SITC 2024 Poster Slides

Nov 2024

ADAGENE

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)

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Background

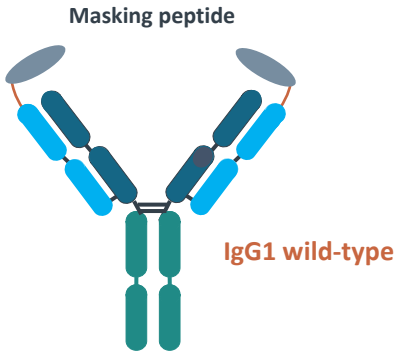
- Decoupling dose-dependent efficacy from toxicity of anti-CTLA-4 therapies is essential to enable enhanced clinical therapeutic index (TI) which is reflected in the Recommended Phase II Dose (RP2D) used in monotherapy and in combination with anti-PD-1.

- 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

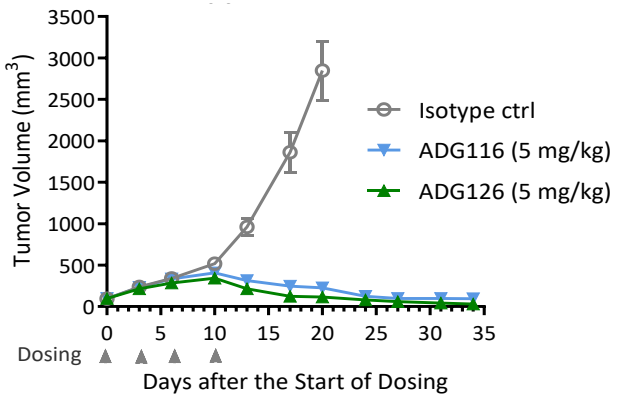
ADG126 SAFEbody®



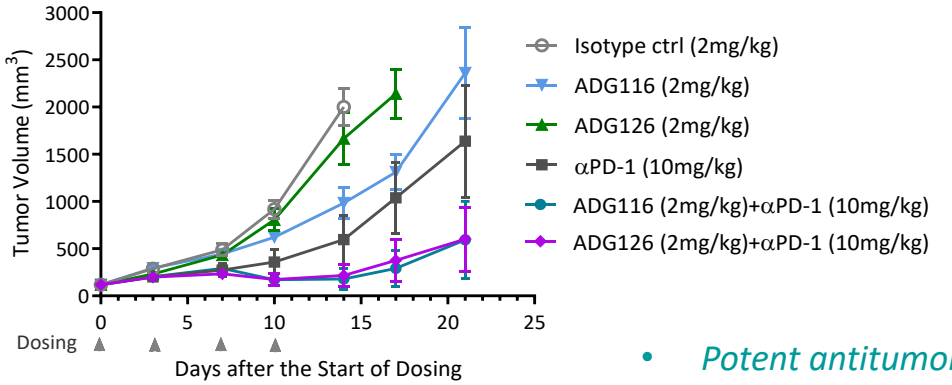
ADG116 NEObody™

(Cleaved ADG126)

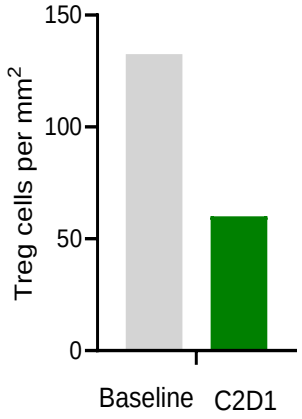
Monotherapy in H22 Mouse Liver Cancer Model



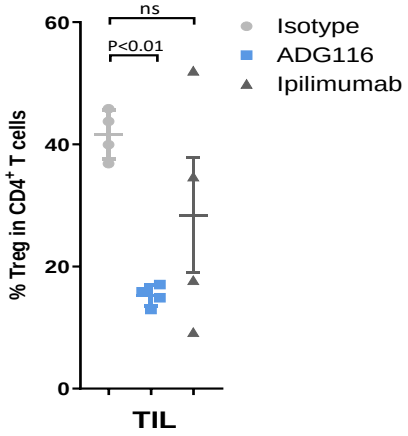
Combination with αPD-1 in Lewis Lung Cancer Model



