Abstract 1841

IMGC936, an investigational ADAM9-targeting antibody drug conjugate, is active against patient-derived ADAM9-expressing xenograft models

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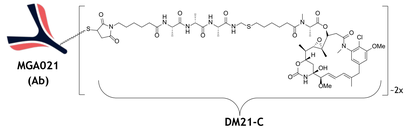
INTRODUCTION

ADAM9 is a cell surface protein that belongs to the ADAM (a disintegrin and metalloproteinase) family of proteases, which have been implicated in cytokine and growth factor shedding, and cell migration. Dysregulation of ADAM9 has been involved in tumor progression and metastasis, as well as pathological neovascularization. We have previously shown that ADAM9 is overexpressed in multiple solid tumor indications and that anti-ADAM9 antibodies are efficiently internalized and degraded by tumor cell lines making ADAM9 an attractive target for antibody-drug conjugate (ADC) development[1,2].

IMGC936 is an investigational ADAM9-targeting ADC, comprised of a high-affinity humanized monoclonal antibody site-specifically coupled to DM21 at a drug-antibody ratio (DAR) of 2. DM21 is a next-generation linker-payload that combines a maytansine-derived microtubule-disrupting payload with a stable tripeptide linker. IMGC936 is being investigated in a phase 1 dose escalation study evaluating safety and pharmacokinetics in patients with solid tumors (NCT04622774).

Here we explore ADAM9 expression and prevalence in solid tumors and evaluate the activity of IMGC936 in clinically relevant patient-derived xenograft (PDX) models with ADAM9 expression similar to that observed in human solid tumors.

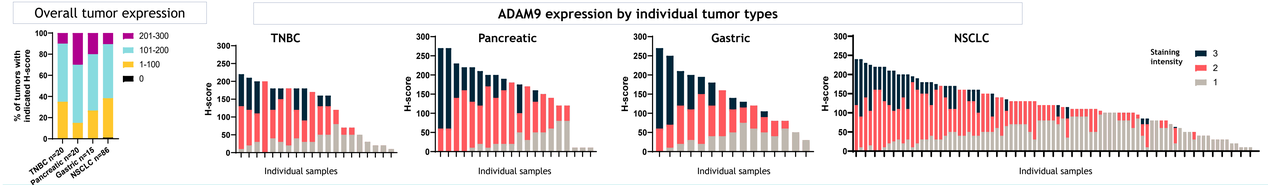
IMGC936: An Innovative ADC to a Novel Target



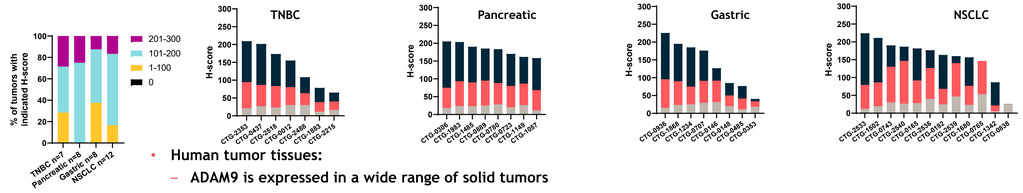
- **MGA021: Humanized anti-ADAM9 antibody**
  - Includes YTE mutation (M252Y/S254T/T256E) to increase *in vivo* half-life and exposure
- **DM21C: Next generation maytansine-derived linker/payload**
  - Greater stability and bystander activity than other DM compounds
- **DM21C linked to the antibody by site-specific conjugation to two engineered cysteines (DAR=2)**
  - Homogeneous drug product
  - DAR=2 chosen to facilitate tumor penetration with higher dosing

ADAM9 Expression by IHC

Human Solid Tumor Tissue



Patient Derived Xenograft (PDX) Models Used for the Efficacy Study



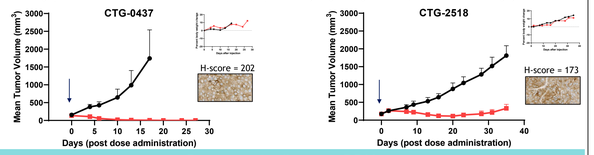
- Human tumor tissues:
  - ADAM9 is expressed in a wide range of solid tumors
  - ADAM9 expression is highly heterogenous both within and across indications
  - Infrequent incidence of ADAM9 negative tumors
- PDX models used for the efficacy study had ADAM9 expression similar to that of the majority of human tumors

- *ADAM9 expression was evaluated on human solid tumors and PDX FFPE samples with the anti-ADAM9 antibody D64B5 (Cell Signaling Technology).*
- *ADAM9 expression was quantitated by H-score (0 - 300) = 0 x (%cells with 0 intensity) + 1 x (%cells with 1+ intensity) + 2 x (%cells with 2+ intensity) + 3 x (%cells with 3+ intensity)*

