A Phase 1, First-in-Human, Open-label, Dose Escalation Study of MGD013, a Bispecific DART® Protein Binding PD-1 and LAG-3 in Patients with Unresectable or Metastatic Neoplasms

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http://ir.macrogenics.com/events.cfm

Background

MGD013: First Bispecific Checkpoint Molecule in Clinic

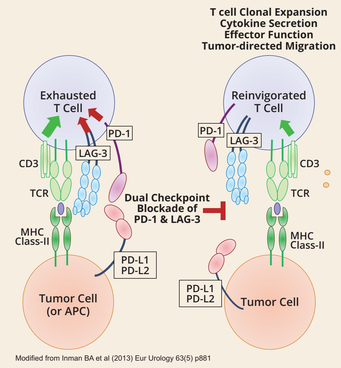
- Humanized, proprietary PD-1 x LAG-3 DART® molecule
  - Hinge-stabilized human IgG4
  - Benchmarks favorably against leading monoclonal antibodies (mAbs)

Function/MoA: Reactivation of exhausted T cells

Indications: Multiple solid tumors and hematological malignancies

Rationale for Dual Targeting of PD-1 and LAG-3

- Tumors activate immune inhibitory pathways
- PD-1 & LAG-3 receptors overexpressed on "exhausted" T-cells
- Animal tumor models demonstrate synergy of anti-PD-1 + anti-LAG-3 mAbs
- Combination clinical trials of anti-PD-1 and anti-LAG3 are ongoing



Modified from Inman BA et al (2013) Eur Urology 63(5) p881

Overlap of PD-1 and LAG-3 Expressing TIL Detection in NSCLC and TNB Cancers

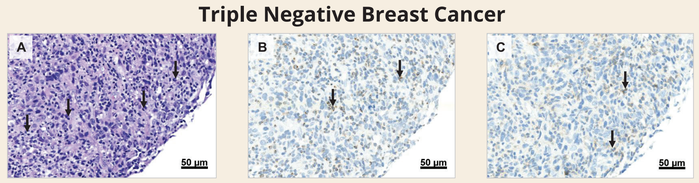
Validation Study Performed by MG

	Expression of Checkpoint(s) Across All TMAs*			Overlapping Expression**	
Tumor MicroArray (TMA) Spot Count for Particular Indication	LAG-3+ Total	PD-1+ Total	LAG-3+PD-1+ Total	LAG-3+ PD-1+	PD-1+ LAG-3+
Lung Squamous Cell Carcinoma	18/36 50%	15/36 42%	10/36 28%	10/15 67%	10/18 56%
Lung Adenocarcinoma	19/33 58%	18/33 55%	15/33 46%	15/18 83%	15/19 79%
Triple Negative Breast Cancer	16/29 55%	12/29 41%	10/29 35%	10/12 83%	10/16 63%

*Spot Counts indicate the number of TMA positive for LAG-3, PD-1, or LAG-3 + PD-1 expression divided by the total TMAs

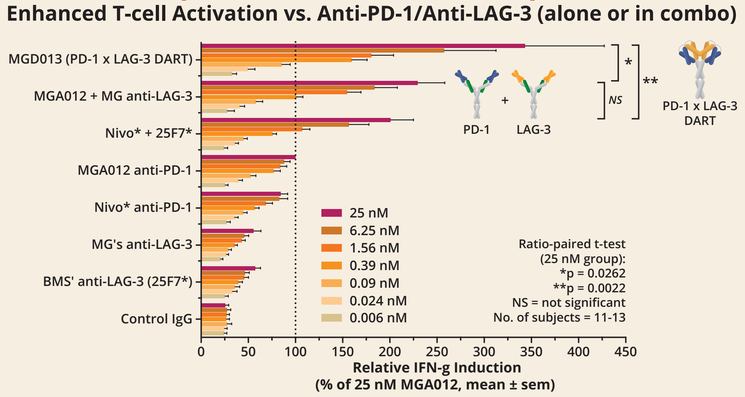
**Spot Counts indicate the number of TMA with overlapping checkpoint expression of PD-1 and LAG-3

