ADG138, A Novel HER2xCD3 POWERbody™ Integrating Bispecific TCE with Precision Masking to Control Cytokine Release Syndrome and On-Target Off-Tumor Toxicity for Single Agent and Combination Therapies in HER2-Expressing Solid Tumors

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INTRODUCTION

Bispecific T-cell engagers (TCEs) are clinically validated in treating hematologic cancers. However, their utility in treating solid tumors remains to be demonstrated due to much more serious systemic cytokine release syndrome (CRS) and on-target off-tumor toxicity.

To explore the full potential of TCEs as a powerful modality of immunotherapy for solid tumors, we developed ADG138, a novel HER2×CD3 POWERbody™ TCE by applying our SAFEbody® precision masking technology to mask both arms of ADG138 using covalently linked designer peptides (Fig 1). The double masked ADG138 prodrug enables concomitant in situ binding to the targeted cancer cells by the HER2 arm and to T cells by the CD3 arm through activation of ADG138 bispecific TCE for selective T cell mediated tumor killing in the tumor microenvironment (TME).

Our data show that the double masked ADG138 POWERbody has achieved the goal in designing novel bispecific TCE for treating solid tumors: 1) potent induction of T cell mediated cytotoxicity for tumor regression of high, low and resistant/refractory HER2-expressing tumor models in mice; 2) strong synergistic antitumor activities in combination with an anti-CD137 or anti-PD-1 antibody in HER2 positive solid tumor models; 3) an excellent safety profiles with >300-fold higher tolerated dose over its non-masked parental TCE in cynomolgus monkeys, with favorable PK profiles; 4) high expression cell line with robust CMC profile is in progress for IND-enabling studies.

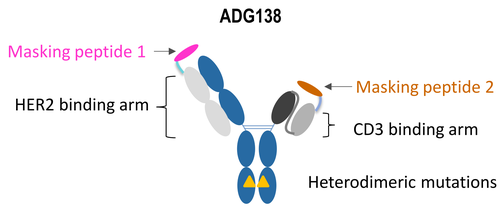

Fig 1. ADG138 is a HER2×CD3 bispecific TCE engineered with SAFEbody technology. Both HER2 and CD3 binding sites are masked by specific covalently linked masking peptides. In un-activated state, HER2 and CD3 binding sites remain masked to minimally bind to HER2 expressing cancer cells and T cells. However, in the activated state, ADG138 is activated to bind to both HER2 and CD3 in tumor microenvironment, engaging T cells to kill HER2-expressing cancer cells. The ADG138 Parental is not masked.

RESULTS

The high masking efficiency of ADG138

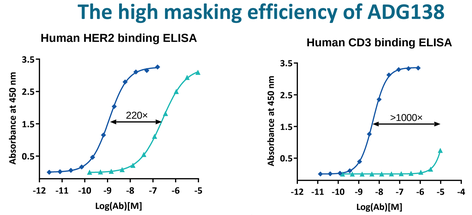

Fig 2. Compared to the parental, masked ADG138 POWERbody exhibited ~220-fold and >1000-fold masking efficiencies for binding to HER2 and CD3, respectively, as determined by in vitro binding to recombinant target proteins.

RESULTS

High masking efficiency of ADG138 POWERbody in stimulating CD3 T cell signaling *in vitro*

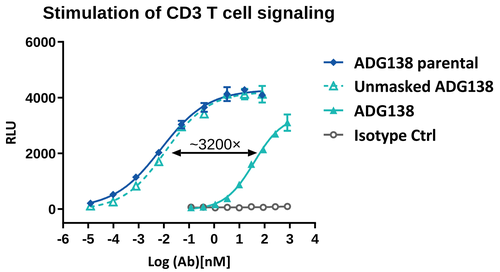

Fig 3. Stimulation of CD3 T cells signaling by ADG138. Jurkat/NFAT-Luc reporter cells were co-cultured with HER2 positive SK-OV3 cells in the presence of HER2xCD3 bispecific TCEs. Masked ADG138 POWERbody exhibited ~3200-fold masking efficiency compared to the parental or unmasked ADG138.

High masking efficiency of ADG138 in T cell mediated target cell killing and T cell activation *in vitro*

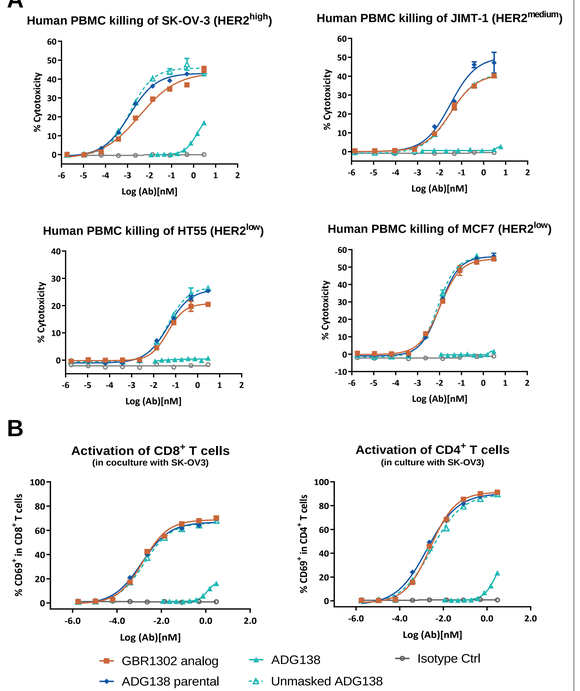

Fig 4. Comparison of masked and unmasked ADG138, its parental TCE, and a clinical reference HER2×CD3 TCE (GBR1302) in mediating human T cell killing of cancer cells with different levels of HER2 expression (A), as well as activation of CD4+ and CD8+ T cells (B). Masked ADG138 POWERbody exhibited >1000-fold masking efficiency in all assays.

