Abs # 506

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 (Toripalimab)

SITC 2024

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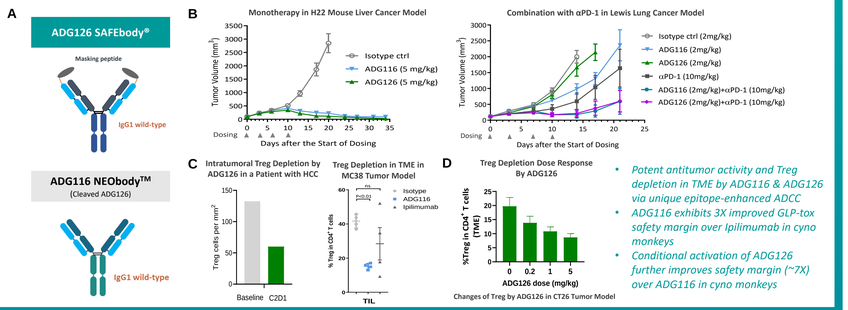
Background

- Decoupling dose-dependent efficacy from toxicity of anti-CTLA-4 therapies is essential to enable enhanced clinical therapeutic index (TI) which is reflected in the Recommended Phase II Dose (RP2D) used in monotherapy and in combination with anti-PD-1. Ipilimumab, the first FDA approved anti-CTLA-4 therapy for monotherapy and in combination with anti-PD-1 therapy, is limited in efficacy due to safety concerns by dosing at 3 or 10 mg/kg Q3W as monotherapy in melanoma for up to 4 cycles, 1 or 3 mg/kg Q3/6W in combination with nivolumab. The second FDA approved anti-CTLA-4 antibody, tremelimumab faces similar challenges. Therefore, we aim to improve TI of anti-CTLA-4 therapy that allows for higher and repeat dosing to unleash its efficacy.
- ADG116, an IgG1 monoclonal antibody targeting a unique epitope of CTLA-4 which is conserved across species, has demonstrated improved TI over ipilimumab and tremelimumab via enhanced epitope-dependent ADCC and T cell priming. ADG126, a masked version of ADG116, is designed to further widen the TI by preferential cleavage in the extracellular proteases rich tumor microenvironment (TME) and targeting the constitutively over-expressed CTLA-4 on T regulatory cells in TME for potent CTLA-4 mediated intratumoral Treg depletion, achieving tumor-specific targeting with minimal on-target off-tumor toxicities.

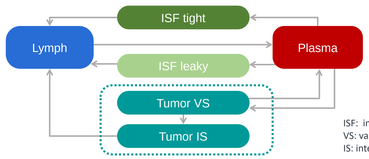
ADG116/ADG126 Target a Distinct Epitope of CTLA-4 Compared to Ipilimumab Resulting in Improved Efficacy & Safety Profiles



- *Potent antitumor activity and Treg depletion in TME by ADG116 & ADG126 via unique epitope-enhanced ADCC*
- *ADG116 exhibits 3X improved GLP-tox safety margin over Ipilimumab in cyno monkeys*
- *Conditional activation of ADG126 further improves safety margin (~7X) over ADG116 in cyno monkeys*

Methods

Minimal physiologically-based pharmacokinetic (mPBPK) modeling framework

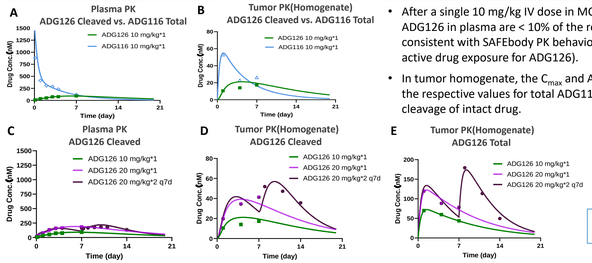


ISF: interstitial fluid
VS: vasculature space
IS: interstitial space

- Clinical PK, safety and efficacy data from four studies (ADG116-1003, ADG116-1002, ADG126-1001 and ADG126-1002) across cancer types were analyzed by mPBPK models.
- Known molecular transformation and mass balance for Total, Intact and Cleaved forms of ADG126 were integrated for all compartments.
- The same model structure was applied to ADG116 without cleavage and was used for different species (e.g., mice and human).

Tumor-specific parameters in humans were modeled by fitting measured PK data (e.g., tumor PK and plasma PK) from MC38 tumor-bearing mice for ADG126 and ADG116.