Triple Negative Breast Cancer



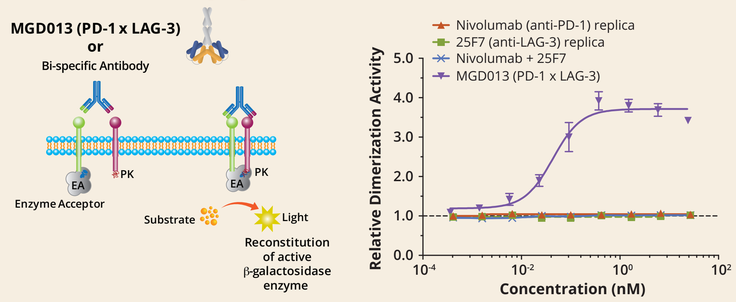
MGD013: Bispecific Coordinate Checkpoint Blockade

Enhanced T-cell Activation vs. Anti-PD-1/Anti-LAG-3 (alone or in combo)

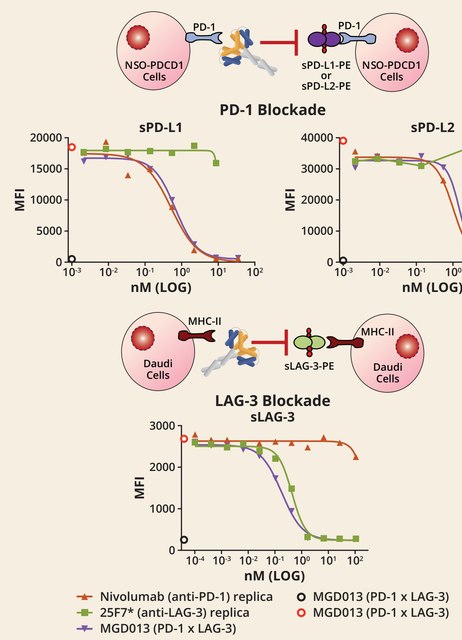


IFN-γ release by 25 nM MGA012 = 3276 ± 744 pg/mL

MGD013 Co-engages Both PD-1 and LAG-3

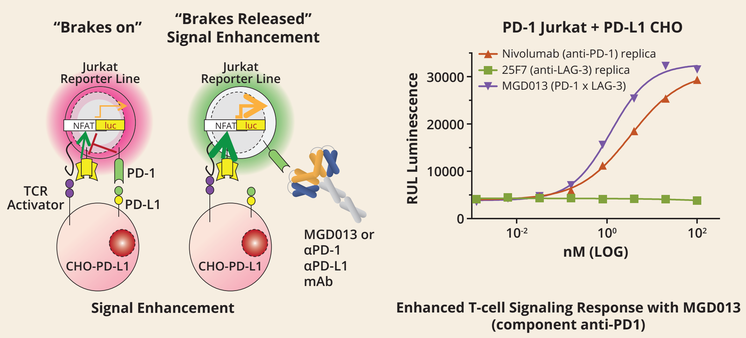


MGD013 Blocks PD-1 and LAG-3 Interactions



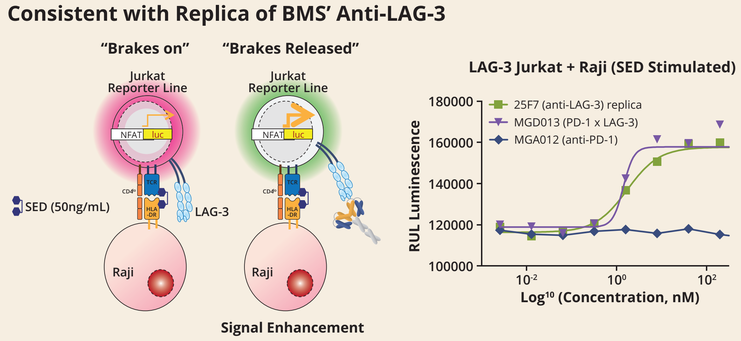
MGD013 Reverses PD-1/PD-L1 Mediated T-cell Signal Inhibition

