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

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Abstract #37

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 cytoskeleton 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 total progenitor and stem-like cancer cell lines followed by screening on tumor and normal tissues, we identified ADAM9 as a promising cell surface 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
- Anti-ADAM9(C442)-DGN549

ADAM9 is overexpressed in multiple solid tumor indications

- A number of tumor types demonstrated a high percentage of ADAM9 expression

ADAM9 expression was analyzed by FFPE-IHC in 20 different tumor types

- Percentage of Samples
  - 20%
  - 40%
  - 60%
  - 0%
  - 44%
  - 50%
  - 17%
  - 3%
  - 3%
  - 6%
  - 6%
  - 6%
  - 6%
  - 25%
  - 63%
  - 46%
  - 39%
  - 47%
  - 31%
  - 6%
  - 6%

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

- Anti-ADAM9 ADCs are active against a broad panel of ADAM9-positive tumor cell lines

- Treatment %T/C (Day 46)
  - IgG1-DGN549, 10mg Ab/kg 90% 0/6 0/6
  - ADAM9-DGN549, 0.2mg Ab/kg 92% 0/6 0/6
  - ADAM9-DGN549, 0.25mg Ab/kg 7% 8/8 4/8
  - ADAM9-DGN549, 0.04mg Ab/kg 17% 7/8 0/8
  - ADAM9-DM4, 2.5mg Ab/kg 25% 3/8 0/8
  - ADAM9-DM4, 1.25mg Ab/kg 50% 3/8 0/8
  - IgG1-DM4, 10mg Ab/kg 90% 0/6 0/6
  - ADAM9-DGN549, 0.08mg Ab/kg 3% 8/8 2/8
  - IgG1-sSPDB-DM4
  - ADAM9-DGN549, 0.04mg Ab/kg 17% 7/8 0/8

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.