Novel Antibody-Drug Conjugates Targeting ADAM9-expressing Solid Tumors Demonstrate Potent Preclinical Activity

Abstract #37

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ImmunoGen

Introduction

ADAM9, also known as MDC9 or meltrin-γ, is a member of 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. ADAM9 overexpression has been shown to correlate with poor prognosis in prostate, renal, and pancreatic cancers. Using an immunization approach in which antibodies were raised to fetal progenitor and stem-like cancer cell lines followed by screening on tumor and normal tissues, we identified ADAM9 as a promising cell surface tumor target (AACR 2017 Abstract #38). Here, we describe the preclinical evaluation of two antibody-drug conjugates (ADC) targeting ADAM9-expressing tumors.
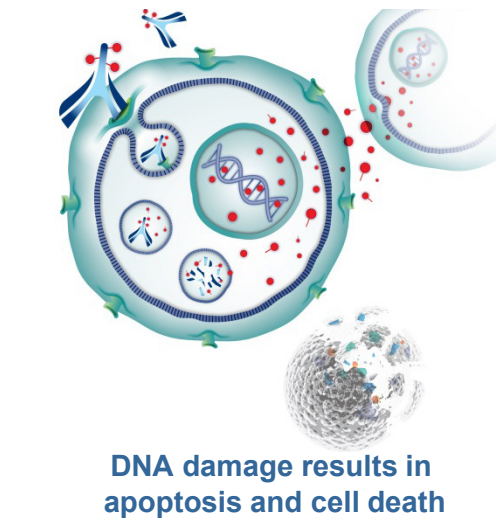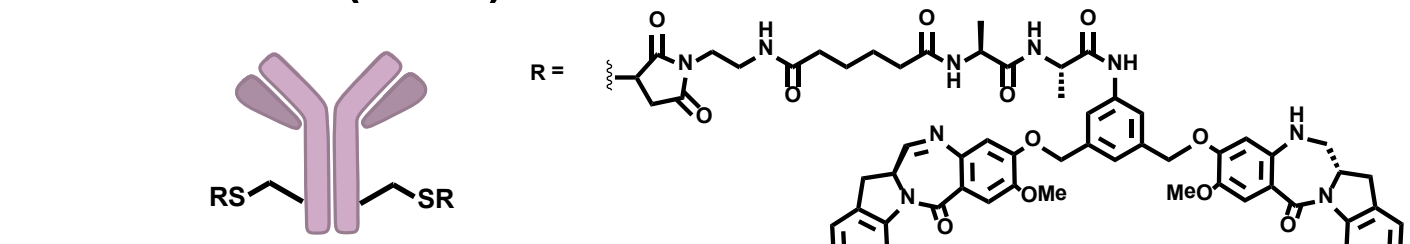
Anti-ADAM9 Antibody-Drug Conjugates

▶ ADCs were generated based on a high affinity humanized anti-ADAM9 antibody using two different linker/payloads

Anti-ADAM9-sulfoSPDB-DM4
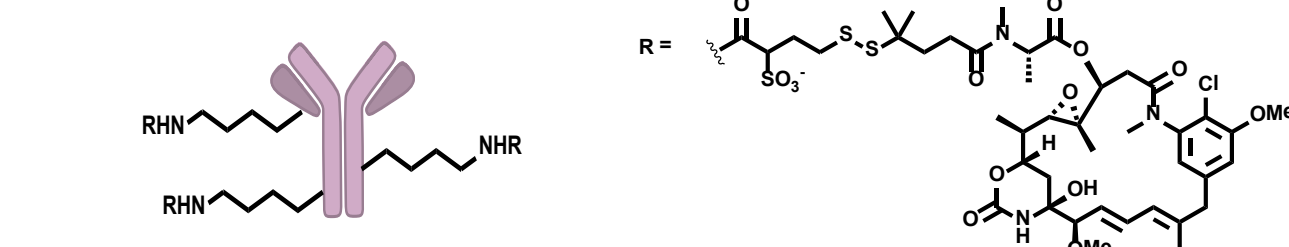
- Humanized anti-ADAM9 antibody: AEX6003
- Maytansine-derived microtubule disruptor (drug-to-antibody ratio of ~3.5)
- Lysine-linked via cleavable sulfo-SPDB linker

