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 (Disintegrin and metalloproteinase) family of proteins, which are 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 ADC targeting ADAM9. IMGC936 is comprised of a high-affinity humanized antibody dermically-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 M2551/S2542/T2562 (YTE) mutation was introduced into the C2 domain of the antibody to enable internalization in vivo and plasma half-life and exposure.

IMGC936: Innovative ADC to a novel target

IMGC936 is active in multiple vivo tumor models

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 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 vivo activity, IMGC936 shows compelling efficacy in ADAM9-expressing xenograft models. Importantly, IMGC936 showed favorable safety and toxicokinetic profiles in a repeat-dose toxicology study in non-human primates. IMGC936 represents a promising therapeutic candidate to target a wide range of ADAM9-expressing tumors.

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IMGC936 is well-tolerated in cynomolgus monkeys

The toxicity and toxicokinetic profile of IMGC936 was evaluated in cynomolgus monkeys after repeated exposure on a C72M73 schedule.

• No adverse events observed.
• The macroscopic and microscopic toxicities were consistent with a DM platform and were reversible or showed signs of recovery.
• No effects on cardiovascular, renal, or respiratory endpoints.

Total Antibody (FAB) and ADC PK Profiles for IMGC936

PK Parameters

IMGC936 was stable in plasma following IV administration. Both PK profiles with detectable concentrations of both intact ADC and total mAbs through the two week dosing interval. There was a linear PK trend between 10 and 22.5 mg/kg doses.

Table shows mean ± SEM (n=6).

4. 2017 AACR Annual Meeting. April 1-4, 2017