Consistent with Replica of Nivolumab



MGD013 Reverses LAG-3/Class II Mediated T-cell Signal Inhibition

Consistent with Replica of BMS' Anti-LAG-3



Rationale

- MGD013 can enhance T-cell activation in a synergistic fashion beyond that observed with the anti–PD-1 and anti–LAG-3 mAbs alone or the combination of the single agents
- Bispecific approach to target these checkpoint proteins with a single molecule may confer additional benefits beyond that realized with the individual mAb combination and represents a rationale for dual checkpoint blockade
- MGD013 may offer clinical opportunities to checkpoint naïve patients as well as to checkpoint experienced patients who have progressed on prior therapy with PD-1/PD-L1 inhibitors

Key Study Objectives

Primary Objective

- Characterize safety, tolerability, DLT, maximum tolerated dose (MTD) or maximum administered dose (MAD) of MGD013 when administered IV every two weeks to patients with relapsed/refractory unresectable or metastatic neoplasms

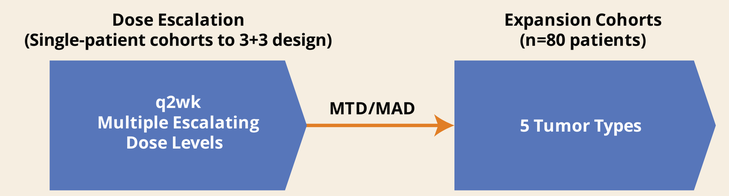
Secondary Objectives

- Characterize pharmacokinetics (PK) and immunogenicity of MGD013
- Investigate preliminary anti-tumor activity of MGD013 using both conventional RECIST 1.1 and immune-related response criteria (irRC)

Exploratory Objectives

- Explore relationships between PK, pharmacodynamics, patient safety, and antitumor activity of MGD013
- Investigate immune-regulatory activity of MGD013 in vivo, including various measures of T-cell activation in peripheral blood and/or tumor biopsy specimens
- Determine relationships between PD-1, PD-L1, LAG-3, and MHC-II expression in tumor cells and immune cell infiltration within biopsy specimens (including $CD4^+$ and $CD8^+$ T cells) and antitumor activity

Study Design



- Multi-center, Phase 1, open-label, study with single-patient escalation followed by 3+3 design dose escalation and cohort expansion
- MGD013 administered at escalating doses by intravenous infusion every 2 weeks in 8-week cycles
- MTD: Dose at which <33% of patients experience a drug-related DLT during the first 28 days of Cycle 1. If no DLT defined, highest dose level will be designated as MAD
- Patient management according to immune response principles and may receive up to 12 cycles

Entry Criteria

Key Inclusion Criteria

- Dose escalation: histologically proven, locally advanced unresectable or metastatic solid tumors of any histology with no approved therapy. Disease-specific criteria to be applied in Cohort Expansion
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Life expectancy ≥12 weeks
- Measurable disease per RECIST 1.1
- Previous immune checkpoint inhibitor toxicities resolved to ≤ Grade 1/baseline
- Acceptable laboratory parameters
- Must have a formalin-fixed, paraffin embedded tumor specimen

Key Exclusion Criteria

- Symptomatic central nervous system metastases
- History of known or suspected autoimmune disease with specific exceptions
- Treatment with any systemic anti-neoplastic therapy, or investigational therapy within 4 weeks; radiation therapy or corticosteroid treatment within 2 weeks
- Clinically significant cardiovascular, pulmonary, or gastrointestinal disease

Presented at the Society for Immunotherapy of Cancer (SITC) 32nd Annual Meeting, November 8–12, 2017, National Harbor, MD