ADG153, a novel masked anti-CD47 IgG1 SAFEbody, demonstrates strong *in vivo* anti-tumor activities in preclinical solid tumor models and preferential CD47 target engagement in the tumor microenvironment

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2023 AACR Annual Conference, Abstract Number #2930

BACKGROUND AND SIGNIFICANCE

- Anti-CD47 therapies have demonstrated promising clinical activity; however, expression of CD47 on many normal human cells, especially RBCs, serves as an antigen sink. Consequently, many current anti-CD47 therapies have limited single agent activity and cause significant anemia.
- ADG153 is a highly differentiated masked anti-CD47 IgG1 SAFEbody® with strong ADCC and ADCP functions.
- In normal tissues and circulation, the SAFEbody masking moiety is expected to shield ADG153 from binding to CD47; however, in the protease-rich tumor microenvironment (TME), the masked antibody can be cleaved, enabling efficient binding to CD47, blocking CD47/SIRPα signaling, and triggering strong anti-tumor activities.
- Here, we demonstrate that ADG153 as a single agent has strong anti-tumor activities in solid tumor xenograft models and demonstrates preferential target engagement in TME.
- We anticipate ADG153, with its strong Fc-dependent anti-tumor activities and significantly reduced safety and PK liabilities, to show superior clinical benefit in both hematological and solid tumor indications.

- IgG1 subclass, chosen for strong Fc-mediated effector functions (ADCC and ADCP)
- Adagene's SAFEbody technology is used for precision masking of the CD47 binding sites on ADG153
- Using Adagene's NEObody™ technology, ADG153 is designed to target a novel epitope on CD47

Fig. 1. Schematic diagram of ADG153 (anti-CD47) SAFEbody. An Adagene SAFEbody, masked by covalently linked peptides, can be conditionally activated to bind its target in tumor, thereby decoupling the efficacy from the safety and PK liabilities.

RESULTS

ADG153 demonstrates stronger anti-tumor activity than magrolimab analog in the MDA-MB-231 triple negative breast cancer (TNBC) xenograft model

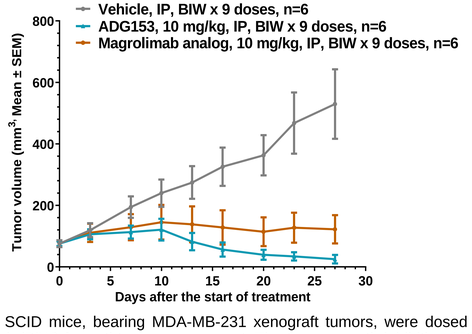
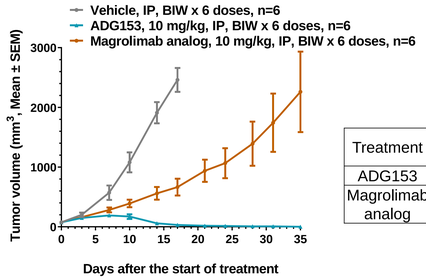


Fig. 2. SCID mice, bearing MDA-MB-231 xenograft tumors, were dosed twice per week (BIW) for anti-tumor assessment. The tumor growth inhibition (TGI) for ADG153 and magrolimab analog on Day 27 was 95.3% and 76.9%, respectively.

RESULTS

ADG153 demonstrates stronger anti-tumor activity than magrolimab analog in the SHP-77 small cell lung cancer (SCLC) xenograft model



Treatment	CR at Day 17	CR at Day 35
ADG153	3/6	6/6
Magrolimab analog	0/6	0/6

Fig. 3. SCID mice, bearing SHP-77 xenograft tumors, were dosed twice per week (BIW) for anti-tumor assessment. TGI for ADG153 and magrolimab analog on Day 17 was 98.7% and 73%, respectively. ADG153 treatment resulted in complete regression (CR) of tumors in all animals at the end of the study.

ADG153 stays predominantly as masked form in mouse circulation and shows increased exposure in tumor TME for cleaved form

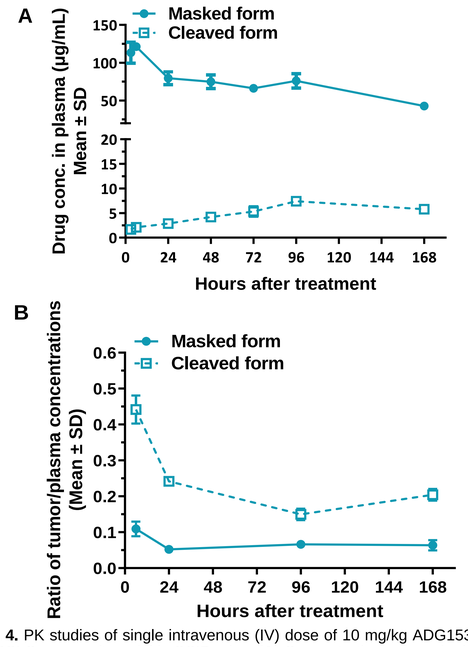


Fig. 4. PK studies of single intravenous (IV) dose of 10 mg/kg ADG153 in SHP-77 SCLC xenograft model in SCID mice. **(A)** Concentrations of masked form and cleaved form of ADG153 in plasma were measured with ELISA based methods. ADG153 stays predominantly as masked form in plasma. **(B)** The ratio of tumor/plasma concentrations was calculated as concentration of masked or cleaved form in tumor divided by that of same form in plasma. The tumor/plasma ratio of cleaved form was ~2-5 folds higher than that of masked form, indicating increases in relative exposure in tumor TME for the cleaved form.

