Preclinical Development of MGC026, a Glycan-linked, Exatecan-based Antibody-drug Conjugate (ADC) Targeting B7-H3 for Solid Cancer

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Abstract

Introduction: Antibody-drug conjugates (ADCs) have emerged as an important class of therapeutic agents for the treatment of cancer. A duocarmycin-based B7-H3-targeted DNA-alkylating ADC, vobramitamab duocarmazine (vobra duo), has shown encouraging clinical activity in the treatment of metastatic castration-resistant prostate cancer. Given the broad spectrum of tumor indications addressable by targeting B7-H3, we developed MGC026, an ADC incorporating a B7-H3-targeting antibody and a novel glycan-linked topoisomerase 1 inhibitor (TOP1i). With distinct mechanisms of action, vobra duo and MGC026 can address different cancers, tumor stages, or be used in combination with alternate agents to enhance their clinical utility.

Methods: MGC026 is comprised of the cleavable linker-payload, bicyclononyne carbamoyl sulfamide Val-Ala-PABC exatecan (SYNtecan E®) site-specifically conjugated at asparagine 297 of the heavy chain through enzymatic glycan remodeling and metal-free click chemistry, using Synaffix's GlycoConnect® technology. In vivo efficacy studies were conducted in immunodeficient mice with human tumor cell-line or patient-derived xenografts to identify the spectrum of MGC026-sensitive tumors and the relationship between exposure and antitumor activity. A toxicology study was conducted in cynomolgus monkeys in which MGC026 was administered by 15-minute IV infusion once every three weeks. Pharmacokinetic (PK) analysis and detailed toxicology evaluation was performed.

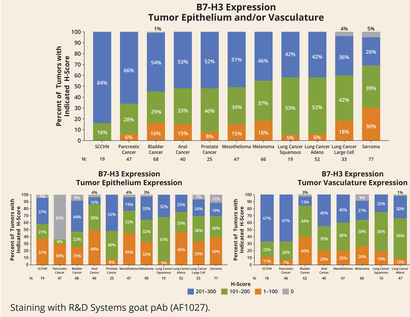
Results: MGC026 demonstrated specific, dose-dependent in vivo antitumor activity toward B7-H3-positive tumor xenografts representing lung, pancreatic, and prostate cancers, head and neck squamous cell carcinoma, and melanoma. Additionally, MGC026 demonstrated antitumor activity toward B7-H3-positive patient-derived xenograft models of lung and prostate cancer, with additional indications under investigation. MGC026, administered to cynomolgus monkeys at dose levels of 10, 30, and 50 mg/kg every 3 weeks for a total of 3 doses, exhibited approximate dose-proportional PK and high stability in circulation. MGC026 was well tolerated, with no lung toxicity observed, and the highest dose level tested (50 mg/kg) was declared as the highest non-severely toxic dose.

Conclusions: MGC026 exhibited a favorable preclinical profile, with potent in vivo activity toward B7-H3-expressing tumor xenografts representing a range of cancer indications. MGC026 was tolerated in cynomolgus monkeys, a relevant toxicology model, at exposure levels likely exceeding those required for antitumor activity. These data support clinical development of MGC026 for the treatment of B7-H3-expressing solid cancers.

B7-H3

- Member of the B7-family of immune regulators
- Overexpressed in multiple cancer types, and overexpression is correlated with disease severity and outcome
- Limited expression on normal tissue, with strong tumor-versus-normal tissue binding differential

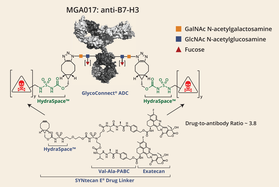
B7-H3 Expression Summary



Staining with R&D Systems goat pAb (AF1027).

MGC026

MGC026 ADC Structure

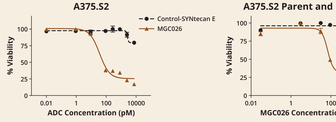


A Clinical-stage Anti-B7-H3 ADC Therapeutic Antibody

- Comprised of a humanized antibody targeting B7-H3 (MGA017)
  - Same antibody used for vobramitamab duocarmazine (MGC018)
- Site-specifically conjugated to exatecan, a topoisomerase type 1 inhibitor payload (SYNtecan E®), using Synaffix's GlycoConnect® technology
  - Cleavable linker with high stability and bystander activity
  - Retains potency in multi-drug resistant lines
  - Null for Fc-γ and mannose receptor binding
  - Phase 1 clinical study in advanced solid cancers in progress (NCT06242470)
- **With distinct payload-related mechanisms of action, MGC026 and vobramitamab duocarmazine can potentially address different cancers, tumor stages, or be used in combination and also with alternate agents to enhance their clinical utility**

