Preclinical Development of MGC028, an ADAM9-targeted, Glycan-linked, Exatecan-based Antibody-drug Conjugate for the Treatment of Solid Cancers

Juniper A. Scribner, Jennifer G. Brown, Thomas Son, Linda Jin, Carroll McKenzie, Viktoriya Nam, Curtis Bush, Dienis Quinonez, Delta Ford, Verlene Gonzalez, James Tamura, Sergey Gorlatov, Monirath Hav, Hua Li, Shelley Butler, Ezio Bonvini, Deryk Loo

MacroGenics, Inc., San Mateo, CA and Rockville, MD

1897

Presenter Contact Information:
scribnerj@macrogenics.com

Abstract

Introduction: Antibody-drug conjugates (ADCs) seek to increase the therapeutic window of potent cytotoxic agents by linking them with monoclonal antibodies (mAbs) to selectively deliver cytotoxic payloads to tumor cells. The effectiveness and safety of ADCs rely on both the mAb specificity and the linker-payload employed. Several approved ADCs using microtubule inhibitor payloads are impacted by ocular adverse events that have been observed both preclinically and in patients. A class of linker-payloads incorporating topoisomerase 1 inhibitors (TOP1i) has emerged recently as an effective alternative to tubulin inhibitor-based ADCs. To date, TOP1i ADCs have not been associated with dose-limiting ocular toxicity seen with microtubule inhibitor payloads. Here we report the preclinical development of an ADAM9 (a disintegrin and metalloprotease domain 9)-targeted ADC that incorporates a novel glycan-linked TOP1i. ADAM9, a member of the ADAM family of multifunctional type 1 transmembrane proteins, plays a role in tumorigenesis and cancer progression and is overexpressed in multiple cancers, making it an attractive target for cancer treatment.

Methods: MGC028 incorporates 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 performed in immunodeficient mice with ADAM9-expressing human tumor cell-line (CDX) or patient-derived (PDX) xenografts. A non-human primate toxicology study was conducted in which MGC028 was administered by 15-minute IV infusion every two weeks at dose levels of 22.5 and 55 mg/kg for a total of two doses.

Results: MGC028 exhibited specific, dose-dependent in vivo antitumor activity toward ADAM9-positive CDX models representing gastric, lung, pancreatic and colorectal cancer, and head and neck squamous cell carcinoma. Furthermore, MGC028 demonstrated antitumor activity toward ADAM9-positive PDX models of lung and pancreatic cancer, and cholangiocarcinoma. MGC028 was well tolerated in a repeat-dose non-human primate toxicology study, up to 55 mg/kg, the highest dose level tested. Observations were limited to mild, reversible increases in liver enzymes, without microscopic correlates, and decreased lymphoid cellularity in the thymus. In particular, ocular toxicities were not observed.

Conclusions: MGC028 exhibited potent antitumor activity in in vivo models representing various solid cancer indications and was well tolerated in non-human primates at exposure levels exceeding those required for antitumor activity. Our findings support continued investigation of MGC028 as an ADC therapeutic for the treatment of ADAM9-expressing solid cancers.

Background

ADAM9: A Disintegrin And Metalloprotease 9

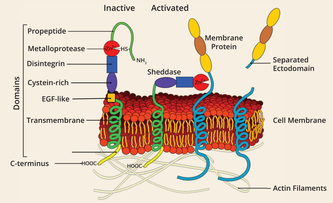
- Type I transmembrane protein
  - Involved in cell migration, inflammatory response, proliferation, cell-cell interactions (adhesion, migration, ectodomain shedding)
- Overexpressed in multiple cancer types
- Dysregulation of ADAM9 associated with tumor progression and metastasis
- Overexpression correlates with disease severity and poor prognosis in multiple cancers, including prostate, pancreatic, lung, gastric, renal, and breast cancer

MGC028: A Novel ADAM9-Targeted Topoisomerase 1 Inhibitor-Based ADC

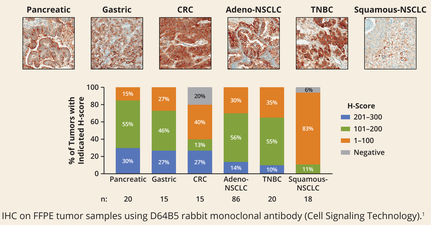
- Comprised of a humanized antibody targeting ADAM9
- Site-specifically conjugated to exatecan, a potent topoisomerase 1 inhibitor payload, using Synaffix's GlycoConnect® technology
- Cleavable SYNtecan E® linker-payload with improved stability; facilitates bystander activity
- Retains potency in multi-drug resistant lines
- Null for Fc-γR binding
- Active toward dividing and non-dividing tumor cells

