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Optimal Dose Selection of ADG126 (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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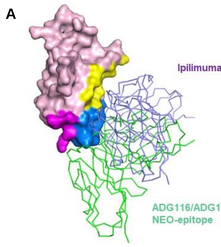
Background

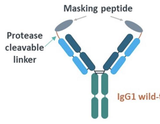
- Dose-dependent toxicity of anti-CTLA-4 therapies has severely limited their efficacy and therapeutic index (TI). Ipilimumab, the first FDA approved anti-CTLA-4 therapy for monotherapy and in combination with anti-PD-1 therapy, is limited due to safety concerns by dose level, frequency and cycles that may not maximize anti-tumor efficacy. The second FDA approved anti-CTLA-4 antibody, tremelimumab faces similar challenges in combination despite efficacy in front-line settings with limited number of doses. Next generation anti-CTLA-4 therapies must achieve better efficacy with an improved TI that allows for repeat dosing and sufficiently active dose levels.
- ADG126, a masked anti-CTLA-4 SAFEbody, is designed to allow for repeat dosing at active dose levels due to its improved TI by targeting a unique and highly conserved epitope of CTLA-4 on Treg cells in tumor microenvironment (TME) that is preferentially enriched and activated to enable CTLA-4-mediated depletion of Tregs in TME via epitope dependent effector functions such as ADCC.
- Optimal dose selection of ADG126 in combination with anti-PD-1 antibodies requires quantitatively assessing different dosing regimens including PK/PD modeling of effects of plasma/intratumoral masked vs cleaved drug concentrations on efficacy and safety.
- The species cross-reactivity of fully activated ADG126 or ADG116 enables quantitative approaches for TI assessment through seamless integration of preclinical and clinical data to predict cleaved ADG126 in TME in patients vs *in vivo* animal models using the same molecule, with a unified set of physiologically relevant parameters for population PK modeling for more than 50 patients across trials.

ADG126 Targets a Distinct Epitope of CTLA-4 Compared to Ipilimumab Resulting in Unique MOAs

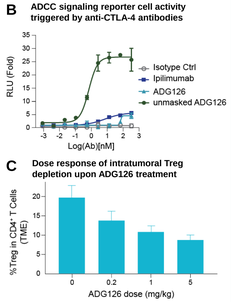
KD (nM)	Human	Cyno Monkey	Mouse	Rat
ADG116 (Fully activated ADG126)	2.8	1.2	2.4	1.8



ADG126 SAFEbody®



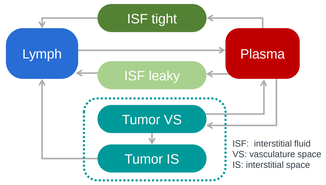
- Masking results in > 2X higher activated ADG126 drug concentration in TME vs blood
- Enables dose-dependent CTLA-4-mediated Treg depletion in TME
- 20X higher GLP-tox HNSTD over Ipi



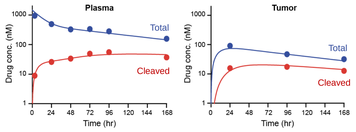
Binding Epitopes and Activities of ADG126 vs. Ipilimumab. The unique binding epitope of ADG126 and its parental antibody ADG116 with species cross-reactivity (A), results in stronger ADCC activity compared with ipilimumab (B), and dose-dependent intratumoral Treg depletion in vivo in CT26 model by ADG126 anti-CTLA-4 SAFEbody (C).

Minimal physiologically-based pharmacokinetic (mPBPK) modeling

- Known molecular transformation and mass balance for Total, Intact and Cleaved forms of ADG126 was integrated for all compartments.
- The same model structure was used for different species (e.g., mice, rat, monkey and human).



mPBPK model can characterize plasma and tumor PK in tumor-bearing mice well after a 10 mpk single dose, allowing the estimation of tumor cleavage parameter of ADG126.



For tumor related parameters, measured PK data (e.g., tumor PK and plasma PK) in tumor-bearing mice was modeled to estimate the tumor cleavage rate constant in mice and was kept the same for human PK modeling.

