ADG152, a Novel CD20xCD3 T Cell Engager Prodrug with Enhanced Therapeutic Index, Demonstrates Strong Anti-Tumor Activity with Improved Safety

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2021 ASH Annual Conference, Abstract Number #1204

INTRODUCTION

Recent clinical data illustrate the effectiveness of CD20xCD3 T cell engagers (TCEs) that redirect the patient's endogenous T cells to eliminate CD20-positive tumor cells. While several of these products have demonstrated promising clinical activities in B-cell malignancies, their potential therapeutic utility is limited by cytokine release syndrome (CRS), even after strategies such as step-up dosing are implemented.

ADG152 is a novel CD20xCD3 POWERbody™ integrating Adagene's proprietary bispecific TCE platform with SAFEbody® masking technology to minimize CRS and other on-target/off-tumor toxicities. The anti-CD20 arm of ADG152 has been engineered for enhanced binding to CD20 compared to other clinical stage or approved antibodies, while its anti-CD3 arm has been engineered with tailor-made affinity and precision masking technology. Both arms are integrated into our proprietary bispecific antibody platform with robust CMC properties (Fig 1). In normal tissues, the masking moiety on the anti-CD3 arm can function to block the binding of ADG152 to T cells; however, in an activable condition, ADG152 bispecific TCE can be activated to simultaneously engage T cells and neighboring CD20-expressing tumor cells for tumor cell killing.

ADG152: CD20xCD3 POWERbody integrating Adagene's bispecific TCE with SAFEbody Technology

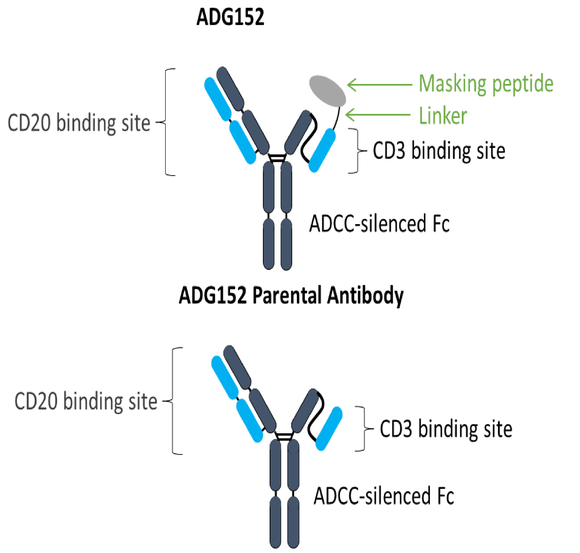

Fig 1. ADG152 is a CD20xCD3 bispecific TCE engineered with SAFEbody technology. The CD3 binding site of ADG152 is masked by a covalently linked masking peptide. In un-activated state, the CD3 binding site of ADG152 remains masked to minimally bind to T cells. However, in activated state, ADG152 bispecific TCE is activated to bind to both CD20 and CD3 on T cells around tumor cells, enabling depletion of CD20$^+$ tumor cells by CD3$^+$ T cells. The ADG152 Parental is an unmasked antibody.

RESULTS

ADG152 binds strongly to human B cells and CD20-positive tumor cells *in vitro*

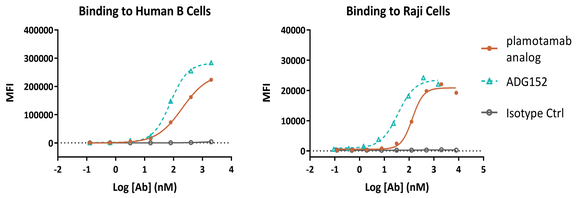

Fig 2. ADG152 shows stronger binding than the plamotamab analog on CD20-positive human B cells and Raji lymphoma cells *in vitro,* because the CD20 binding site of ADG152 is engineered to have higher binding affinity

ADG152 has high masking efficiency for binding to CD3 δ/ε dimer and human T cells *in vitro*

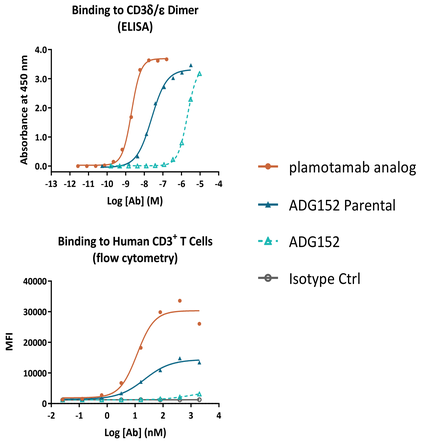

Fig 3. Since the CD3 binding site of ADG152 is masked, its binding to CD3δ/ε dimeric protein and CD3+ T cells is greatly reduced, showing strong masking efficiency *in vitro*. The ADG152 Parental antibody is tailor-made to have weaker CD3 binding than the plamotamab analog in the assays.

