# A Phase 1/2, First-in-Human, Dose Escalation Study of MGC018 (Anti-B7-H3 Antibody-Drug Conjugate) Alone and in Combination with MGA012 (Anti-PD-1 Antibody) in Patients with Advanced Solid Tumors

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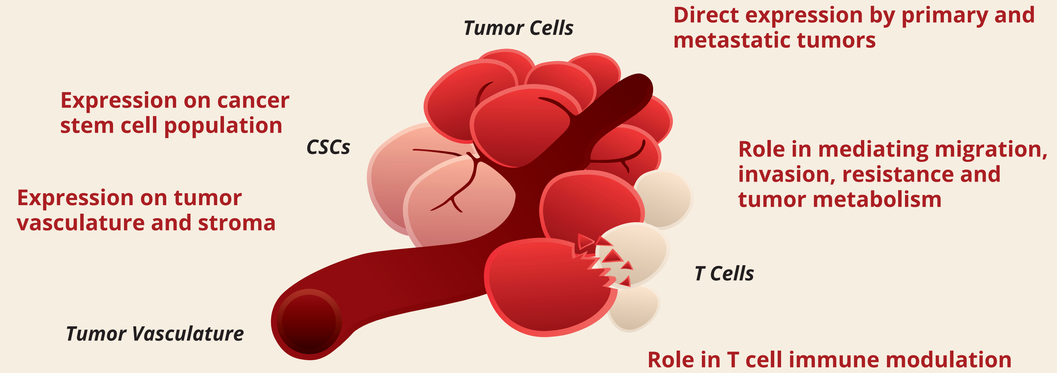
## Background

- Antibody-drug conjugates (ADCs) are a powerful class of agents for targeted cancer treatment
  - Combine specificity of monoclonal antibody with highly-potent cytotoxic "payloads" for selective delivery of cytotoxic agents to cancer cells
  - Offer potential for increased efficacy while minimizing exposure to normal tissues
- B7-H3, a member of B7 family of immune regulators, is overexpressed in a wide range of solid tumors, with limited normal tissue expression, making it suitable for targeted therapies

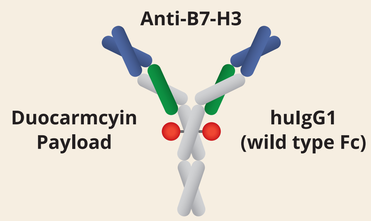
### Rationale for Targeting B7-H3 in Cancer




- This study evaluates MGC018 (ADC) as monotherapy and in combination with MGA012 (anti-PD-1; also known as INCMGA00012)
- Working hypotheses:
  - MGC018 monotherapy may mediate antitumor activity against B7-H3-positive tumors
  - Administration of B7-H3-directed cytotoxic agent could enhance tumor cell death and drive "auto-vaccination" of the host immune system
  - Added engagement of T-cell response by administration of MGC018 in combination with the anti-PD-1 antibody MGA012

### MGC018: Antibody-Drug Conjugate

- Humanized ADC targeted against B7-H3
- Cleavable linker-duocarmycin payload
- Designed to bind to cell-surface B7-H3, internalize into cells, and release the cytotoxic duocarmycin drug




## Study Rationale

- MGC018 exhibited potent cytotoxic activity toward human tumor cell lines expressing a range of B7-H3 levels in in vitro studies and xenograft studies in mice
  - Cytotoxic activity was dependent on B7-H3 expression
- Non-clinical studies with MGC018 established dose-response profiles following single- and repeat-dose administration and identified cancer types that exhibit sensitivity to MGC018
  - MGC018 exhibited antitumor activity toward human tumor xenografts representing breast, lung, ovarian cancer, and melanoma
- MGC018 exhibited an acceptable safety profile following repeat-dose administration in cynomolgus monkeys
  - Favorable tissue cross-reactivity profile across a panel of 34 normal human tissues

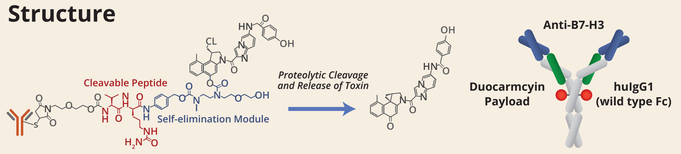
## Study Design

- Phase 1/2, first-in-human, open-label study of MGC018 monotherapy and MGC018 in combination with MGA012
- 3+3+3 dose escalation design followed by cohort expansion phase
- Combination dose escalation will commence only after the maximum tolerated dose/maximum administered dose (MTD/MAD) identified in MGC018 monotherapy
- Patients with solid tumors of any histology will be enrolled in the dose escalation phase; cohort expansion will include patients with squamous cell carcinoma of the head and neck, prostate carcinoma, triple negative breast cancer, and uveal melanoma
- Pharmacokinetics (PK), immunogenicty, and impact of treatment on various measures of immune function and tumor cell death will be assessed
- Patients who do not experience dose-limiting/unacceptable toxicity or meet criteria for permanent discontinuation may undergo additional cycles
- 2-year survival follow-up every 3 months after last dose

