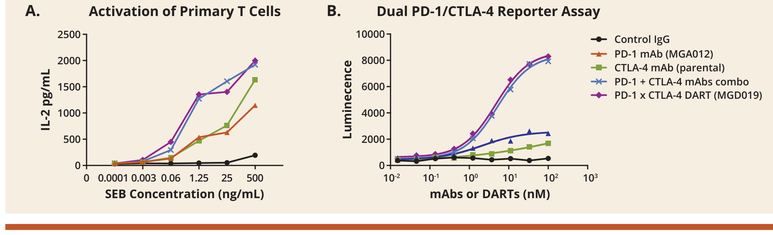
Enhanced Blockade of CTLA-4 on Dual Expressing Cells



Anchoring via PD-1 Contributes to anti-CTLA-4-mediated Blockade of B7 Binding



MGD019 Enhances T-cell Activation



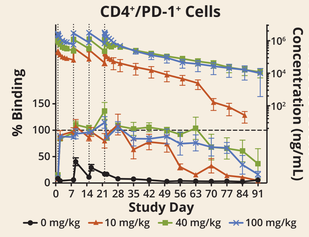
MGD019 was Well-tolerated in Non-human Primates

MGD019 GLP Toxicology Results

Finding	PD-1 x CTLA-4 Bispecific (MGD019)			PD-1 mAb (MGA012)	PD-1 + CTLA-4 Two mAbs Combo[6]
	10 mg/kg	40 mg/kg	100 mg/kg	≥100 mg/kg	
Adverse clinical signs	-	-	-	-	+[a]
Body weight loss	-	-	-	-	+
Increased spleen weight	+	++	++	-	+
Lymphoid hyperplasia/ hypertrophy in spleen	-	+	++	-	++
GI tract inflammation	-	-	-	-	+[b]
Cytokine induction	-	-	-	-	Not reported
T cell expansion	+	++	++	+	++

[a]Dose-related diarrhea; decreased food consumption at the high dose [50 mg/kg anti-PD-1 + 10 mg/kg anti-CTLA-4].
[b]Large intestine: diffuse lymphoplasmacytic inflammation in the lamina propria with concurrent enlargement of the colonic or pelvic lymph nodes.

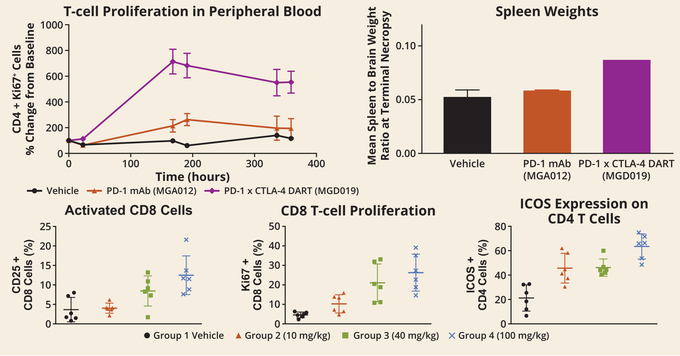
MGD019 Pharmacokinetics and Receptor Occupancy



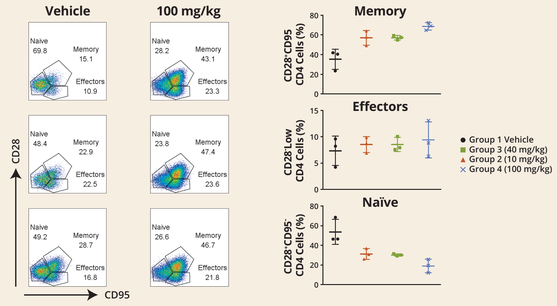
- MGD019 demonstrates good pharmacokinetics consistent with IgG4 Fc backbone
- MGD019 receptor occupancy correlates with its serum concentration

Cynomolgus monkeys (3F/3M) were infused with 10, 40 or 100 mg/kg/dose MGD019 at Day 1, 8, 15, and 22. Serum concentration was measured by ELISA (left axis) and receptor occupancy was measured by flow cytometry (right axis).

MGD019 Supports Homeostatic Proliferation of T Cells in Monkeys



MGD019 Enhances the Number of Circulating Memory T Cells



Cynomolgus monkeys were injected weekly with indicated amounts of MGD019. Shortly after 4th injection, T cells of necropsied animals were analyzed for expression of CD28 and CD95 by flow cytometry.