Microtubule disruption leads to apoptosis and cell death

Anti-ADAM9(C442)-DGN549

- Humanized anti-ADAM9 antibody: AEX6003(S442C)
- Indolinobenzodiazepine DNA-alkylating monoimine (drug-to-antibody ratio of 2)
- Conjugated to engineered cysteine residues via a cleavable peptide linker

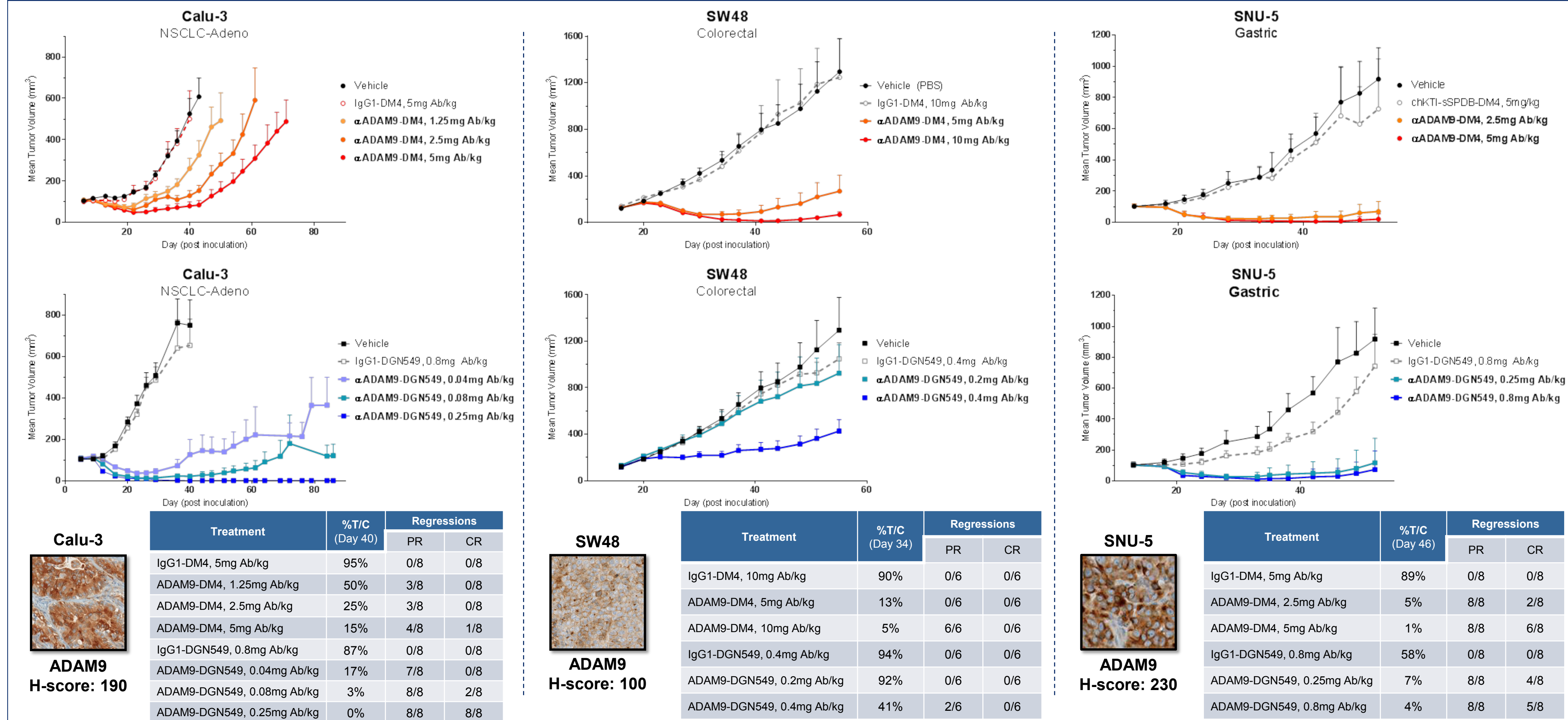DNA damage results in apoptosis and cell death

Methods

▶ An FFPE-IHC assay was developed using a rabbit monoclonal anti-ADAM9 antibody to evaluate the prevalence of ADAM9 expression in a variety of patient tumors, normal and xenograft tissues.