ADG153 demonstrates reduced CD47 RO in normal tissues and significantly increased CD47 RO in tumors compared with magrolimab analog

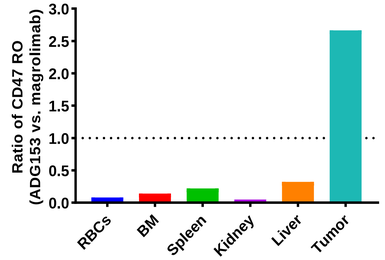


Fig. 5. Human CD47/SIRPα KI mice bearing MDA-MB-231 TNBC xenograft tumors were intraperitoneally dosed with 10 mg/kg ADG153 or magrolimab analog on Days 0, 3, and 7. RBCs, normal tissues, and tumors were harvested at 24h post last dose for a flow cytometry-based CD47 RO assay using dissociated cells (n=3 per group). The ratio of CD47 RO was calculated as RO achieved by ADG153 in each tissue type divided by RO achieved by magrolimab analog in the same tissue type.

ADG153 demonstrates significantly reduced blood cell depletion and RO on RBCs compared with magrolimab analog in human CD47/SIRPα knock-in (KI) mice

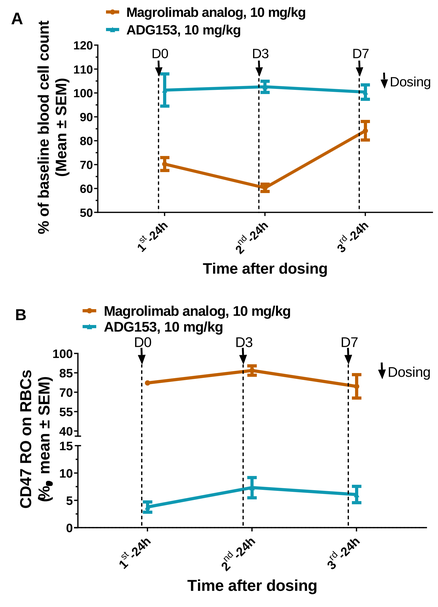


Fig. 6. Human CD47/SIRPα KI mice were dosed intraperitoneally with magrolimab analog or ADG153 at 10 mg/kg. **(A)** Magrolimab analog caused significant blood cell depletion while ADG153 caused little changes in blood cell count. **(B)** CD47 receptor occupancy (RO) on RBCs was determined with a flow cytometry-based method. Magrolimab analog resulted in high CD47 RO on RBCs while ADG153 resulted in much lower CD47 RO, which was maintained at low level throughout the dosing cycles.

ADG153 demonstrates favorable PK properties with significantly less sink effect during the 1st Cycle and at steady state (e.g., the 3rd Cycle) in cynomolgus monkeys

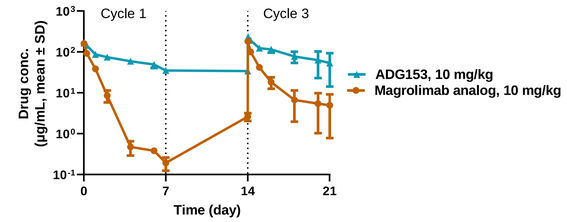


Fig. 7. Cynomolgus monkeys were dosed with 10 mg/kg magrolimab analog or ADG153 intravenously once per week. PK studies of ADG153 demonstrated significantly less sink effect throughout the dosing cycles compared with magrolimab analog.

ADG153 causes minimal RBC reduction in cynomolgus monkeys compared with magrolimab analog

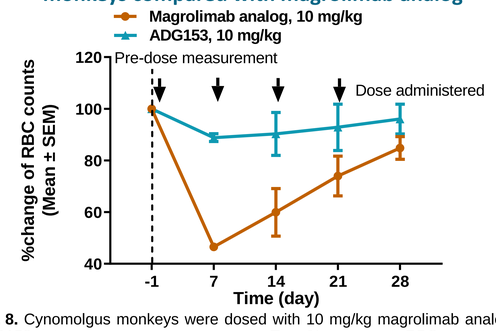


Fig. 8. Cynomolgus monkeys were dosed with 10 mg/kg magrolimab analog or ADG153 intravenously once per week. The %change of RBC counts was calculated as RBC counts at each measurement relative to the pre-dose measurement of the same animal. In contrast to magrolimab analog, ADG153 caused only minimal RBC reduction.

SUMMARY

- ADG153 demonstrates stronger anti-tumor activities in solid tumor xenograft models than magrolimab analog, supporting the importance of IgG1 in introducing ADCC- and ADCP-mediated solid tumor killing effects.
- ADG153 stays predominantly as masked form in circulation and shows increased exposure in tumor TME for cleaved form.
- In contrast to magrolimab analog, ADG153 demonstrates preferential target engagement in TME.
- ADG153 shows significantly reduced RBC binding and depletion and favorable PK properties than magrolimab analog.
- The preclinical profiles for the anti-CD47 ADG153 IgG1 SAFEbody suggest it has the potential to overcome the challenges of developing anti-CD47 antibodies and provide a strong rationale for its advancement into clinical development.

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