Intratumoral Treg Depletion by ADG126 in a Patient with HCC



Treg Depletion in TME in MC38 Tumor Model



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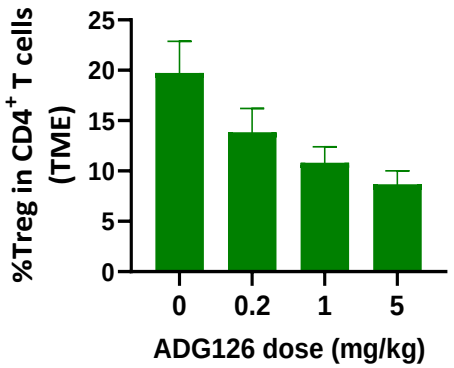
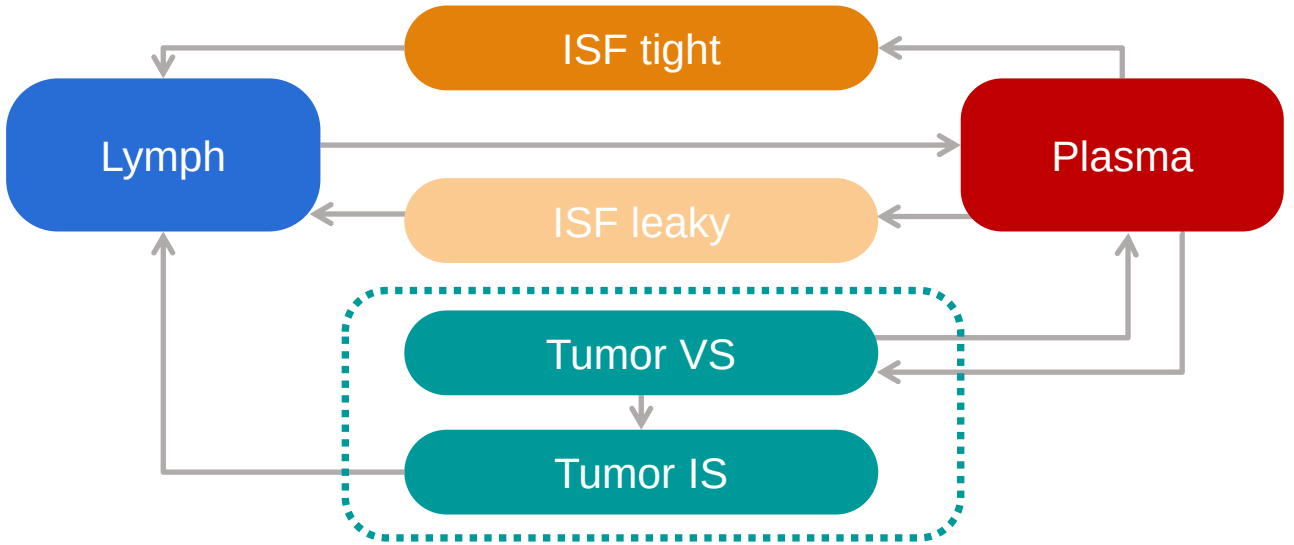
Treg Depletion Dose Response By ADG126