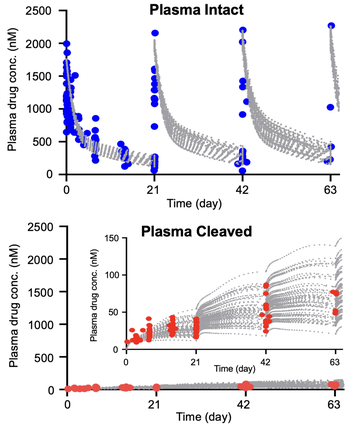
References

1. Sanghavi, K., et al. , CPT Pharmacometrics Syst. Pharmacol. 2020, 9: 29-39.
2. Ariyapperuma M, Park J, Khattak A, et al. Cancer Res 2023;83(8_Suppl):Abstract nr CT227.
3. Li D, Sharma S, She K, et al. Cancer Res 2023;83(8_Suppl):Abstract nr CT233.
4. Kumar R, Thiagarajan K, Jagannathan L, et al. CPT Pharmacomet Syst Pharmacol. 2021; 10(7): 684- 695.
5. Park J, Ariyapperuma M, Richardson G, et al. Journal of Clinical Oncology 2023, 41, no. 16_suppl
6. Jedd D. Wolchok, et al. N Engl J Med 2017. 377(14): p. 1345-1356.

Cross-species reactivity of ADG126 in mice allows for integrating mPBPK model-estimated tumor cleavage parameter from tumor-bearing mice to human

Population mPBPK model fitting in patients (10 mpk Q3W)

The mPBPK model succeeded in simultaneously fitting the measured plasma intact and cleaved drug concentrations across studied dose levels.



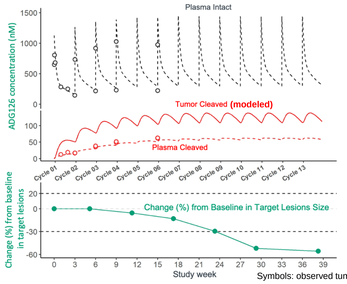
Cycle 3 mean plasma cleaved drug PK *(e.g., model-predicted maximum)* is <5% of mean C_{max} of intact drug

Symbols: Observed (PK data generated using ELISA)

Lines: mPBPK model-predicted

Individual mPBPK model fitting in patients (10 mpk Q3W)

Supported by PK modeling, ADG126 10 mg/kg Q3W + Pembrolizumab shows ability to overcome Pembrolizumab resistance in a 3L cervical cancer patient.



mPBPK model-predicted tumor cleaved PK at steady state is above the upper bound of in vitro EC_{90} (~90nM) for cleaved ADG126 (human T cell binding)

Symbols: observed (PK data generated using ELISA)

Lines: mPBPK model-predicted

Tumor Type:	Female, 70 years old, advanced cervical cancer (stage IV) • PD-L1 CPS score = 1, TMB high: 24 Muts/Mb
Prior Therapies:	Previously received 2 lines of therapies: • Carboplatin/paclitaxel/bevacizumab x 6 cycles • Pembrolizumab monotherapy × 9 cycles
Safety Profile:	Only G2 TRAEs

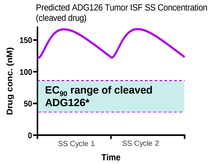
mPBPK Modeling for Enhanced Therapeutic Index of SAFEbody ADG126 over Ipilimumab in combination with anti-PD-1

Dosage	Predicted $AUC_{ss,tumor\ ISF}$ fold difference	Predicted $C_{max,ss,tumor\ ISF}$ fold difference
ADG126 (10 mpk Q3W) vs. Ipilimumab (1 mpk Q6W) in combination with anti-PD-1	~30X	~10X

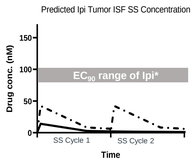
Predicted higher TI of ADG126 over ipilimumab is due to

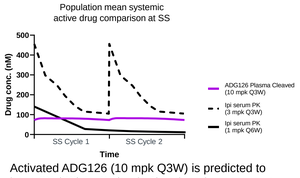
- >90% CTLA4 RO in tumor achieved by activated ADG126 (predicted) at SS
- Reduced exposures of activated ADG126 in plasma

Steady-State (SS) drug exposure of activated ADG126 or Ipilimumab in tumor (predicted) vs. in blood circulation (measured)



Activated ADG126 is predicted to achieve >90% RO throughout steady-state (SS) dosing cycle in TME at 10 mpk Q3W in tumor while Ipi at 3mpk Q3W may not.