Rationale

- Potential improvement of safety/efficacy of MGD019 vs PD-1 + CTLA-4 CPI combinations
- MGD019 binds to and blocks its targets with increased activity on dual PD-1/CTLA-4-expressing cells
- MGD019 enhances T-cell responses in vitro to the level achieved by a combination of nivolumab and ipilimumab replicas
- MGD019 was well tolerated in cynomolgus monkeys, with a safety profile similar to that observed with PD-1 blockade alone, while demonstrating biological effects of CTLA-4 antagonism

Key Study Objectives

Primary Objective:

- Characterize safety, including tolerability, dose limiting toxicities (DLTs), and maximum tolerated dose (MTD) or maximum administered dose (MAD) if no MTD is defined, of MGD019 given intravenously to patients with advanced solid tumors

Secondary Objectives:

- Characterize PK and immunogenicity
- Describe preliminary evidence of antitumor activity using conventional RECIST v1.1 and immune-related RECIST

Exploratory Objectives:

- Explore relationship between PK, pharmacodynamics, and antitumor activity; immune-regulatory effects of MGD019, including measures of immune cell activation/exhaustion in peripheral blood and/or tumor biopsy specimens; relationships among PD-1, PD-L1, and CTLA-4 expression on tumor cells and immune cell infiltrates within biopsy specimens (including CD4⁺ and CD8⁺ T cells) and antitumor activity; relationship between gene profiles and antitumor activity; relationship between tumor mutational burden and antitumor activity

Study Design

Dose Escalation

All-Comer Advanced Solid Tumors
Up to 7 Planned Cohorts

MTD/MAD

Cohort Expansion

- CPI-Naïve NSCLC N = 20
- Post-PD-1 NSCLC N = 20
- Post-PD-1 SCCHN N = 16
- CPI-Naïve RCC N = 16
- Cervical Cancer N = 16
- Soft Tissue Sarcoma N = 16

- Dose escalation: 3+3+3 design
- Starting dose based on in vitro biocomparability and clinical experience with anti-PD-1/CTLA-4 therapies
- MTD/MAD evaluated in 6 expansion cohorts

Entry Criteria

Key Inclusion Criteria

- Dose escalation: Patients with histologically proven, unresectable, locally advanced or metastatic solid tumors for whom no approved therapy with demonstrated clinical benefit is available or patients who are intolerant to standard therapy
- Cohort Expansion Phase: Disease-specific prior therapy requirements to be specified
- ECOG performance status of 0–1
- Life expectancy ≥12 weeks
- Measurable disease as per RECIST 1.1 for the purpose of response assessment must either (a) not reside in a field that has been subjected to prior radiotherapy or (b) have demonstrated clear evidence of radiographic progression since the completion of prior radiotherapy and prior to study enrollment
- All patients must have an identified formalin-fixed, paraffin embedded tumor specimen for immunohistochemical evaluation of pharmacodynamic markers of interest
- Acceptable laboratory parameters and adequate organ reserve

Key Exclusion Criteria

- In patients who have previously received an immune checkpoint inhibitor, toxicities related to the CPI must have resolved to ≤ Grade 1 or baseline. Patients with well controlled immune endocrinopathies secondary to prior checkpoint therapy are eligible
- Patients with symptomatic CNS metastases. Patients with history of CNS metastasis must have been treated, must be asymptomatic, and must not have concurrent treatment for the CNS disease, progression of CNS metastases on MRI or CT for at least 14 days after last day of prior therapy for the CNS metastases, or concurrent leptomeningeal disease or cord compression
- Patients who experienced the following Grade 3 CPI-related AEs are ineligible: ocular AE, changes in liver function tests that met the criteria for Hy's law, neurologic toxicity, colitis, renal toxicity, pneumonitis
- Patients with prior therapy with a combination of monoclonal antibodies against PD-1/PD-L1 and CTLA-4 will be excluded in Cohort Expansion
- Patients with any history of known or suspected autoimmune disease with certain exceptions
- History of prior allogeneic bone marrow, stem cell, or solid organ transplantation
- History of trauma, major surgical procedure, systemic antineoplastic therapy, or investigational therapy within 4 weeks and treatment with radiation therapy within 2 weeks prior to initiation of study drug administration

References

1. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med.* 2015 Jul 2;373(1):23-34. **2.** Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med.* 2013;369(2):122-33. **3.** Opdivo (nivolumab) injection for intravenous use (prescribing information). Princeton, NJ: Bristol-Myers Squibb, 2017. **4.** Jarantow SW, Bushey BS, Pardinas JR, Boakye K, Lacy ER, e al. Impact of Cell-surface Antigen Expression on Target Engagement and Function of an Epidermal Growth Factor Receptor × c-MET Bispecific Antibody* *The Journal of Biological Chemistry* 290 2015, 24689-24704. **5.** Sengers BG, McGinty S, Nouri FZ, Argungu M, Hawkins E, et al. Modeling bispecific monoclonal antibody interaction with two cell membrane targets indicates the importance of surface diffusion. *MAbs.* 2016 Jul; 8(5): 905–915. **6.** Selby M. et al. Preclinical Development of Ipilimumab and Nivolumab Combination Immunotherapy: Mouse Tumor Models, In Vitro Functional Studies, and Cynomolgus Macaque Toxicology. *PLoS One.* 2016 Sep 9;11(9):e0161779.

Presented at the 2019 ASCO Annual Meeting, May 31 – June 4, 2019, Chicago, IL