- *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*

Minimal physiologically-based pharmacokinetic (mPBPK) modeling framework

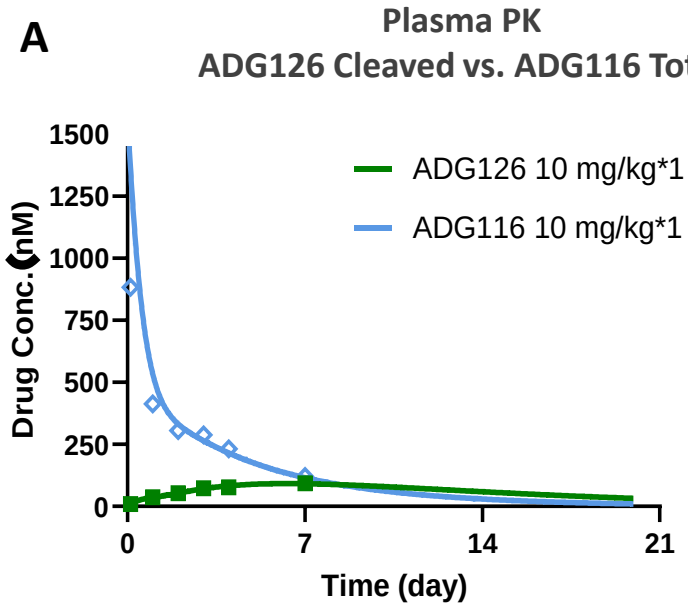


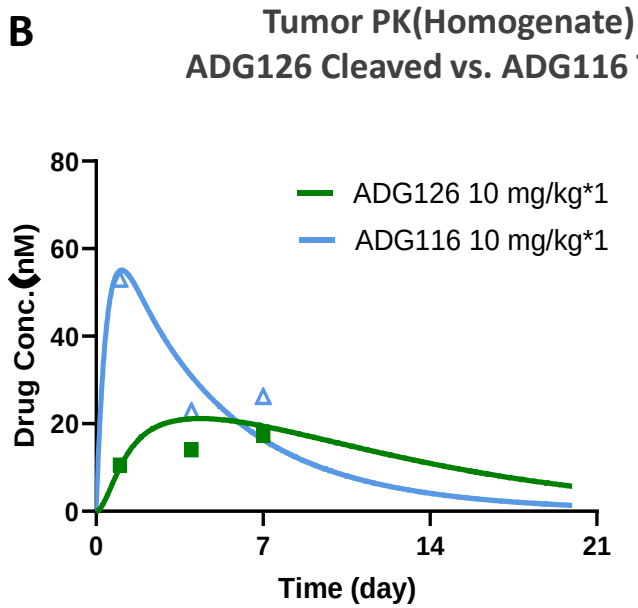
ISF: interstitial fluid
VS: vasculature space
IS: interstitial space

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.

- 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).

ADG116 and ADG126 MC38 Mice Model mPBPK modeling

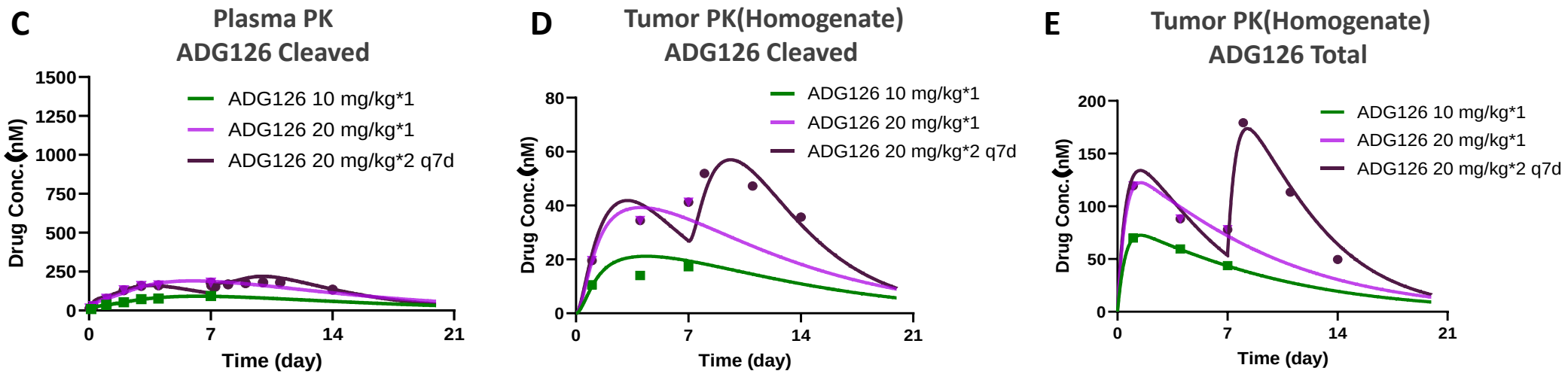




- After a single 10 mg/kg IV dose in MC38 mice, the Cmax and AUC of cleaved ADG126 in plasma are < 10% of the respective values for total ADG116 (A), consistent with SAFEbody PK behavior (e.g., representing minimal normal tissue active drug exposure for ADG126).
- In tumor homogenate, the Cmax and AUC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