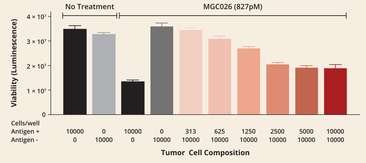
Results

MGC026 Mediates In Vitro Cytotoxicity and Bystander Killing Activity

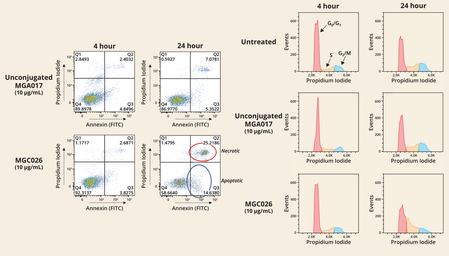


		IC_{50} (pM)	
Cell Line	B7-H3 Density (ABC)	MGC026	Control-SYNtecan E®
A375.S2	169,000	41.9	24,596.0

ABC = antibody binding capacity (determined by BANGS QFACS kit)

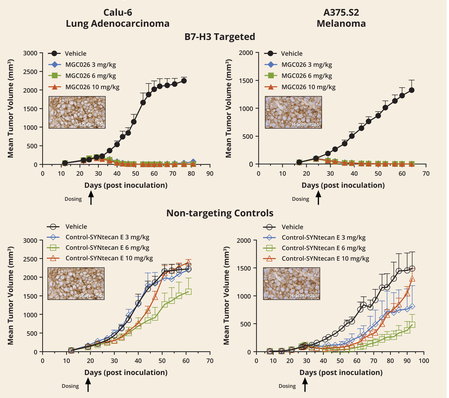


MGC026 Cytotoxicity is Associated with Apoptosis and Accumulation of Cells in S Phase

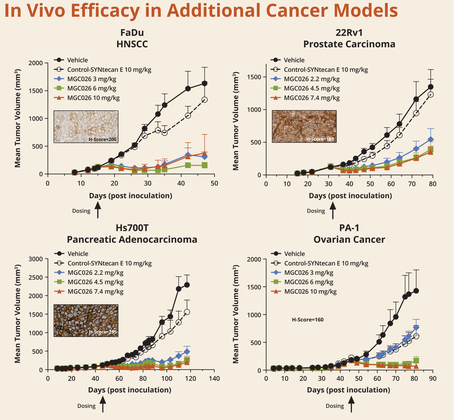


Results

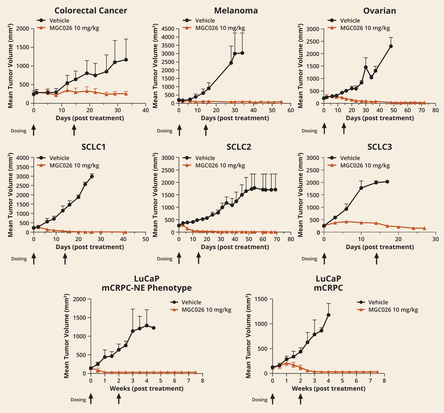
In Vivo Efficacy of MGC026



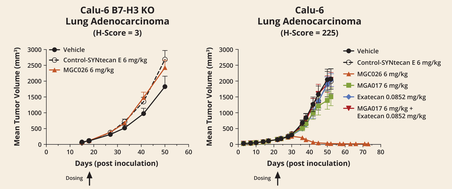
In Vivo Efficacy in Additional Cancer Models



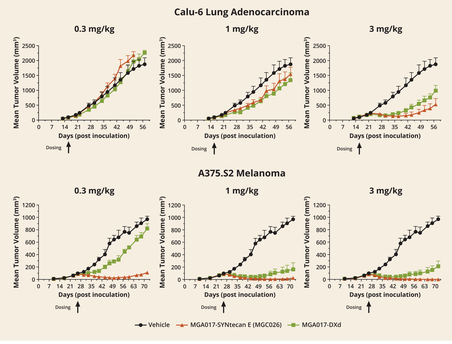
MGC026 Activity in PDX Cancer Models



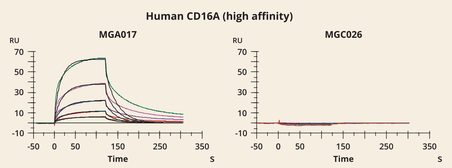
Target Expression and Delivery of Exatecan Is Required for Antitumor Activity



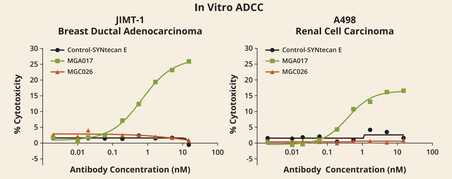
MGC026 Shows Improved Efficacy Profile Compared to Matched DXd ADC



MGC026 Does Not Bind Fc-γ Receptors Nor Does It Mediate ADCC



Binding of MGA017 and MGC026 (12.5–200 nM) to hCD16AHis captured anti-Penta His surface.