Activated ADG126 (10 mpk Q3W) is predicted to have 2X (SS) to 4X (cycle 1) reduced exposure vs. Ipi (3 mpk Q3W) in blood.

This panel contains information from various studies which are not head-to-head comparisons. Data on file.
Ipi steady-state (SS) PK digitized from **[1];** the middle figure is based on the assumption that Ipi SS conc. in tumor ISF ~10% of Ipi SS serum PK (e.g., tumor partition ~10%) as one possible clinical scenario
*EC_{90} range determined for cleaved ADG126 or Ipi for human T cell binding (in-house data)

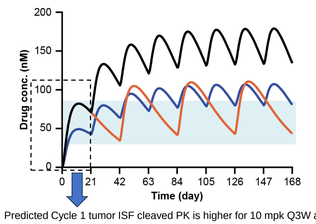
mPBPK model predicted tumor ISF cleaved PK is consistent with the dose-dependent efficacy seen in the clinic

ADG126 clinical data summary for safety and efficacy when combined with Pembrolizumab

ADG126 + Pembrolizumab (NCT05405595)	Dose escalation + Dose expansion				
	Safety (TRAEs)			Efficacy	
ADG126 Dosing Regimen	Patients Dosed[1] (N=46)	≥ G3 TRAEs*	Discontinuation Rate due to TRAEs	Patients Evaluable[2] (N=37)	DCR
6 mg/kg Q3W	5	**20%**	0%	5	**20%**
10 mg/kg Q6W	17	**6%**	0%	16	**56%**
10 mg/kg Q3W	24	**13%**	0%	16	**75%**

** No G4,G5 TRAE Only one patient used infliximab for safety control*
*NCT05405595, data cutoff: August 29, 2023, following reported dose escalation and preliminary efficacy data reported at AACR 2023 **[2, 3]** and in Adagene SEC filing August 2023.*
[1] Dosed: Patient received at least one dose, used for safety evaluation
[2] Evaluable: Patient received at least one tumor assessment, used for efficacy evaluation

Model-predicted mean tumor ISF cleaved ADG126



EC_{90} range of cleaved ADG126 for human T cell binding

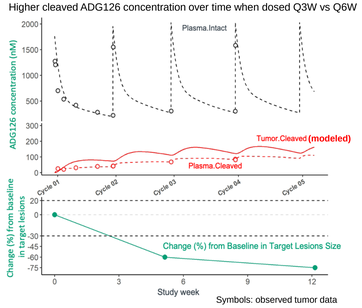
Predicted Cycle 1 tumor ISF cleaved PK is higher for 10 mpk Q3W and Q6W, compared to 6 mpk Q3W

This study is funded by Adagene Inc., who retains global development and commercialization rights to ADG126. Contact ir@adagene.com.
ADG126-P001 (NCT05405595) clinical study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.
The presenting author Peter Luo, PhD is CEO of Adagene Inc. We would like to acknowledge PIs and patients involved in ADG126-1001, ADG126-1002 and ADG126-P001 trials **[2, 3, 5]**. We would like to thank Drs. Stanley Frankel, Dana HuLowe, Wenda Li, Yanyan Zhang, Wenqing Song, Mingjun Jing, Zhining Wan, Ming Zhang, Hong Jin, Zhengxi Dai, Jiagui Qu, Alex Goergen, Raymond Tam and Ami Celeste Knoeffler for their input. Copies of this poster obtained through QR are for personal use only and may not be reproduced without written permission of the authors.