ADG116 and ADG126 MC38 Mice Model mPBPK modeling

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



- 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).

Symbols: measured PK
Lines: mPBPK model-predicted PK

ADG116 and ADG126 Clinical 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

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%)

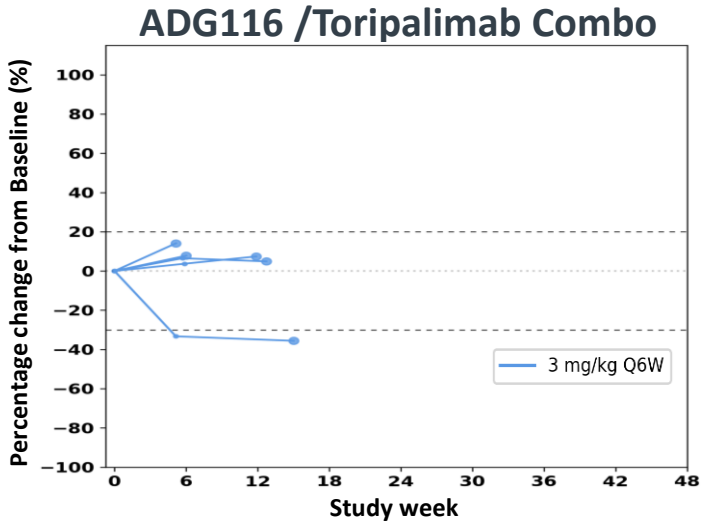
*TEAE leading to drug discontinuation

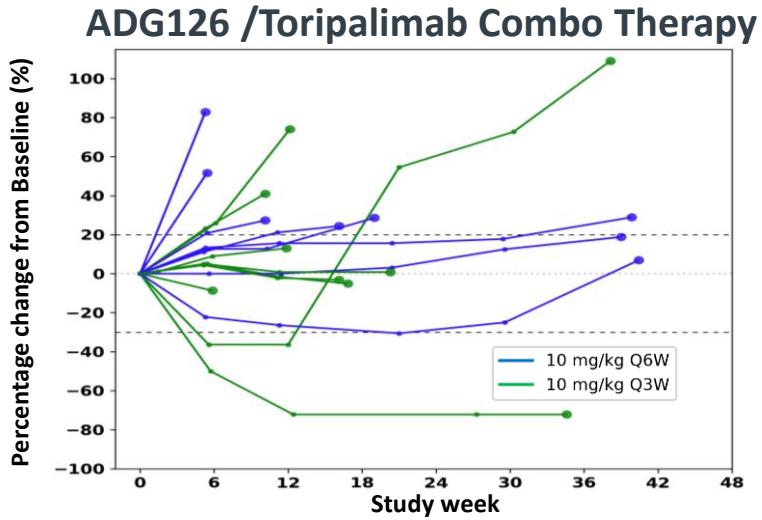
Dose and Subpopulation (N)	ADG116 + Toripalimab	ADG126 + Toripalimab	
	3 mg/kg Q6W Evaluable (N = 5)	10 mg/kg Q6W Evaluable (N = 8)	10 mg/kg Q3W Evaluable (N = 9)
ORR, % (95% CI)	20 (1-72)	0 (0-37)	22 (3-60)
BoR, N (%)			
PR	1* (20)	0 (0)	2 (22)
SD	3 (60)	5 (63)	4 (44)
DCR (CR+PR+SD), %, (90% CI)	80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