Antibody-dependent cell-mediated cytotoxicity of MGA017 and MGC026, measured as lactate dehydrogenase (LDH) release from target cells when exposed to fresh human peripheral blood mononuclear cells (PBMCs) from two independent donors. LDH release was measured using the CytoTox 96® assay. Control-SYNtecan E® was included as a non-targeting negative control.

- Interstitial lung disease (ILD) is an important adverse event associated with trastuzumab deruxtecan and other DXd-based ADCs
- In preclinical models, ILD is associated with non-targeted uptake in alveolar macrophages, potentially by Fc-γ receptors[1]
- GlycoConnect® conjugation abrogates binding to Fc-γ receptor, potentially reducing the risk to patients

MGC026: NHP GLP Toxicity Study

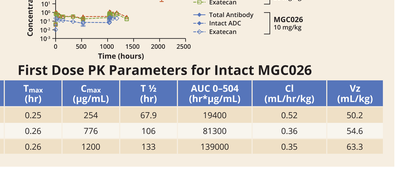
Group No.	Test Material	Dose Level (mg/kg/day)	Main Study		Recovery Study	
			Males	Females	Males	Females
1	Vehicle	0	2	2	–	–
2	MGC026	10	3	3	–	–
3	MGC026	30	3	3	2	2
4	MGC026	50	3	3	2	2

Animals dosed on Study Days 1, 22, 43.

MGC026 Tolerated at All Dose Levels Tested

- No MGC026-related clinical observations or changes in respiratory rate, blood pressure, ECG, ophthalmology, neurological assessment, coagulation or urinalysis parameters
- Minimal, reversible, MGC026-related body weight loss (<10%) noted at ≥10 mg/kg
- Reversible clinical pathology findings observed in one 50 mg/kg female that was most pronounced on Study Day 14
  - Moderately decreased red cell mass, with markedly increased mean corpuscular volume, RDW, reticulocyte and platelet counts
  - Mildly decreased total protein and albumin concentrations
- Non-adverse MGC026-related findings at the terminal necropsy were limited to the thymus
  - Decreased thymus size and weight in 3/6 animals (30 mg/kg) and 6/6 animals (50 mg/kg)
  - Correlated with mild to moderate decreased thymus cellularity
  - Not present at recovery necropsy
- **MGC026-related changes were non-adverse**
- **HNSTD – 50 mg/kg**

Dose-dependent TK Profile



First Dose PK Parameters for Intact MGC026

Dose (mg/kg)	T_{max} (hr)	C_{max} (μg/mL)	T ½ (hr)	AUC 0–504 (hr*μg/mL)	Cl (mL/hr/kg)	Vz (mL/kg)
10	0.25	254	67.9	19400	0.52	50.2
30	0.26	776	106	81300	0.36	54.6
50	0.26	1200	133	139000	0.35	63.3

Conclusions

- MGC026 is a B7-H3-targeting ADC site-specifically conjugated to exatecan, a topoisomerase type 1 inhibitor payload (SYNtecan E®), using Synaffix's GlycoConnect® technology
  - Greater potency than DXd[2,3] and SN-38[4]
  - Less susceptible to multi-drug resistance mechanisms than DXd[5] and SN-38[4]
  - Conjugation abolishes Fc-γ receptor binding—potentially reducing risk of lung toxicity associated with non-specific uptake by alveolar macrophages
- **With an alternate payload-related mechanism of action, MGC026 complements vobramitamab duocarmazine in the B7-H3 ADC tool arsenal to address different cancers and tumor stages, alone or in combination**

Reference

1. Kumagai, K. et al. *Cancer Sci.* 111; 2020. **2.** Ogitani et al. *Bioorg. Med. Chem. Lett.* 2016, 26(20), 5069–72. **3.** Ogitani et al. *Cancer Sci.* 2016, 107(7), 1039–46. **4.** Rowinsky, E.K. Humana Press. 2005, https://doi.org/10.1385/1-59259-866-8:317. **5.** Weng, W. et al. *Cancer Discov.* 2023, 13(4), 950-73.

Acknowledgements

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