ADG116 and ADG126 MC38 Mice Model mPBPK modeling



- After a single 10 mg/kg IV dose in MC38 mice, the C_{max} and AUC of cleaved ADG126 in plasma are < 10% of the respective values for total ADG116 (**A**), consistent with SAFEbody PK behavior (e.g., representing minimal normal tissue active drug exposure for ADG126).
- In tumor homogenate, the C_{max} and AUC of cleaved ADG126 are within 2-fold of the respective values for total ADG116 (**B**), representing significant intratumoral cleavage of intact drug.

The tumor ISF conc. is ~ 2-fold higher than the measured tumor homogenate PK based on the reported volume of ISF vs. cellular space.

Symbols: measured PK
Lines: mPBPK model-predicted PK

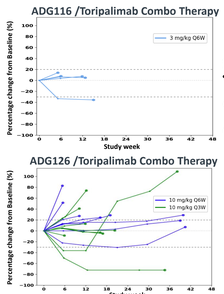
- Dose-dependent and approximately linear PK was observed for ADG126 in plasma and in tumor (10 mg/kg vs. 20 mg/kg single dose, **C, D, E**).
- A second 20 mg/kg dose (day 7) further increased the tumor cleaved (**D**) and total (**E**) PK, but less for plasma cleaved PK (**C**) compared with PK after a 20 mg/kg single dose, demonstrating continuous intratumoral cleavage of intact ADG126 and accumulation of cleaved ADG126 within TME. The % cleaved using cleaved drug AUC vs. calculated intact drug AUC (e.g., Total minus Cleaved) in tumor homogenate is 67.3% ± 6.3% (mean ± SD).

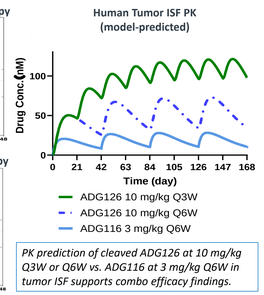
Combination Efficacy and Safety

Study	Dose level	Pts Num	Evaluable Pts Num
ADG116 + Toripalimab	3 mg/kg Q6W	7	5
ADG126 + Toripalimab	10 mg/kg Q6W	10	8
ADG126 + Toripalimab	10 mg/kg Q3W	11	9

Dose and Subpopulation (N)	ADG116 + Toripalimab 3 mg/kg Q6W Evaluable (N = 5)	ADG126 + Toripalimab 10 mg/kg Q6W Evaluable (N = 8)	ADG126 + Toripalimab 10 mg/kg Q3W Evaluable (N = 9)
ORR, % (95% CI)	20 (1-72)	0 (0-37)	22 (3-60)
BoR, N (%)			
PR	1* (20)	0 (0)	2 (22)
SD	3 (60)	5 (63)	4 (44)
DCR (CR+PR+SD), %, (90% CI)	80 (28-99)	63 (24-91)	67 (30-93)
6-month CBR, %, (90% CI)	20 (1-72)	13 (0-53)	22 (3-60)

* Unconfirmed PR





PK prediction of cleaved ADG126 at 10 mg/kg Q3W or Q6W vs. ADG116 at 3 mg/kg Q6W in tumor ISF supports combo efficacy findings.

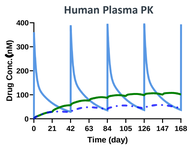
ADG116/Toripalimab Combo Therapy TRAE

Dose Level	N	All G n (%)	G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)	G5 n (%)	Discont. Rate*
3 mg/kg Q6W	7	5 (71)	2 (29)	0	3 (43)	0	0	1 (14%)
3 mg/kg Q3W	6	6 (100)	2 (33)	0	3 (50)	1 (17)	0	0 (0%)
6 mg/kg Q3W	3	3 (100)	0	0	3 (100)	0	0	1 (33%)

ADG126/Toripalimab Combo Therapy TRAE

Dose Level	N	All G n (%)	G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)	G5 n (%)	Discont. Rate*
10 mg/kg Q6W + Q3W	21	12 (57)	6 (29)	2 (10)	4 (19)	0	0	2 (10%)

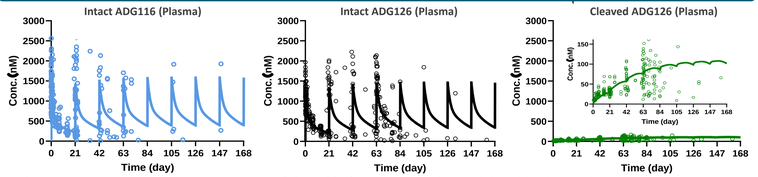
*TEAE leading to drug discontinuation



- When combined with toripalimab, ADG126 at 10 mg/kg Q3W resulted in significantly better safety and similar, if not better efficacy versus ADG116 at 3 mg/kg Q6W (highest tolerable regimen).
- 10 mg/kg Q6W ADG126 + toripalimab resulted in encouraging DCR and CBR, despite limited ORR.