Model-informed PK and efficacy of case studies support ADG126 dose selection of 10 mpk Q3W in microsatellite stable (MSS)-colorectal cancer (CRC)

Case study of confirmed PR with ADG126 10 mpk Q3W + Pembro in ongoing MSS CRC cohort

Higher cleaved ADG126 concentration over time when dosed Q3W vs Q6W



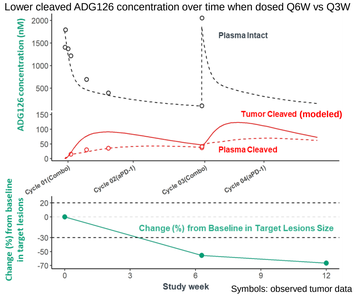
mPBPK model-predicted tumor cleaved PK at steady state is above the upper bound of in vitro EC_{90} (~90nM) for cleaved ADG126 (human T cell binding)

Symbols: observed (PK data generated using ELISA)
Lines: mPBPK model-predicted

Tumor Type:	Female, 55 years old, advanced colon adenocarcinoma with mediastinal, paraaortic lymph nodes metastasis • MSS CRC
Prior Therapies:	Previously received 2 lines of therapies: • bevacizumab + FOLFOX • aflibercept + FOLFIRI
Safety Profile:	G2, G3 TRAEs • Grade 3 Hyperglycemia (542 mg/dL) in setting of known diabetes • Grade 3 Generalized Weakness; Grade 2 Whole body pruritus

Case study of initial PR with ADG126 10 mpk Q6W + Pembro, yet subsequent PD in MSS CRC

Lower cleaved ADG126 concentration over time when dosed Q6W vs Q3W



Greater fluctuations in mPBPK model-predicted tumor cleaved PK, as well as reduced cleaved AUC/C_{max} by Q6W vs Q3W dosing

Symbols: observed (PK data generated using ELISA)
Lines: mPBPK model-predicted

Tumor Type:	Female, 58 years old, advanced colorectal adenocarcinoma Stage IV • KRAS Q61, MSS CRC, TMB low
Prior Therapies:	Previously received 2 lines of therapies: • Clinical trial GI306 w/FOLFOXIRI + bevacizumab + trilaciclib/placebo • ChemoXRT+5-FU
Safety Profile:	Only G2 TRAEs: • Grade 2 hypothyroidism • Grade 2 arthralgia

QSP modeling for efficacy and safety integrating mPBPK modeling predicted increased clinical TI of ADG126 vs. Ipi

- A quantitative systems pharmacology (QSP) model was developed by incorporating drug-specific dosage across melanoma trials into a published model **[4]** evaluating ipilimumab and pembrolizumab. Data from ipilimumab and nivolumab were further used. Characteristics of ADG126 were integrated by mPBPK modeling **[5]**. Furthermore, a novel safety model was developed incorporating data for ipilimumab, tremelimumab, pembrolizumab and nivolumab.
- In a hot tumor, 10 mg/kg Q3W ADG126 with limited dosing cycles is predicted to result in comparable tumor objective response rate as ipilimumab 3 mg/kg Q3W*4 with anti-PD-1, but with significantly improved safety.
- 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 **[6]**, confirmed by ADG126 clinical findings.

Conclusions

- Unique molecular design and properties of masked SAFEbody ADG126 allows for meaningful mPBPK and QSP modeling assessment of translational and clinical studies. These models predict an increased TI of ADG126 compared to ipi both as monotherapy or in combination with anti-PD-1, and have informed ADG126 dose selection.
- The widened TI of ADG126 enables ADG126 10 mg/kg Q3W repeat dosing with anti-PD-1, resulting in significantly increased CTLA-4 engagement by activated ADG126 in steady state in tumors vs circulating blood.
- Initial clinical data support that ADG126 may provide greater clinical benefit than Ipi in combination with anti-PD-1 in hot and cold tumors, including MSS CRC, driven by better target engagement in the TME and a favorable safety profile that allows for higher, more frequent and repeat dosing.