▶ The in vitro cytotoxicity of anti-ADAM9 ADCs was evaluated in a panel of tumor cell lines after continuous exposure for 5 days using WST-8.

▶ The anti-tumor in vivo activity of anti-ADAM9 ADCs was assessed in multiple subcutaneous in vivo models following single IV injections of either vehicle, non-targeted control IgG1 ADCs or anti-ADAM9 ADCs as indicated.

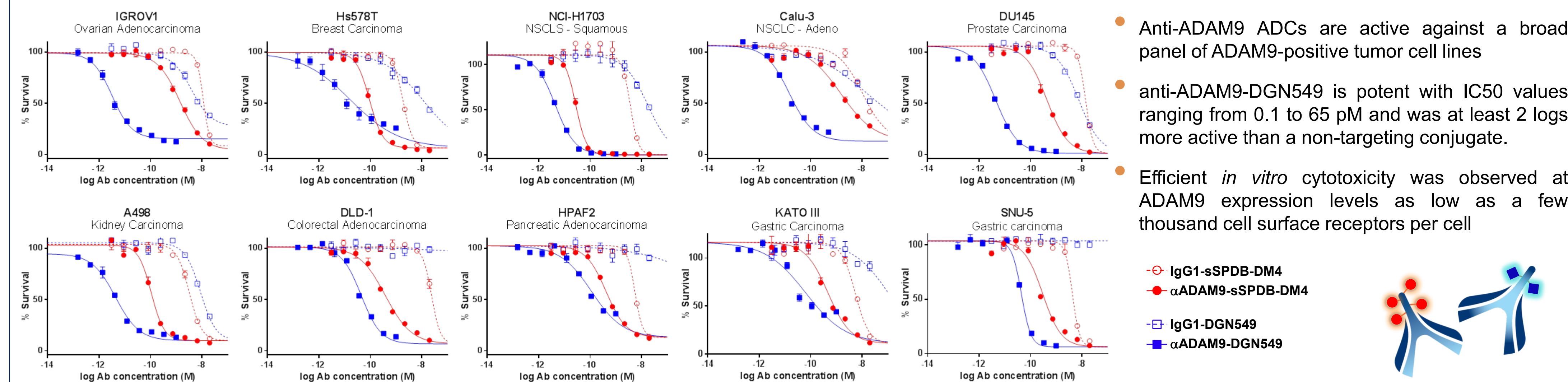## ADAM9 is overexpressed in multiple solid tumor indications