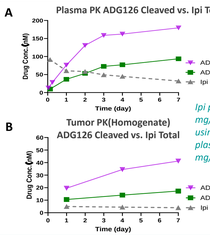
PK prediction of cleaved ADG126 at 10 mg/kg Q3W or Q6W vs. ADG116 at 3 mg/kg Q6W in plasma supports combo safety findings.

Representative Clinical PK Model Fitting of Measured ADG116 and ADG126



- The same mPBPK general model structure was successfully used for fitting ADG116 and ADG126 clinical data (e.g., ADG126-1001 and ADG116-1003 monotherapy at 10 mg/kg Q3W), with in vivo cleavage included in ADG126 fitting.
- The estimated PK parameters allowed for prediction of tumor and normal leaky tissue ISF PK for both ADG116 and ADG126.
- The measured maximum plasma cleaved ADG126 is <5% or <10% of maximum ADG116 in plasma in Cycle 1 or at steady state, respectively, directly supporting significantly improved safety of ADG126 over ADG116.

Ipilimumab (Ipi) vs. ADG126 PK Comparison in MC38 Mice



*Ipi plasma and tumor PK at 1 mg/kg*1 is linearly scaled (e.g., using 10%) from measured ipi plasma and tumor PK at 10 mg/kg*1 in the same MC38 model*

ADG126 showed >3X increased active drug exposure in tumor homogenate (**B**) at 10 mg/kg (single dose) vs. Ipi at 1 mg/kg (single dose) while maintaining similar plasma drug exposures (**A**), demonstrating SAFEbody PK advantage.

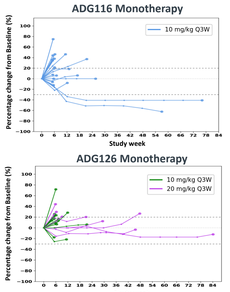
ADG126 PK Fold Change From Ipi at 1 mg/kg Single Dose

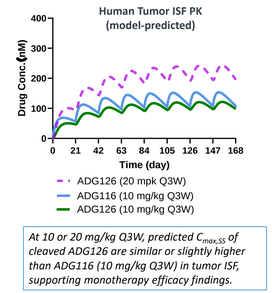
	ADG126 (10 mg/kg*1)	ADG126 (20 mg/kg*1)
Plasma $AUC_{0\text{-}7d}$	~1.3	~2.8
Plasma $C_{max,0\text{-}7d}$	~1.0	~2.0
Tumor $AUC_{0\text{-}7d}$	~3.1	~7.3
Tumor $C_{max,0\text{-}7d}$	~3.5	~8.3

Monotherapy Efficacy and Safety

Study	Dose Level	Pts Num	Evaluable Pts Num
ADG116 Monotherapy	10 mg/kg Q3W	26	20
ADG126 Monotherapy	10 mg/kg Q3W	17	16
	20 mg/kg Q3W	9	9

Dose and Subpopulation (N)	ADG116 Monotherapy 10 mg/kg Q3W Evaluable (N = 20)	ADG126 Monotherapy 10 mg/kg Q3W Evaluable (N = 16)	ADG126 Monotherapy 20 mg/kg Q3W Evaluable (N = 9)
ORR, % (95% CI)	10 (1-32)	0 (0-21)	0 (0-34)
BoR, N (%)			
PR	2(10)	0 (0)	0 (0)
SD	6 (30)	6 (38)	6 (67)
DCR (CR+PR+SD), %, (95% CI)	40 (19-64)	38 (15-65)	67 (30-93)
6-month CBR, %, (95% CI)	10 (1-32)	0 (0-21)	33 (7-70)





Dose-dependent efficacy observed for ADG126 monotherapy, with 20 mg/kg Q3W showing higher DCR and 6-month CBR than ADG116 at 10 mg/kg Q3W

At 10 or 20 mg/kg Q3W, predicted $C_{max,SS}$ of cleaved ADG126 are similar or slightly higher than ADG116 (10 mg/kg Q3W) in tumor ISF, supporting monotherapy efficacy findings.

