A Phase 1, Open Label, Dose Escalation Study of MGD009 (Orlotamab), A Humanized B7-H3 x CD3 Bispecific DART® Molecule, in Combination with MGA012, An Anti-PD-1 Antibody, in Patients with Relapsed or Refractory B7-H3-Expressing Tumors

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Poster P305

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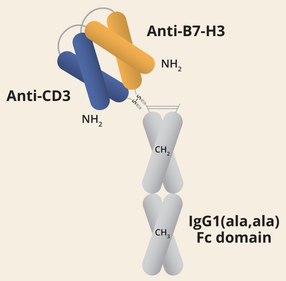
Background

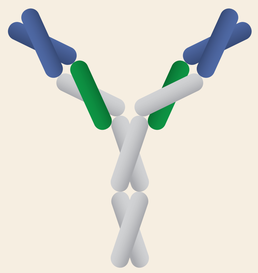
Orlotamab: B7-H3 x CD3 Bispecific DART Molecule

- Humanized Fc-bearing B7-H3 x CD3 DART molecule designed to redirect T cells to eliminate B7-H3-expressing target cells through co-engagement of B7-H3 on target cells and CD3 on T cells
- Human IgG1 Fc domain mutated to reduce/ eliminate effector function via binding to FcγRs and complement
- Retains binding to neonatal Fc receptor, enabling use of IgG salvage pathway to prolong circulating half-life
- Enhances activation and proliferation as well as production of cytokines and mediators (granzyme/perforin) of T-cell cytolytic activity
- Currently enrolling a Phase 1 study of orlotamab in patients with advanced B7-H3-positive solid tumors



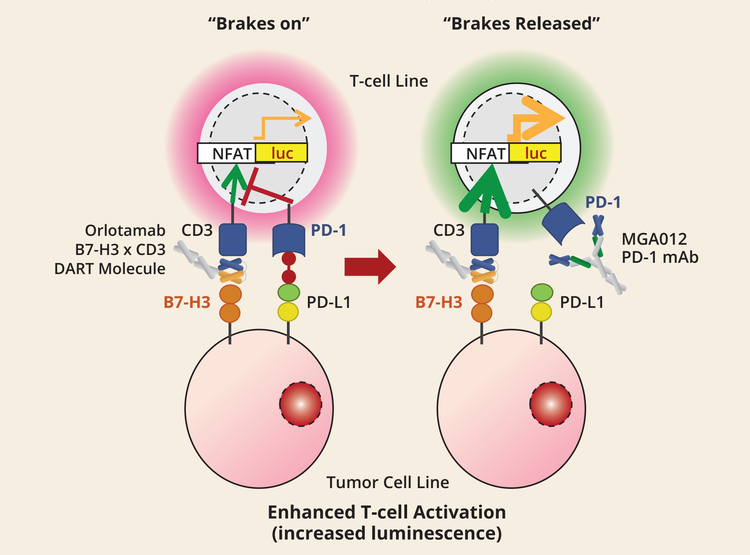
MGA012: Anti-PD-1 Monoclonal Antibody (mAb)*

- 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

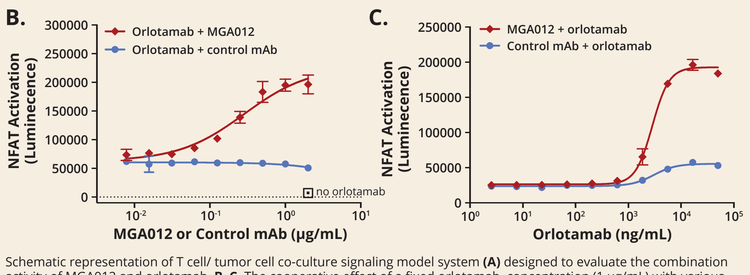


*Also known as INCMGA00012; licensed to Incyte 2017.