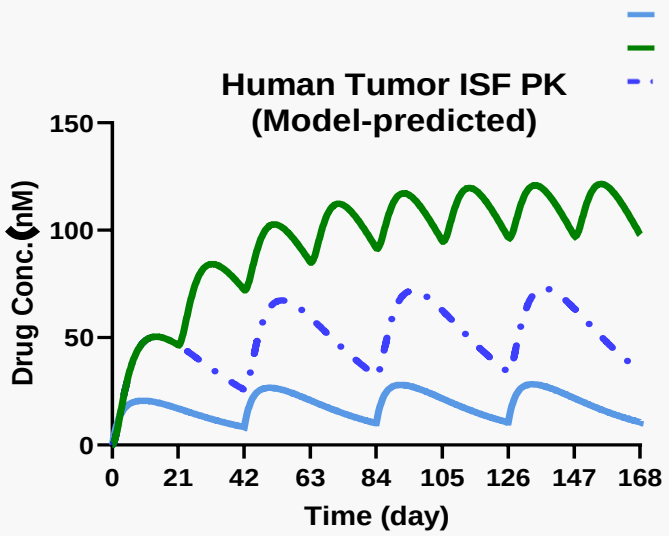
* Unconfirmed PR

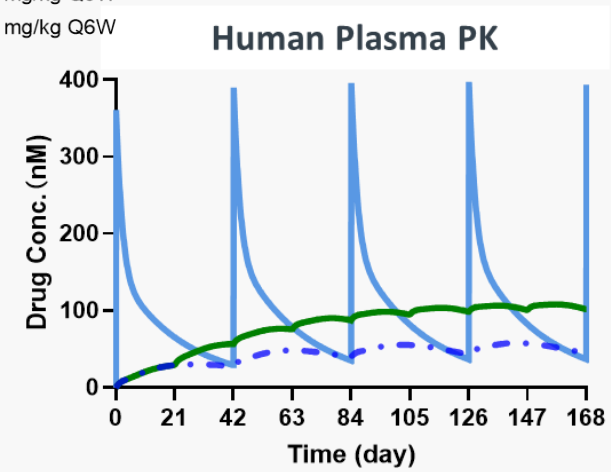
- When combined with toripalimab, ADG126 at 10 mg/kg Q3W resulted in significantly better safety and similar, if not better efficacy versus ADG116 at 3 mg/kg Q6W (highest tolerable regimen).
- 10 mg/kg Q6W ADG126 + toripalimab resulted in encouraging DCR and CBR, despite limited ORR.

