Deciphering Improved Clinical Therapeutic Index (TI) of Muzastotug (ADG126), a Masked Anti-CTLA-4 SAFEbody® over its Unmasked Form (ADG116) as Monotherapy or in Combination with anti-PD-1 Therapy

Songmao Zheng, John J. Park, Mihitha Ariyapperuma, Gary Richardson, Ruihua Xu, Tony Tolcher, Michelle Morris, Boon Cher Goh, Matthew Ng Chau Hsien, Suxia Luo, Sang Joon Shin, Justina Lam, Kristine She, Yanyan Zhang, John Skinner, Zhining Wan, Ming Zhang, Xuesong Chen, Guizhong Liu, Jiangchun Xu, Yan Li, Jiping Zha, Peter Luo

Background

Decoupling dose-dependent efficacy from toxicity of anti-CTLA-4 therapies is essential to enable enhanced TI and efficacy. ADG116, an IgG1 monoclonal antibody targeting a unique epitope of CTLA-4 conserved cross species, has demonstrated improved TI over ipilimumab via enhanced epitope-dependent ADCC and T cell priming. Muzastotug, a masked version of ADG116, is designed to further widen the TI by preferential cleavage and targeting the constitutively over-expressed CTLA-4 on T regulatory cells in TME, achieving potent intratumoral Treg depletion.

Aim

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.

Method

Clinical PK, safety and efficacy data from four studies (ADG116-1003, ADG116-1002, ADG126-1001 and ADG126-1002) across cancer types were analyzed by minimal physiologically-based pharmacokinetic (mPBPK) models integrating also nonclinical data. .

Results

Key clinical data are summarized in **Table 1**. Muzastotug at 20 mg/kg Q3W resulted in better safety than ADG116 at 10 mg/kg Q3W as monotherapy. When combined with TORI, muzastotug at 10 mg/kg Q3W resulted in significantly better safety and similar efficacy versus ADG116 at 3 mg/kg Q6W (highest tolerable regimen). mPBPK models characterized preclinical (mouse plasma and tumor PK) and clinical plasma PK well. Delivery of high concentrations of active drug into the tumor while minimizing active drug concentrations in normal tissue and blood is shown to optimize the TI of muzastotug. Under the same dosing regimen, maximum Steady-State (SS) cleaved (i.e., active) muzastotug concentrations in leaky normal tissue and plasma are predicted to be <5-fold and <10-fold lower than $C_{max,SS}$ of ADG116, respectively, while in tumor interstitial fluid, $C_{max,SS}$ of cleaved muzastotug and ADG116 are similar. Pharmacodynamic biomarker comparisons showed significantly lower systemic IFN-γ levels for muzastotug than for ADG116 when the same or higher doses of muzastotug were administered. As monotherapy, ~30 mg/kg Q3W muzastotug is predicted to reach the same $C_{tumor\ cleaved}$ in Cycle 1 (C1) as SS ADG116 at 10 mg/kg Q3W. For combo therapy, 10 mg/kg Q3W muzastotug could reach $C_{tumor\ cleaved}$ in C1 as SS ADG116 at 3 mg/kg Q6W, supporting combo efficacy comparison.

References

Li, Daneng, et al. "Results of a phase 1b/2 study of ADG126 (a masked anti-CTLA-4 SAFEbody) in combo with pembrolizumab (Pembro) in patients (Pts) with metastatic microsatellite-stable (MSS) colorectal cancer (CRC)." (2024): 127-127. Meeting Abstract: 2024 ASCO Gastrointestinal Cancers Symposium

Conclusion

Both ADG116 and muzastotug demonstrated improved TI over ipilimumab. The SAFEbody technology allows for ~2-fold higher dosing of muzastotug compared to ADG116 as monotherapy and more than 6-fold higher dosing (e.g., total drug amount within 2 cycles) when combined with anti-PD1. Muzastotug results in significantly higher and sustained predicted SS tumor-specific engagement of CTLA-4 in patients, and its potential best-in-class profile supports further clinical development.