ADG116 Monotherapy TRAE

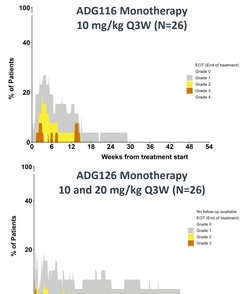
Dose Level	N	All G n (%)	G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)	G5 n (%)	Discont. Rate*
10 mg/kg Q3W	26	19 (73)	9 (35)	6 (23)	3 (12)	1 (4)	0	4 (15%)

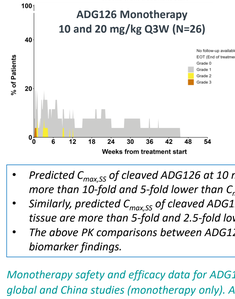
ADG126 Monotherapy TRAE

Dose Level	N	All G n (%)	G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)	G5 n (%)	Discont. Rate*
10 mg/kg Q3W	17	9 (53)	4 (24)	5 (29)	0	0	0	1 (6%)
20 mg/kg Q3W	9	8 (89)	5 (56)	2 (22)	1** (11)	0	0	0 (0%)

*TEAE leading to drug discontinuation;
** 1 case of G3 Acquired thalassaemia was considered due to the underlying disease rather than the treatment

Dose-dependent safety observed for ADG126 monotherapy, with both 10 and 20 mg/kg Q3W showing significantly better safety than ADG116 at 10 mg/kg Q3W

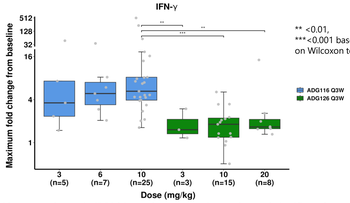




- *Predicted $C_{max,SS}$ of cleaved ADG126 at 10 mg/kg Q3W in plasma and leaky normal tissue are more than 10-fold and 5-fold lower than $C_{max,SS}$ of ADG116 (10 mg/kg Q3W), respectively.*
- *Similarly, predicted $C_{max,SS}$ of cleaved ADG126 at 20 mg/kg Q3W in plasma and leaky normal tissue are more than 5-fold and 2.5-fold lower than $C_{max,SS}$ of ADG116 (10 mg/kg Q3W).*
- *The above PK comparisons between ADG126 and ADG116 support monotherapy safety and PD biomarker findings.*

Monotherapy safety and efficacy data for ADG116 and ADG126 were combined from their respective global and China studies (monotherapy only). A detailed description of each study is provided below: ADG116-1003 global study (NCT04501276, monotherapy and combination with anti-PD-1 toripalimab), ADG116-1002 (China monotherapy study), ADG126-1001 (NCT04645069, global monotherapy and combination with toripalimab), and ADG126-1002 (China monotherapy study).

Monotherapy PD Biomarker



Pharmacodynamic (PD) biomarker comparisons showed significantly lower fold change from baseline for systemic IFN-γ for ADG126 compared to ADG116 given the same or higher doses of ADG126.

Conclusions

- The species cross-reactivity of ADG126 and ADG116 enables quantitative approaches for TI assessment through seamless integration of preclinical and clinical data to predict tissue PK for intact and cleaved ADG126 in patients vs. in vivo animal models using the same molecule, with a unified set of physiologically relevant parameters for modeling in patients. A quantitative framework is developed to decipher the origin of the unmasked (i.e. cleaved) ADG126 at 20 mg/kg Q3W compared to its unmasked parental Ab ADG116 at 10 mg/kg Q3W as monotherapy, and ADG126 at 10 mg/kg Q3W vs ADG116 at 3 mg/kg Q6W in combination with anti-PD-1 antibodies (e.g., toripalimab and pembrolizumab, refer to SITC 2024 Poster 744) while maintaining a significant safety margin. This approach explained how SAFEbody technology allows >6-fold higher dosing in combination with anti-PD-1 antibodies.
- ADG126 demonstrated further improved TI over ADG116, which was shown to be differentiated from ipilimumab. The integration of preclinical and clinical data in combination with mPBPK modeling allows us to predict a significantly higher and sustained steady state tumor-specific engagement of CTLA-4 but reduced exposure in periphery by cleaved ADG126 compared to ADG116 in patients. This framework was also used to demonstrate even greater clinical TI differences of ADG126 vs. other unmasked anti-CTLA-4 antibodies (e.g., ipilimumab, refer to SITC 2023 Poster 847).
- The best-in-class therapeutic index of ADG126 supports its further clinical development, such as with pembrolizumab and drugs with other MOAs.

We would like to acknowledge all patients, PIs and medical staff involved in all four listed trials and Adagene team members for critical review and technical contributions;