MGA012 Cooperates with Orlotamab to Enhance Reporter Cell Activity in a T Cell/Tumor Cell Co-culture Signaling Model System



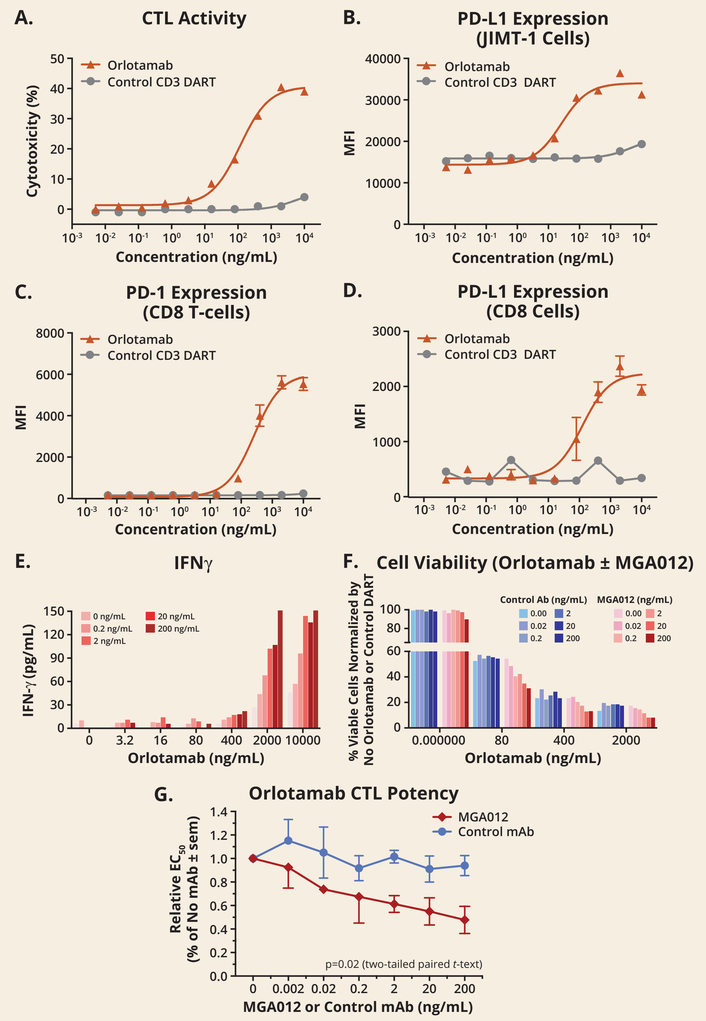
Cooperation Between MGA012 and Orlotamab



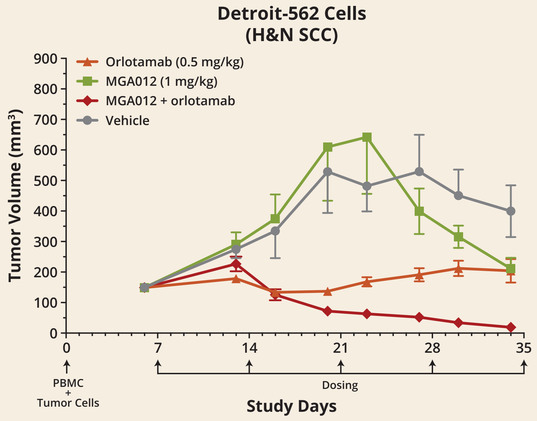
Schematic representation of T cell/ tumor cell co-culture signaling model system **(A)** designed to evaluate the combination activity of MGA012 and orlotamab **B–C.** The cooperative effect of a fixed orlotamab concentration (1 μg/mL) with various concentrations of MGA012 (red line) or control mAb (blue line) as indicated **(B)** or a fixed concentration of MGA012 (1.87 μg/mL, red line) or the negative mAb control (blue line) with various concentrations of orlotamab at indicated concentrations **(C)** following 24 hours of co-culture with the Jurkat reporter line (30,000 cells/well) and the MDA-MB-231 stimulator line (10,000 cells/well) was evalauted by measuring luminescence relative light unit (RLU) as the readout. The data were plotted as mean luminescence against orlotamab concentration and fitted using a log (agonist) vs. response–variable slope (4 parameter) function.

MGA012 Enhances Orlotamab-Mediated T-cell Killing

In Vitro



In Vivo



NSG MHC-I$^{-/-}$ mice. Detroit-562, 5x10^6 cells, ID. PBMC, 10^6 cells, IP.