ADAM9

ADAM9 Structure



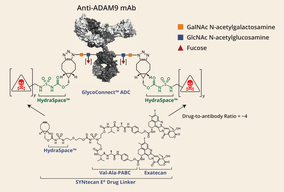
ADAM9 Is Highly Expressed on Solid Cancers



IHC on FFPE tumor samples using D64B5 rabbit monoclonal antibody (Cell Signaling Technology).[1]

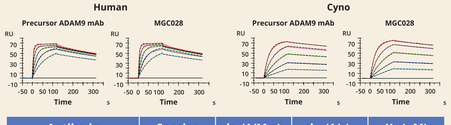
MGC028: ADAM9 Exatecan-Based ADC

SYNtecan E® Linker-Payload Structure



Binding Properties

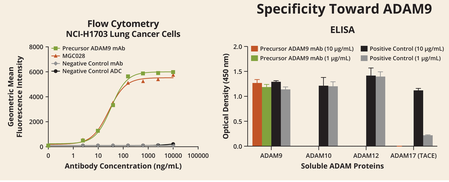
MGC028 Maintains Binding Affinity After Conjugation



Antibody	Species	k_a (1/M•s)	k_d (1/s)	K_D (nM)
Precursor ADAM9 mAb	Human	2.1×10^6	1.5×10^{-3}	0.7
Precursor ADAM9 mAb	Cyno	9.5×10^5	6.5×10^{-4}	0.7
MGC028	Human	2.2×10^6	1.5×10^{-3}	0.7
MGC028	Cyno	1.0×10^6	6.5×10^{-4}	0.7

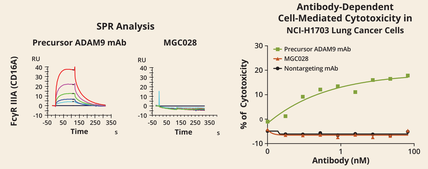
Variants captured on Fab2 GAH Fc surface (1:1 Binding fit).

Specificity Toward ADAM9



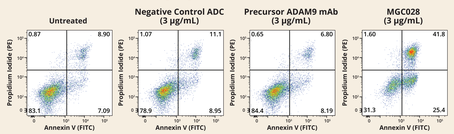
Results

MGC028 Does Not Bind Fc-γ Receptors or Mediate ADCC in ADAM9-Expressing Cells



- Conjugation of SYNtecan E® linker-payload to the native glycosylation site in the C_H2 domain eliminates Fc-γR binding
  - Abolishes ADCC
  - Potentially reduces the risk of interstitial lung disease observed with other TOP1 ADCs which is strongly associated with non-targeted uptake by alveolar macrophages likely by Fc-γR[2]

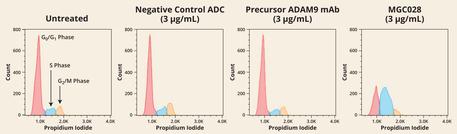
MGC028 Induces Apoptosis in Cancer Cells



Dead	Late Apoptotic
Viable	Early Apoptotic

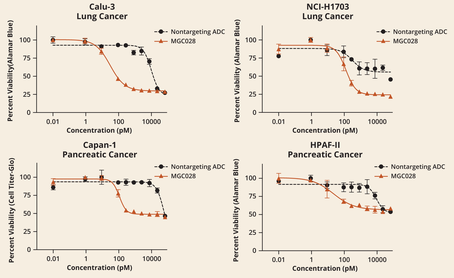
- NCI-H1703 lung cancer tumor cells exhibit markers of apoptosis (early and late) following treatment with MGC028 at 72 hours

MGC028 Exposure Leads to Cell Cycle Arrest



- NCI-H1703 lung cancer cells accumulated in the S phase 48 hours after treatment with MGC028, consistent with the mechanism of action of exatecan

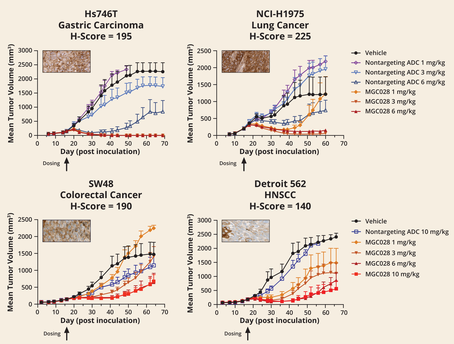
In Vitro Cytotoxicity



		IC_{50} (pM)	
Cell Line	Antibody Binding Capacity	MGC028	Nontargeting ADC
Calu-3	91,200	31	10030
NCI-H1703	90,500	127	313
Capan-1	19,000	110	60838
HPAF-II	12,000	22	9052

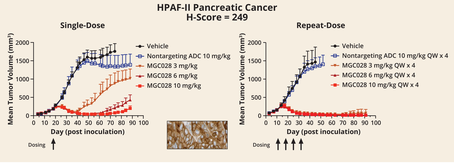
Antibody Binding Capacity determined by the Bangs QFAC Kit.