ADG116 and ADG126 Clinical Combination Efficacy and Safety



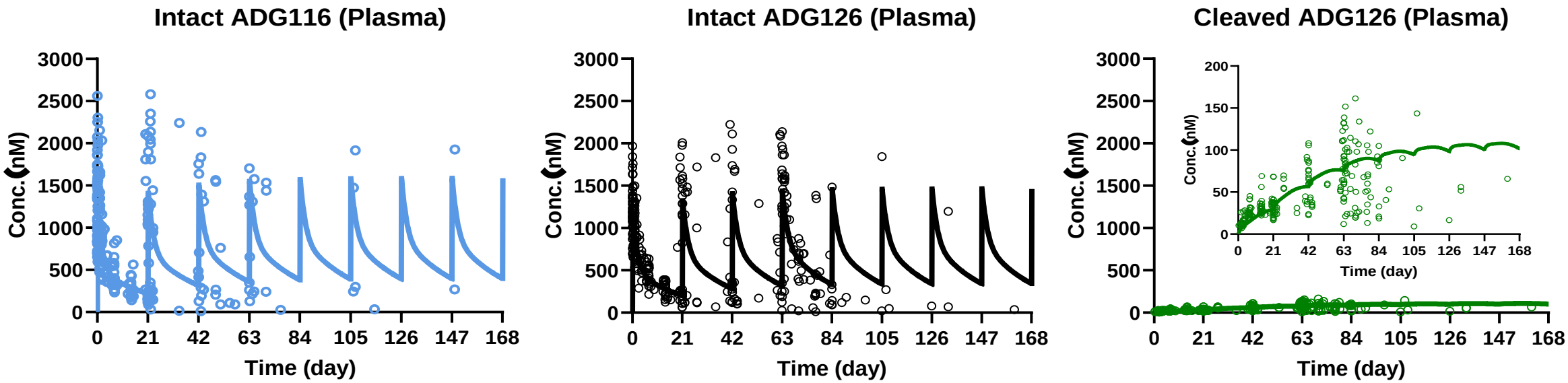






- Left: PK prediction of cleaved ADG126 at 10 mg/kg Q3W or Q6W vs. ADG116 at 3 mg/kg Q6W in tumor ISF supports combo efficacy findings.
- Right: PK prediction of cleaved ADG126 at 10 mg/kg Q3W or Q6W vs. ADG116 at 3 mg/kg Q6W in plasma supports combo safety findings.

Representative Clinical PK Model Fitting of Measured ADG116 and ADG126

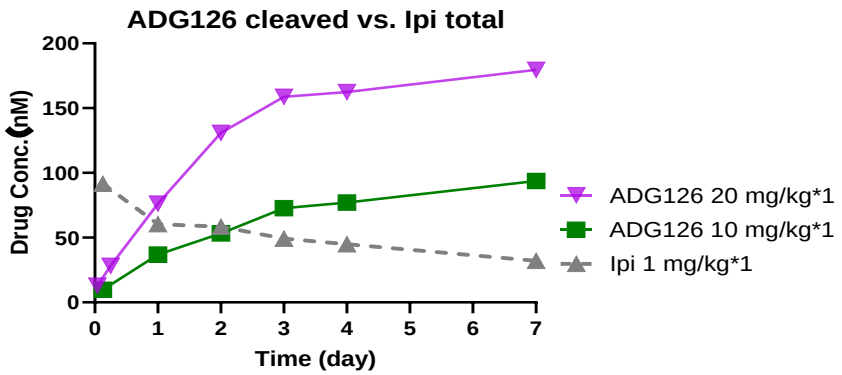


- The same mPBPK general model structure was successfully used for fitting ADG116 and ADG126 clinical data (e.g., ADG126-1001 and ADG116-1003 monotherapy at 10 mg/kg Q3W), with in vivo cleavage included in ADG126 fitting.
- The estimated PK parameters allowed for prediction of tumor and normal leaky 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.

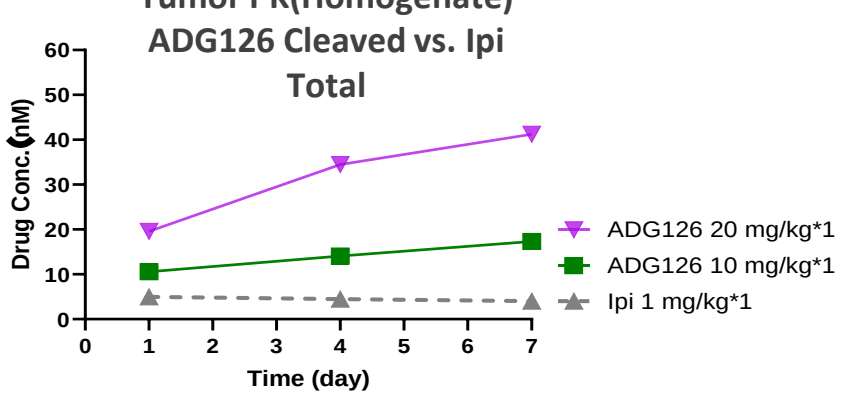
Ipilimumab (Ipi) vs. ADG126 PK Comparison in MC38 Mice

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

A



B



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

- 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.