Potent *in vivo* anti-tumor activity by ADG138 POWERbody in HER2-high, -low, and resistant/refractory tumor models

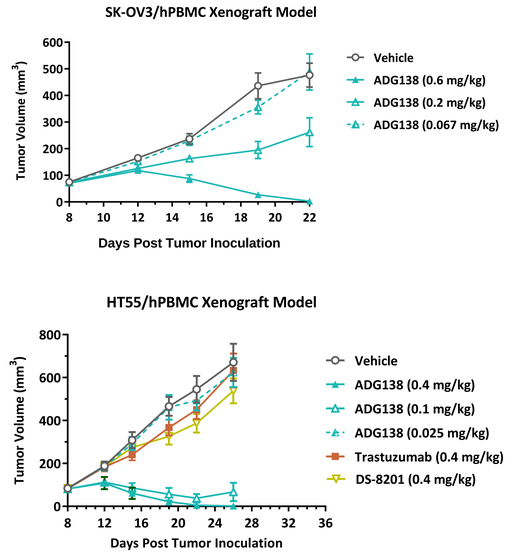

Fig 5. ADG138 exhibited potent antitumor activity in HER2^{high} (SK-OV3) and HER2^{low} (HT55) xenograft tumor models in human PBMC engrafted NSG mice. ADG138, reference anti-HER2 antibody trastuzumab or HER2-ADC (DS-8201), was administered twice a week by *i.p.* injection.

Combinations of ADG138 with I-O agents exhibited synergistic anti-tumor activities in mouse tumor models

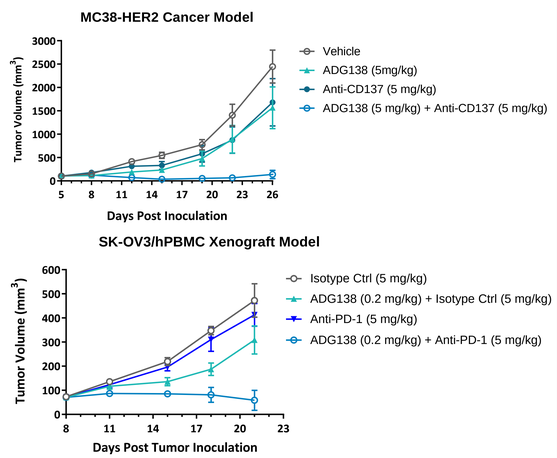

Fig 6. Combination of ADG138 with the anti-CD137 antibody (ADG106 with mouse IgG1 Fc) mediated synergistic antitumor effect in MC38-HER2 syngeneic tumor model in hCD3e knock-in mice (upper); ADG138 also synergized with an anti-PD-1 mAb to enhance antitumor activity in the SK-OV3/hPBMC xenograft model (lower).

ADG138 caused ~100-fold reduced cytokine release compared with parental TCE in cynomolgus monkeys

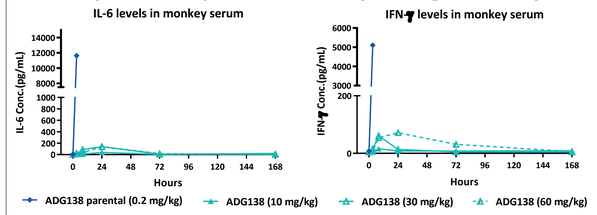

Fig 7. In exploratory toxicology studies in cynomolgus monkeys, ADG138 showed remarkably reduced cytokine release compared with the parental antibody. There was ~100-fold lower IL-6 peak levels in ADG138 administered animals at doses up to 60 mg/kg than parental antibody at 0.2 mg/kg. Other cytokines, including IL-2 and TNF-α, also demonstrated much reduced levels. A single dose at 0.2 mg/kg of ADG138 parental TCE was lethal to monkey, whereas monkeys tolerated well to the masked ADG138 up to 60 mg/kg in this study.

Favorable PK properties in cynomolgus monkeys

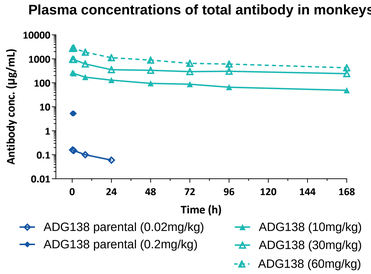

Fig 8. Pharmacokinetic (PK) studies demonstrated ~2-fold longer apparent half-lives or >3-fold higher dose-normalized systemic exposure (Area Under the Curve, AUC) for ADG138 over the non-masked parental TCE.

SUMMARY

- As a novel HER2×CD3 TCE, ADG138 POWERbody was developed using the precision masking technology for conditional activation in tumor microenvironment.
- When activated, ADG138 was highly potent in inducing T cell mediated cytotoxicity of both high and low HER2-expressing tumor cells and T cell activation *in vitro*, whereas in its double masked prodrug form ADG138 exhibited high masking efficiency with greatly reduced HER2 binding, T cell activation, and T cell mediated cytotoxicity.
- ADG138 induced robust tumor regression of both high and low HER2-expressing tumor models in mice, including tumor model resistant/refractory to DS-8201 (HER2-ADC).
- Combination of ADG138 with an anti-CD137 agonist antibody, or an anti-PD-1 antibody, exhibited strong synergistic antitumor activities in HER2 positive solid tumor models.
- ADG138 exhibited an excellent safety profiles in cynomolgus monkeys, with remarkably reduced CRS and achieving over a 300-fold higher tolerated dose in striking contrast to its non-masked parental TCE, and with favorable PK properties.
- The preclinical safety and efficacy profiles support advancing ADG138 into clinical development.

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