Assessing therapeutic window and dose selection of ADG126 (a masked anti-CTLA-4 SAFEbody): Integrating nonclinical and clinical data using mathematical modeling

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Background

New developments have rejuvenated anti-CTLA-4 therapies, yet dose-dependent adverse events remain a core challenge, leaving dose-dependent clinical efficacy on the table. ADG126 is an anti-CTLA-4 fully human IgG1 SAFEbody with a masking peptide blocking the antigen binding site, designed to be preferentially activated in the tumor microenvironment (TME). Activated ADG126 binds to a unique and conserved epitope of CTLA-4, allowing for cross-species demonstration of improved therapeutic window and prolonged exposure to active drug in the TME through preclinical imaging/pharmacokinetic (PK) studies. Activated ADG126 potentiates T cell activation and depletes immunosuppressive Tregs through strong antibody-dependent cellular cytotoxicity specifically in the TME. Clinical data are obtained from ongoing Phase 1b/2 studies of ADG126 mono or combination therapy with toripalimab (NCT04645069) and Phase 1 monotherapy study in China (CTR20220571), to inform on its therapeutic window and dose selection.

Aims

Primary Objectives:

- To assess the safety and tolerability of ADG126 administered intravenously (IV) at escalating dose levels in adult patients with advanced malignancies.

Secondary Objectives:

- To assess the pharmacokinetic (PK) profile of ADG126 (intact and activated).
- To assess the immunogenicity of ADG126 (intact and activated).
- To evaluate the preliminary clinical activity of ADG126 in the patients with specific cancer indications (ie, melanoma, non-small cell lung cancer, colorectal carcinoma, renal cancer, and hepatocellular carcinoma).

Methods

ADG126 in intact and total (i.e. intact + cleaved) forms in plasma were measured. Physiologically based PK modelling was conducted, leveraging clinical PK and tumor tissue PK from tumor-bearing mice. Clinical data of its parental antibody (Ab) was integrated..

Results

The cleaved ADG126 plasma PK showed ~3-fold observed mean accumulation at steady state (SS) versus cycle 1 with Q3W dosing or <2-fold simulated accumulation with Q6W dosing. Modeling demonstrated that SS is reached between TME and plasma after releasing cleaved ADG126 into circulation, and when the production of the cleaved ADG126 reaches equilibrium with its elimination. Simulated maximum SS cleaved ADG126 exposure ($C_{max,ss}$) at 10mpk Q3W or Q6W dosing is less than $C_{max,ss}$ of its parental Ab dosed at 3mpk Q3W (e.g., with manageable safety when combined with anti-PD-1 mAbs). This is consistent with reduced circulating PD biomarkers, reflective of reduced whole-body immune activation and superior clinical safety profiles for ADG126 as mono or combination therapies. At 10mpk, model-predicted SS tumor cleaved ADG126 exposure is greater than its in vitro binding and functional EC_{90s}, and is higher than the predicted tumor exposure of its parental Ab at 10mpk, consistent with 10mpk Q3W or Q6W as emerging efficacious dose/regimens of ADG126.

Conclusion

The SAFEbody technology enables ADG126 to be dosed at 10mpk, >3-fold higher dose levels than its parental Ab at 3mpk in a combination setting with anti-PD-1. It was demonstrated through modeling that ADG126 has higher and sustained TME active drug exposure, and therefore greater target engagement than what tolerable doses of non-masked anti-CTLA-4 molecules can achieve. The increased therapeutic window and efficacious dose selection of ADG126 is informed by quantitative integration of available data

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