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 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.1-3 Here, we describe the preclinical evaluation of IMGC936, a novel ADC targeting ADAM9. 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 IMGC936 was inactive in isogenic ADAM9 knock-out cells and did not cross-react with ADAM family members.

### PK/Pharmacodynamic Analysis

**Biphasic PK profiles with detectable concentrations of both intact ADC and total mAb through Day 28.** The macroscopic and microscopic toxicities were consistent with a DM platform and were reversible or self-limited.

**Tumor partial regressions (PR) and/or complete regressions (CR) were observed after a single dose toxicology study in cynomolgus monkeys.**

**IHC: ADAM9 protein expression is detected in wide range of ADAM9-expressing tumors.**

**IMGC936 exhibits potent in vitro activity.** The activity of IMGC936 requires ADAM9 expression.

**IMGC936 is active in multiple in vivo tumor models.**

**IMGC936 is well-tolerated in cynomolgus monkeys.**

### 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, demonstrating ADAM9 as an attractive ADC target. IMGC936 is an ADAM9-targeting ADC that has been engineered to include multiple technological advancements to maximize the potential clinical benefit. IMGC936 exhibits cytostatic activity against a broad panel of ADAM9-positive tumor cell lines.

Consistent with the in vitro activity, IMGC936 shows compelling efficacy in ADAM-positive xenograft models in vivo. Importantly, IMGC936 showed favorable safety and toxicokinetic profiles in a repeat-dose pharmacology study in cynomolgus monkeys. IMGC936 represents a promising therapeutic candidate to target a wide range of ADAM9-expressing tumors.

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**References:** AACR 2017 Abstract #37, AACR 2017 Abstract #38, AACR 2017 Abstract #2186 and AACR 2019 Abstract #1546