OPTIMAL DOSE SELECTION OF ADG126 (A MASKED ANTI-CTLA-4 SAFEbody®) WITH SIGNIFICANTLY WIDENED THERAPEUTIC INDEX COMPARED TO IPILIMUMAB IN COMBINATION WITH ANTI-PD-1 ANTIBODIES INFORMED BY QSP MODELING

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Background

For the past 20 years, dose-dependent efficacy and toxicity of anti-CTLA-4 therapies have severely limited dosing and therapeutic index (TI). Ipilimumab, the first FDA approved anti-CTLA-4 therapy for both monotherapy and combination therapy with anti-PD-1, is limited to 3 and 10 mg/kg every 3 weeks for 4 cycles (Q3W*4) for monotherapy, while its combination with nivolumab is approved at Q3W*4 in 2 out of combination therapies and the rest for 1 mg/kg at Q6/3W. The second FDA approved anti-CTLA-4 antibody, in combination with anti-PD-L1 for 1L HCC is dosed at 300 mg*1, and for 1L NSCLC at 75 mg Q3W*4, and a fifth dose at 75 mg at week 16 (BW ≥30 kg), reinforcing the fundamental challenge to select optimal dosing for anti-CTLA-4 therapies. A quantitative approach is introduced to calculate and compare TI of anti-CTLA-4 modalities through seamless integration of preclinical and clinical data with a species cross-reactive antibody ADG116 targeting a unique and highly conserved epitope of CTLA-4. ADG116 has enhanced TI over ipilimumab. ADG126, a prodrug of ADG116, is designed to further widen its TI by being preferentially enriched and activated through CTLA-4-mediated depletion of T regulatory cells within tumor.

Methods

A quantitative systems pharmacology (QSP) model was developed by incorporating drug-specific dosage across melanoma trials into a published model evaluating ipilimumab and pembrolizumab. Data from ipilimumab and nivolumab were further used. Characteristics of ADG116 and ADG126 were integrated by PBPK modeling. Furthermore, a novel safety model was developed incorporating data for ipilimumab, tremelimumab, pembrolizumab and nivolumab.

Results

The novel QSP model described clinical efficacy and safety well. In a hot tumor, 10 mg/kg Q3W ADG126 is predicted to result in comparable tumor objective response rate as ipilimumab 3 mg/kg Q3W*4 with anti-PD-1. In a colder and greater tumor burden scenario, 10 mg/kg or higher Q3W dosing of ADG126 led to better predicted efficacy than ipilimumab 3 mg/kg Q3W*4. The safety model further predicted >2-fold reduction in ≥G3 combination TRAEs by 10 mg/kg Q3W ADG126 vs. ipilimumab 3 mg/kg Q3W*4, confirmed by clinical findings. The two models predict optimal dosing regimens, which warrant further clinical investigation to unleash the full therapeutic potential of ADG126 within targeted toxicities.

Conclusions

The continuously widened TI from ADG116 to ADG126 enables ADG126 to be dosed at 10 mg/kg Q3W and likely higher with anti-PD-1, resulting in significantly higher and sustained tumor target engagement than ipilimumab, potentially translating to greater clinical benefits.

REFERENCES