Activated ADG152 is stronger than the plamotamab analog in T cell-mediated killing of CD20-positive tumor cells *in vitro*

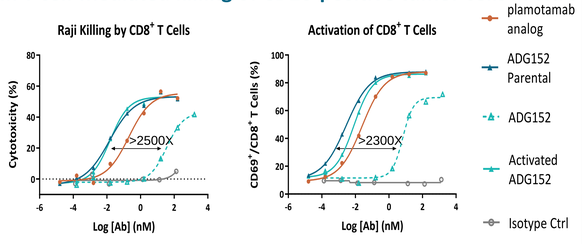

Fig 4. Parental and activated ADG152 induce CD8$^+$ T-cell mediated Raji cell killing activity that is stronger than that of the plamotamab analog. Parental and activated ADG152 also strongly activate human CD8$^+$ T cells in the *in vitro* bioassay, while ADG152 shows significantly weaker (>2300-fold) activity.

ADG152 inhibits tumor growth in huPBMC engrafted mouse xenograft model

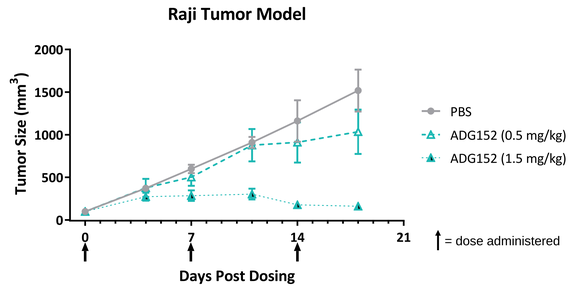

Fig 5. ADG152 demonstrates strong dose-dependent anti-tumor activity in the huPBMC engrafted mouse xenograft tumor model.

ADG152 causes significantly less cytokine release in monkeys than benchmark molecule

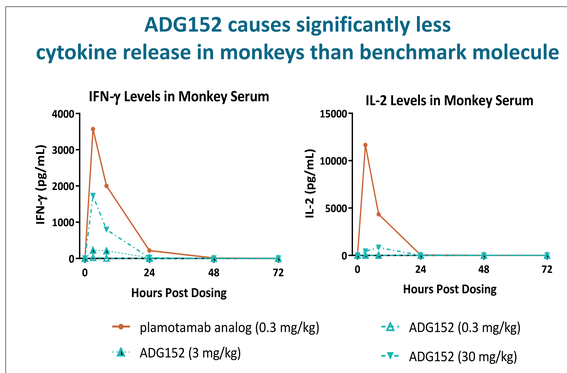

Fig 6. ADG152 induces significantly less cytokine release than the plamotamab analog in cynomolgus monkeys after a single intravenous injection. Serum IFN-γ and IL-2 levels induced by ADG152 at 30 mg/kg are less than those induced by the plamotamab analog at 0.3 mg/kg, suggesting >100-fold safety margin for cytokine induction.

ADG152 induces strong and sustained B cell depletion in monkeys

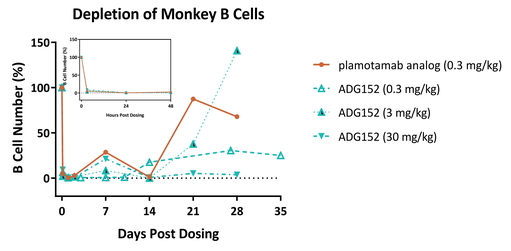

Fig 7. Depletion of circulating B cells is observed in cynomolgus monkeys as early as 3 hours (inset) after a single intravenous injection of ADG152 or the plamotamab analog at 0.3 mg/kg. Depletion of circulating B cells by ADG152 at 30 mg/kg was sustained for more than 28 days.

ADG152 shows improved pharmacokinetics in monkeys

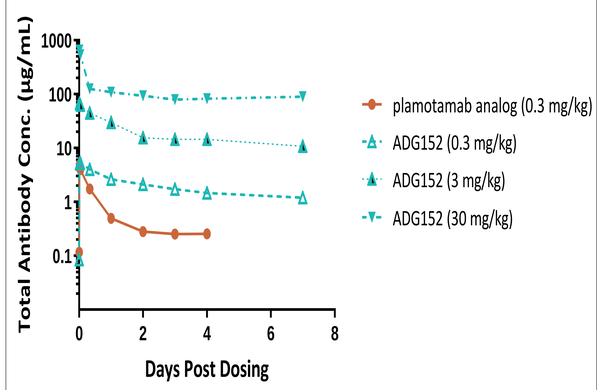

Fig 8. ADG152 shows improved pharmacokinetics [~2X longer half-life (e.g., 7-13 days at 0.3-30 mg/kg) and ~8X higher AUC] compared with the plamotamab analog in cynomolgus monkeys after a single intravenous injection.

SUMMARY

- ADG152 is a tailor-made bispecific CD20xCD3 POWERbody TCE, a conditionally activated prodrug with balanced safety and efficacy.
- ADG152, upon activation *in vitro*, induces potent T cell-mediated killing of CD20-positive lymphoma tumor cells, stronger than the plamotamab analog.
- ADG152 exhibits potent antitumor activity in the huPBMC engrafted mouse xenograft tumor model.
- ADG152 induces significantly less cytokine release than the plamotamab analog in cynomolgus monkeys, demonstrating ~100-fold safety margin for cytokine induction.
- ADG152 shows improved pharmacokinetics in cynomolgus monkeys than the plamotamab analog.
- ADG152 is projected to have at least 10-fold higher therapeutic index than the plamotamab analog.
- Preclinical data supports the advancement of ADG152 to clinical development either as a single agent or in combination with other therapies for the treatment of CD20-expressing B cell malignancies.

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