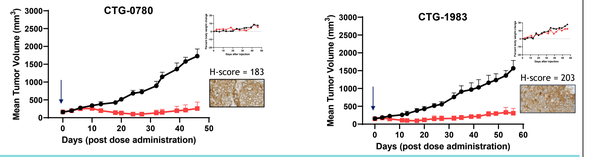
Efficacy in PDX Study

Triple Negative Breast Cancer (TNBC) PDX

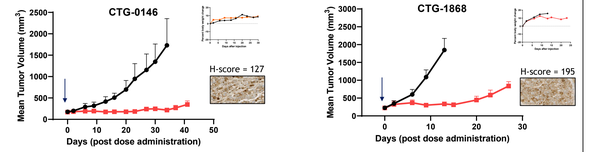
Main graph: tumor volume (mean) over time. Insert graphs: top - percent body weight change over time; bottom - ADAM9 staining by IHC



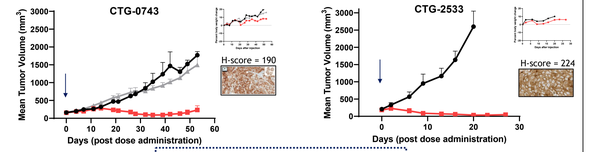
Pancreatic Cancer PDX



Gastric Cancer PDX



Non Small Cell Lung Carcinoma (NSCLC) PDX



- IMGC936 was active against tumors with clinically relevant ADAM9 expression
- IMGC936 was well tolerated across all models tested

PDX Efficacy Study, Summary

Tumor type	Model	Treatment	Stage	H-Score	Outcome	Response Rate
TNBC	* CTG-0437	Not available	III	202	Highly active	6/7 (86%)
	CTG-2488	Pretreated	Not available	108	Highly active	
	CTG-1883	Naïve	IV	78	Highly active	
	CTG-2353	Naïve	II	209	Active	
	* CTG-2518	Pretreated	Not available	173	Active	
	CTG-2215	Pretreated	Not available	65	Active	
	CTG-0012	Pretreated	IV	155	Inactive	
Pancreatic Cancer	* CTG-1983	Naïve	Not available	203	Active	6/8 (75%)
	CTG-1485	Pretreated	IV	190	Active	
	CTG-0889	Naïve	IV	185	Active	
	* CTG-0780	Pretreated	IV	183	Active	
	CTG-0723	Pretreated	IV	170	Active	
	CTG-1149	Pretreated	IV	162	Active	
	CTG-0306	Pretreated	IV	205	Inactive	
	CTG-1057	Pretreated	IV	158	Inactive	
Gastric Cancer	* CTG-1868	Pretreated	Not available	195	Active	4/8 (50%)
	CTG-1234	Pretreated	IV	185	Active	
	CTG-0707	Not available	III	176	Active	
	* CTG-0146	Naïve	I	127	Active	
	CTG-0936	Pretreated	IV	226	Inactive	
	CTG-0148	Naïve	III	85	Inactive	
	CTG-0485	Not available	III	77	Inactive	
	CTG-0353	Not available	Not available	41	Inactive	
NSCLC	* CTG-2533	Pretreated	IV	224	Highly active	8/12 (67%)
	* CTG-0743	Naïve	IV	190	Highly active	
	CTG-0165	Pretreated	IV	182	Highly active	
	CTG-2539	Pretreated	IV	160	Highly active	
	CTG-0765	Naïve	III	147	Highly active	
	CTG-0192	Pretreated	IV	163	Active	
	CTG-1680	Pretreated	IV	157	Active	
	CTG-1342	Pretreated	IV	87	Active	
	CTG-1502	Pretreated	III	211	Inactive	
	CTG2540	Pretreated	III	187	Inactive	
	CTG-2536	Pretreated	IV	177	Inactive	
	CTG-0838	Pretreated	IV	27	Inactive	
TOTAL						24/35 (69%)

* Models shown, panel to the left

- *The efficacy study was performed at Champions Oncology, Rockville, MD*
- *Mice bearing PDX tumors were dosed once at 100 µg DM21/kg or 8.6 mg Ab/kg*
- *Anti-tumor activity was defined by National Cancer Institute standards: mean percent Tumor/Control (%T/C) value > 42% (inactive), ≤ 42% (active), and <10% (highly active)*

CONCLUSIONS

- ADAM9 is expressed in multiple tumor types, including TNBC, pancreatic, gastric, and NSCLC
  - The expression is highly heterogeneous, both within and across tumor types; very few tumors are ADAM9-negative
- IMGC936 showed compelling anti-tumor activity against PDX models with clinically relevant levels and heterogeneity of ADAM9 expression
  - IMGC936 was active to highly active (using the NCI standard evaluation criteria) against 69% of PDX models after a single dose of 8.6 mg/kg (100 µg/kg of DM21 payload); the dose was well tolerated

These data support the current clinical evaluation of IMGC936 (NCT04622774)

2021 AACR Annual Meeting.

References: [1]AACR 2017, abstract 38, [2]AACR 2019, abstract 1538