ADAM9 Expression in Tumors
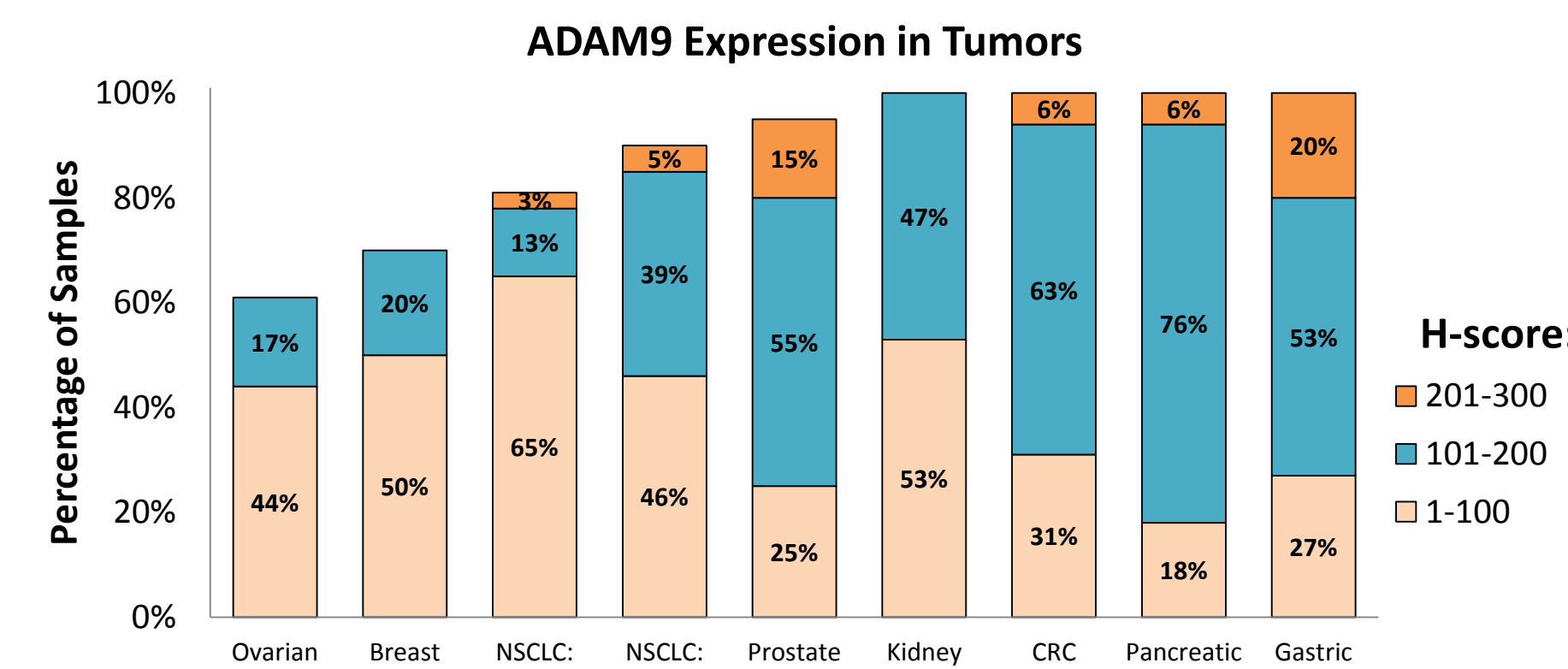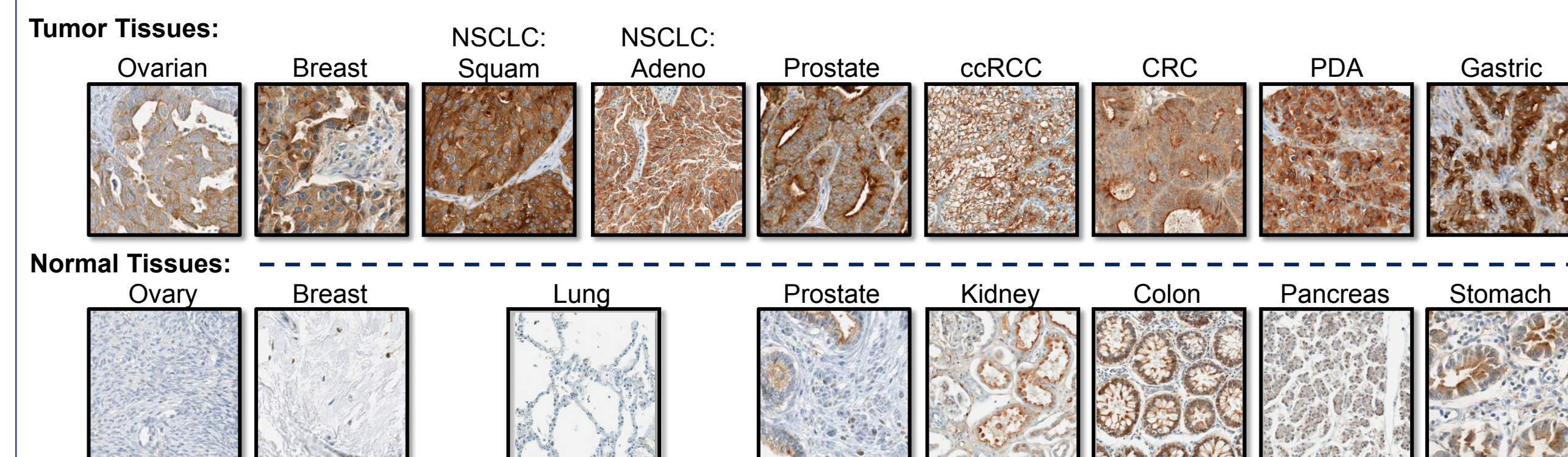
▶ ADAM9 expression was analyzed by FFPE-IHC in 20 different tumor types
  • A number of tumor types demonstrated a high percentage of ADAM9 expression