Dose-Dependent Antitumor Activity in CDX Tumor Models

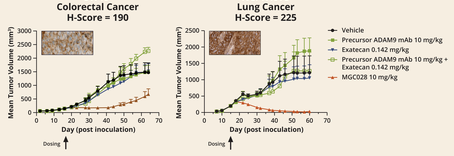


- MGC028 was well tolerated in all models, with no impact on body weight

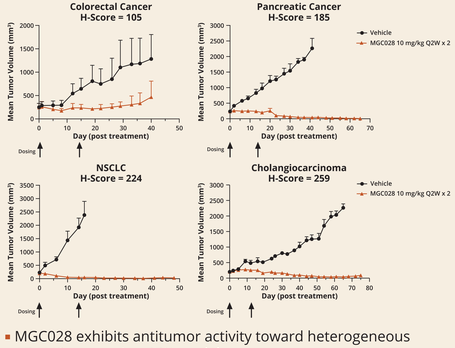
Repeat-Dose Administration Enhances Antitumor Activity in Pancreatic Cancer Xenografts



Antitumor Activity Requires Targeted Delivery of Exatecan



Antitumor Activity Toward PDX Models of Cancer



- MGC028 exhibits antitumor activity toward heterogeneous ADAM9 expressing PDX models

Favorable Safety Profile in Cynomolgus Monkeys

Study Design

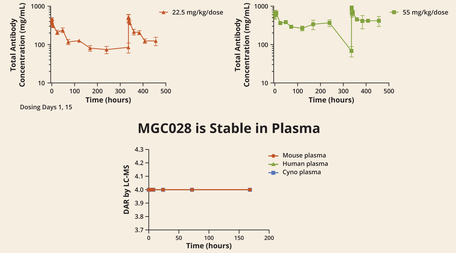
Dose (mg/kg)	Dose Days	Animals Dosed	
		Males	Females
22.5	1, 15	1	2
55	1, 15	1	2

10-minute IV infusion, necropsy Day 22.

Summary of Findings

- MGC028 was well tolerated in a preliminary toxicology study
  - Occasional diarrhea or reduced food consumption at the high dose levels, with no impact on animal body weight
  - Mild increase in ALT and AST, within historical normal ranges and without microscopic correlates
  - Day 22 necropsy
    - Decreased lymphocyte cellularity in the thymus at the high dose level
    - Normal bone marrow smears
  - **No ocular toxicity based on clinical observations and microscopic evaluation**
  - **MGC028 was tolerated at 55 mg/kg, the highest dose tested**
  - **GLP toxicology study in progress**

Dose Proportional PK Profile in Cynomolgus Monkeys



ADC stability in plasma presented as mean DAR calculated at each timepoint.

Conclusions

- ADAM9 is overexpressed on a wide range of cancers
- MGC028 is a novel ADAM9 ADC incorporating Synaffix's GlycoConnect® linker and SYNtecan E® TOP1 inhibitor
- MGC028 induces apoptosis with cell accumulation in the S phase
- MGC028 does not bind Fc-γ receptors
  - Reduced potential risk of interstitial lung disease via nonspecific uptake by alveolar macrophages
  - Lack of effector function
- MGC028 demonstrates dose-dependent antitumor activity in CDX and PDX in vivo models
  - Lung, pancreatic, gastric, colorectal cancer, HNSCC, and cholangiocarcinoma
- MGC028 was tolerated in non-human primates up to 55 mg/kg/dose Q2W x 2, the highest dose administered
- No ocular toxicity observed, a commonly reported adverse event associated with administration of tubulin inhibitor-based ADCs

MGC028 IND submission is targeted for 2024

References

1. Scribner, J.A. et al. *Mol. Cancer Ther.* 21(7); 2022. **2.** Kumagai, K. et al. *Cancer Sci.* 111; 2020.

Acknowledgements

SYNtecan E® linker-payload conjugated by Synaffix B.V. a Lonza company, Oss, the Netherlands.