Abstract 1533

IMGC936, a first in-class ADAM9-targeting antibody-drug conjugate, demonstrates promising anti-tumor activity

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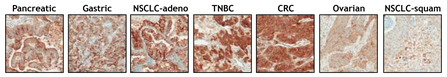
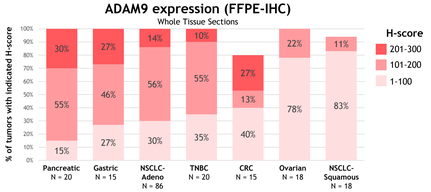
INTRODUCTION

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 implicated 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] Here, we describe the preclinical evaluation of IMGC936, a novel ADAM9-targeting ADC. IMGC936 is comprised of a high-affinity humanized antibody site-specifically conjugated to DM21, a next-generation linker-payload that combines a maytansinoid microtubule-disrupting payload with a stable peptide linker.[3-4] To maximize the potential for IMGC936 activity, the M252Y/S254T/T256E (YTE) mutation was introduced into the CH2 domain of the antibody to increase *in vivo* plasma half-life and exposure.

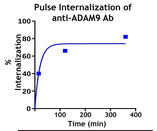
ADAM9: An attractive ADC target

- **ADAM9 is overexpressed in multiple indications of high unmet need**

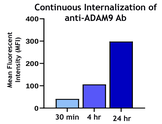




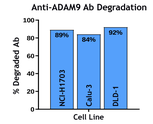
- **ADAM9 is well suited to deliver cytotoxic payload**
  - Anti-ADAM9 antibodies (Abs) are rapidly internalized and degraded



FACS: Pulse Chase (NCI-H1703)			
	% Internalized		
15 min	2 hr	6 hr	
40	66	82	

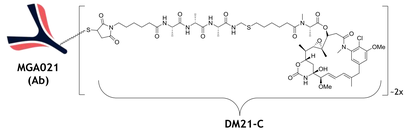


FACS: Continuous Exposure (NCI-H1703)			
MFI	30 min	4 hr	24 hr
Internal	41	106	298
Surface	38	32	35
Total	79	138	333



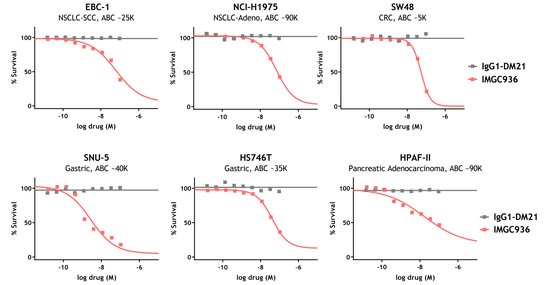
^{125}I-anti-ADAM9 Ab: Pulse Chase	
Cell Line	% Degraded @ 24hr
NCI-H1703 (NSCLC)	89%
Calu-3 (NSCLC)	84%
DLD-1 (CRC)	92%

IMGC936: Innovative ADC to a novel target

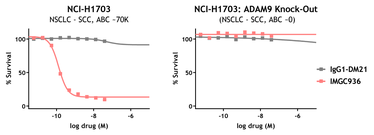


- **MGA021: Humanized anti-ADAM9 antibody (cynomolgus cross-reactive)**
  - Includes YTE mutation to improve pharmacokinetics
- **DM21C: New more potent maytansine-derived linker/payload**
  - Greater stability and bystander activity than other DM platforms
- **Payload linked via site-specific CYSMAB technology (DAR=2)**
  - Homogeneous drug product
  - Low DAR increases potential for tumor penetration and drug delivery