Anti-ADAM9 ADCs show potent in vitro cytotoxicity

- Anti-ADAM9 ADCs are active against a broad panel of ADAM9-positive tumor cell lines
- anti-ADAM9-DGN549 is potent with IC50 values ranging from 0.1 to 65 pM and was at least 2 logs more active than a non-targeting conjugate.
- Efficient in vitro cytotoxicity was observed at ADAM9 expression levels as low as a few thousand cell surface receptors per cell

Legend:
- IgG1-sSPDB-DM4
- αADAM9-sSPDB-DM4
- IgG1-DGN549
- αADAM9-DGN549

Anti-ADAM9 ADCs are highly active in ADAM9-expressing in vivo models

Calu-3 — ADAM9 H-score: 190

Treatment	%T/C (Day 40)	Regressions PR	Regressions CR
IgG1-DM4, 5mg Ab/kg	95%	0/8	0/8
ADAM9-DM4, 1.25mg Ab/kg	50%	3/8	0/8
ADAM9-DM4, 2.5mg Ab/kg	25%	3/8	0/8
ADAM9-DM4, 5mg Ab/kg	15%	4/8	1/8
IgG1-DGN549, 0.8mg Ab/kg	87%	0/8	0/8
ADAM9-DGN549, 0.04mg Ab/kg	17%	7/8	0/8
ADAM9-DGN549, 0.08mg Ab/kg	3%	8/8	2/8
ADAM9-DGN549, 0.25mg Ab/kg	0%	8/8	8/8

SW48 — ADAM9 H-score: 100

Treatment	%T/C (Day 34)	Regressions PR	Regressions CR
IgG1-DM4, 10mg Ab/kg	90%	0/6	0/6
ADAM9-DM4, 5mg Ab/kg	13%	0/6	0/6
ADAM9-DM4, 10mg Ab/kg	5%	6/6	0/6
IgG1-DGN549, 0.4mg Ab/kg	94%	0/6	0/6
ADAM9-DGN549, 0.2mg Ab/kg	92%	0/6	0/6
ADAM9-DGN549, 0.4mg Ab/kg	41%	2/6	0/6

SNU-5 — ADAM9 H-score: 230

Treatment	%T/C (Day 46)	Regressions PR	Regressions CR
IgG1-DM4, 5mg Ab/kg	89%	0/8	0/8
ADAM9-DM4, 2.5mg Ab/kg	5%	8/8	2/8
ADAM9-DM4, 5mg Ab/kg	1%	8/8	6/8
IgG1-DGN549, 0.8mg Ab/kg	58%	0/8	0/8
ADAM9-DGN549, 0.25mg Ab/kg	7%	8/8	4/8
ADAM9-DGN549, 0.8mg Ab/kg	4%	8/8	5/8

Conclusions

▶ ADAM9 is over-expressed in a number of tumor indications with high unmet need.

▶ Anti-ADAM9 ADCs utilizing the microtubule disruptor, DM4, and the DNA alkylating agent, DGN549, were successfully generated

▶ Both anti-ADAM9 ADCs exhibit in vitro anti-tumor activity against a broad panel of ADAM9-positive cell lines

▶ Consistent with their in vitro activity, both anti-ADAM9 ADCs displayed compelling anti-tumor activity in xenograft models.

Anti-ADAM9 ADCs represent a promising therapeutic strategy to target a wide range of ADAM9-expressing tumors.