Rationale

- B7-H3 is over-expressed on wide range of malignant neoplasms, with minimal protein expression on normal tissue; CD3 is expressed almost exclusively by T cells and is present in all stages of T-cell development
- Increased B7-H3 expression may correlate with various adverse clinical features, including advanced disease, metastasis and poorer survival
- B7-H3 tumor expression level inversely correlates with T-cell infiltrate
- Upregulation of PD-1 on T cells and IFNγ inducible upregulation of PD-L1 on tumor cells may be associated with the mechanism of action of orlotamab, suggesting that the antitumor activity of orlotamab could be further enhanced by coordinate blockade of PD-1/PD-L1 pathway
- Inhibition of PD-1/PD-L1 axis with MGA012 could enhance the antitumor activity of orlotamab in patients, a hypothesis supported by various preclinical studies demonstrating enhanced orlotamab-mediated activity in the presence of B7-H3-expressing tumor cells when combined with MGA012 as compared to orlotamab or MGA012 alone

Key Study Objectives

Primary Objective:

- Characterize safety, tolerability, dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD; or maximum administered dose [MAD]) of orlotamab in combination with MGA012

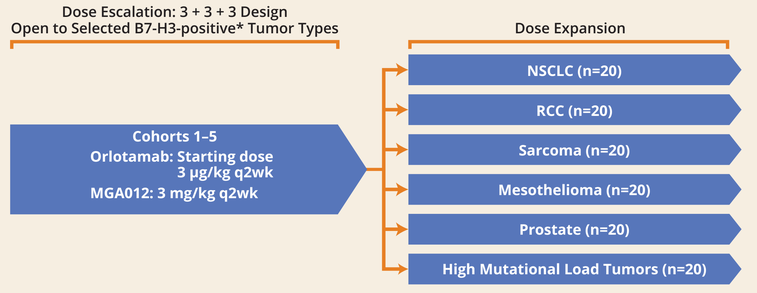
Secondary Objectives:

- Characterize pharmacokinetics (PK) and immunogenicity of combination
- Investigate preliminary anti-tumor activity of combination using both RECIST and immune-related response criteria (irRECIST)

Exploratory Objectives:

- Explore relationships between PK, PD, and patient safety as well as antitumor activity
- Investigate immune-regulatory activity of combination in vivo, including measures of T-cell activation in peripheral blood and/or biopsy specimens
- Determine relationship between B7-H3 and PD-L1 expression in tumor, immune cell infiltration, and antitumor activity
- Characterize transcript profiles and T-cell repertoire

Study Design



*B7-H3 positivity defined as > 10% tumor ≥ 2+ and/or > 25% of vasculature positive.

- MGA012 and orlotamab administered IV every other week
- 8-week tumor assessment cycles; maximum of 14 cycles
- DLT evaluation period through Day 29 of Cycle 1; tumor assessment at Day 56 of each cycle
- 2-year survival follow-up following last dose of study drug
- Trial is ongoing

Entry Criteria

Key Inclusion Criteria

- Patients with selected B7-H3-positive tumors for whom no approved therapy with demonstrated clinical benefit is available. Requirement for previous systemic therapy may be waived if patient was intolerant of or refused standard first-line therapy
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Measurable disease per RECIST 1.1, with the exception of prostate cancer
- Tissue specimen available for B7-H3 and PD-L1 expression testing
- Life expectancy ≥12 weeks
- Acceptable laboratory parameters
- Toxicities related to prior checkpoint inhibitors must be resolved to ≤ Grade 1 or baseline. Patients who experienced previous hypothyroidism toxicity on checkpoint inhibitor are eligible regardless of Grade resolution as long as patient is well controlled on replacement therapy

Key Exclusion Criteria

- Patients with history of prior central nervous system (CNS) metastasis must have been treated, be asymptomatic, and must not have the following at the time of enrollment: concurrent treatment; progression of CNS metastases ≥14 days after last day of prior therapy for CNS metastases; leptomeningeal disease or cord compression
- Patients with any history of known or suspected autoimmune disease, with certain exceptions
- Treatment with any investigational therapy within 4 weeks, systemic chemotherapy within 3 weeks, radiation therapy within 2 weeks, and systemic corticosteroids or other immune suppressive drugs within 2 weeks prior to study drug administration
- Clinically significant cardiovascular or pulmonary disease
- Evidence of active viral, bacterial, or systemic fungal infection requiring parenteral treatment within 7 days prior to initiation of study drug
- Known history of positive testing for human immunodeficiency virus or history of acquired immune deficiency syndrome
- Known 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 participation in this study.