IMGC936 exhibits potent *in vitro* activity

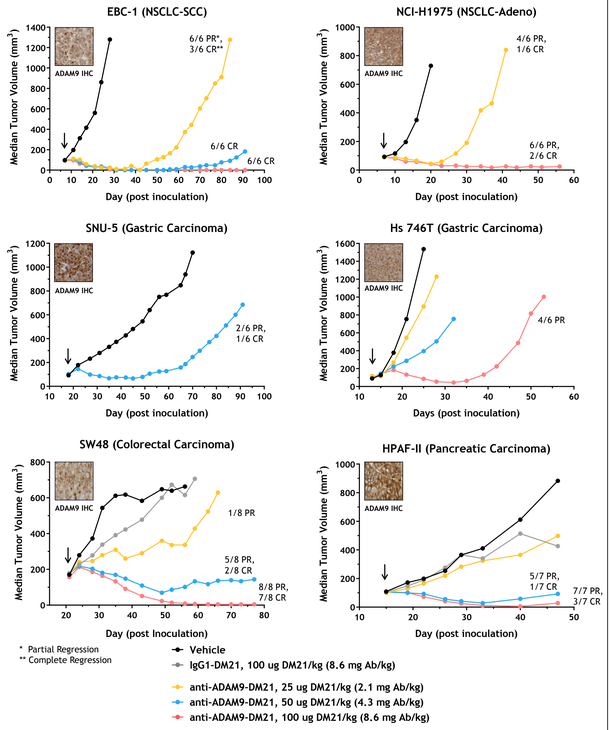


- **IMGC936 is active against a broad panel of ADAM9-positive tumor cell lines**
  - >100-fold more active than a non-targeting conjugate (IgG1-DM21)
  - Cytotoxicity observed in tumor cell lines with as low as 5000 cell surface receptors per cell



- **The activity of IMGC936 requires ADAM9 expression**
  - IMGC936 was inactive in isogenic ADAM9 knock-out cells

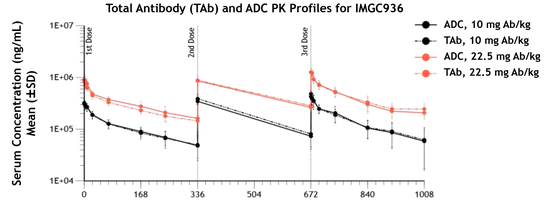
IMGC936 is active in multiple *in vivo* tumor models



- **Anti-ADAM9-DM21 (DAR 2) demonstrates dose dependent anti-tumor activity in ADAM9-positive xenografts that represent patients with medium to high expression of ADAM9**
  - Tumor partial regressions (PR) and/or complete regressions (CR) were observed after a single intravenous administration (↓) of anti-ADAM9-DM21 at doses that were well tolerated
  - The non-targeting IgG1-DM21 is inactive, demonstrating that the activity of anti-ADAM9-DM21 is dependent on ADAM9 expression

IMGC936 is well-tolerated in cynomolgus monkeys

- **The toxicity and toxicokinetic profile of IMGC936 was evaluated in cynomolgus monkeys after repeated exposure on a Q2Wx3 schedule**
  - No ADAM9-targeted toxicities observed
  - The macroscopic and microscopic toxicities were consistent with a DM platform and were reversible or showed signs of recovery by study end
  - No effects on cardiovascular, CNS, or respiratory endpoints



PK Parameters	Dose Group (mg/kg)	Cmax (µg/mL)	AUC-(hr*µg/mL)	$T_{1/2}$ (hr)	Cl (mL/hr/kg)	Vss (mL/kg)
ADC	10	312 ± 41.2	48200 ± 11900	166 ± 54.2	0.223 ± 0.0745	48.1 ± 9.52
	22.5	985 ± 196	154000 ± 59300	192 ± 70.2	0.162 ± 0.0491	40.7 ± 6.29
TAb	10	325 ± 53.5	48200 ± 13800	166 ± 59.1	0.223 ± 0.0625	49.9 ± 12.2
	22.5	912 ± 217	133000 ± 33200	190 ± 68.0	0.179 ± 0.0459	46.8 ± 8.02

Table shows mean ± SD PK parameter values following first dose, N = 8 animals

- **IMGC936 was stable in plasma following IV administration**
  - Biphasic PK profiles with detectable concentrations of both intact ADC and total mAb through the two week dosing intervals
  - There was a linear PK trend between 10 and 22.5 mg/kg doses

CONCLUSIONS

- ADAM9 is a cell surface antigen that is overexpressed on multiple solid tumor indications and has been shown to correlate with poor prognosis in several cancers
- Anti-ADAM9 antibodies are efficiently internalized and degraded by ADAM9-expressing tumor cells making ADAM9 an attractive ADC target
- IMGC936 is an ADAM9-targeting ADC that has been engineered to include multiple technological innovations to maximize the potential clinical benefit
- IMGC936 exhibits cytotoxic activity against a broad panel of ADAM9-positive tumor cell lines
- Consistent with the *in vitro* activity, IMGC936 shows compelling efficacy in ADAM9-positive xenograft models
- Importantly, IMGC936 showed favorable safety and toxicokinetic profiles in a repeat-dose toxicology study in cynomolgus monkeys

IMGC936 represents a promising therapeutic candidate to target a wide range of ADAM9-expressing tumors

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References: [1]AACR 2017 Abstract #37, [2]AACR 2017 Abstract #38, [3]AACR 2017 Abstract #2186 and [4]AACR 2019 Abstract #3546