### Duocarmycin-based Linker Payload

**vc-seco-DUocarmycin-hydroxyBenzamide Azaindole (DUBA)**

**Structure**

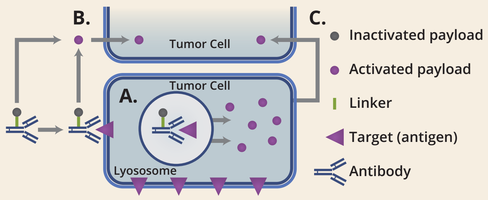



**Duocarmycins**

- DNA alkylating agents — cell cycle independent
- Fully synthetic — picomolar activity in vitro
- Retain potency in multi-drug resistant lines
- Cleavable peptide linker — facilitates bystander effect
- Anti-HER2-DUBA (SYD985) in Phase 3 clinical study (Synthon Biopharmaceuticals)

**Mode of Action**

- Uptake of ADC by internalization and intracellular release of payload **(A)**
- Proteolytic cleavage of payload in tumor microenvironment **(B)**
- Diffusion of active payload to neighboring tumor cells **(C)**




DUBA Linker Payload provided and conjugated by Synthon Biopharmaceuticals, B.V.

## Key Study Objectives

### Primary:

- Characterize safety, tolerability, dose-limiting toxicities, and MTD or MAD (if no MTD is defined) for MGC018 administered as monotherapy or in combination with MGA012 in patients with relapsed/refractory, unresectable locally advanced or metastatic solid tumors

### Secondary:

- Characterize PK and immunogenicity of MGC018 monotherapy or in combination with MGA012
- Describe preliminary evidence of antitumor activity of MGC018 administered as monotherapy or in combination with MGA012 using both conventional Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and immune-related RECIST (irRECIST)

### Exploratory:

- Relationship between PK, pharmacodynamics, and anti-tumor activity; progression-free and overall survival; PD-L1 expression, immunological cell death, T-cell response, IFNγ gene expression signature in pre- and post-treatment biopsies; B7-H3 expression and response; modulation of immune cell subset phenotypes and serum cytokine levels; serum biomarkers; MGA012 receptor occupancy

## Entry Criteria

### Key Inclusion Criteria

- Tissue specimen available for retrospective analysis of B7-H3 and PD-L1 expression
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Life expectancy ≥12 weeks
- Measurable disease
- Dose Escalation Phase: Patients with histologically proven, relapsed or refractory, unresectable locally advanced or metastatic solid tumors of any histology for whom no approved therapy with demonstrated clinical benefit is available. For all tumor types, the requirement for previous systemic therapy may be waived if a patient was intolerant of or refused standard first-line therapy
- Cohort Expansion Phase: Patients with histologically proven, unresectable, locally advanced or metastatic solid tumors for whom no approved therapy with demonstrated clinical benefit is available. For all tumor types, the requirement for previous systemic therapy may be waived if a patient was intolerant of or refused standard therapy
- Acceptable laboratory parameters and adequate organ reserve

### Key Exclusion Criteria

- Patients with history of prior central nervous system (CNS) metastasis must have been treated, be asymptomatic, and not have concurrent treatment for CNS disease, progression of CNS metastases on MRI or CT for at least 21 days after last day of prior therapy for the CNS metastases, or concurrent leptomeningeal disease or cord compression at the time of enrollment
- History of autoimmune disease with certain exceptions
- Patients with a history of the following immune checkpoint inhibitor-related AEs are ineligible despite resolving to ≤ Grade 1 or baseline: ≥ Grade 3 ocular AE, neurologic toxicity, colitis, pneumonitis, renal toxicity; changes in liver function tests that met criteria for Hy's Law
- Prior treatment with orlotamab, enoblituzumab, or other B7-H3-targeted agents for cancer
- Treatment with systemic cancer therapy within 3 weeks, investigational therapy within 4 weeks; radiation within 2 weeks; corticosteroids/other immune suppressive drugs within 2 weeks of first study drug administration
- Clinically significant cardiovascular disease, pulmonary compromise or requirement for supplemental oxygen
- Active viral, bacterial, or systemic fungal infection requiring parenteral treatment within 7 days of first study drug administration; history of hepatitis B or C infection or positive test for hepatitis B surface antigen or core antigen, or hepatitis C polymerase chain reaction; known positive testing for HIV or history of AIDS
- History of allogeneic bone marrow, stem cell, or solid organ transplant

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