ADG116 and ADG126 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

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%)

Dose and Subpopulation (N)	ADG116 Monotherapy	ADG126 Monotherapy	
	10 mg/kg Q3W Evaluable (N = 20)	10 mg/kg Q3W Evaluable (N = 16)	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)

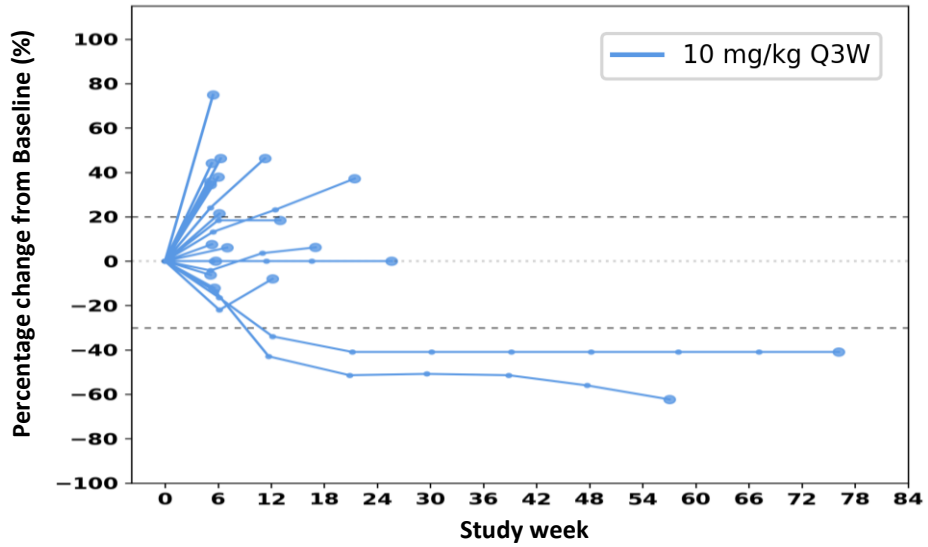
- Dose-dependent safety observed for ADG126 monotherapy, with both 10 and 20 mg/kg Q3W showing significantly better safety than ADG116 at 10 mg/kg Q3W
- Dose-dependent efficacy observed for ADG126 monotherapy, with 20 mg/kg Q3W showing higher DCR and 6-month CBR than ADG116 at 10 mg/kg Q3W

Note: 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).

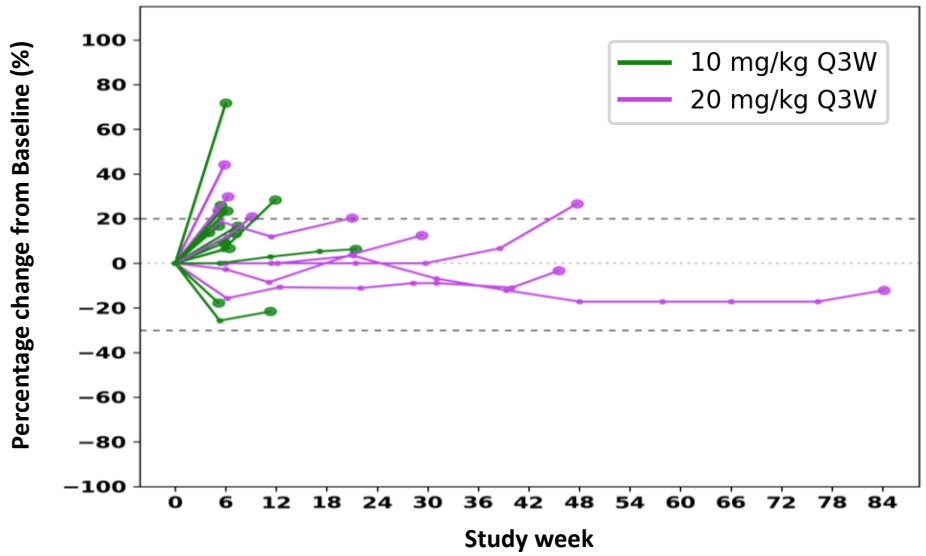
*TEAE leading to drug discontinuation;
** 1 case of G3 Acquired thalassaemia was considered due to the underlying disease rather than the treatment

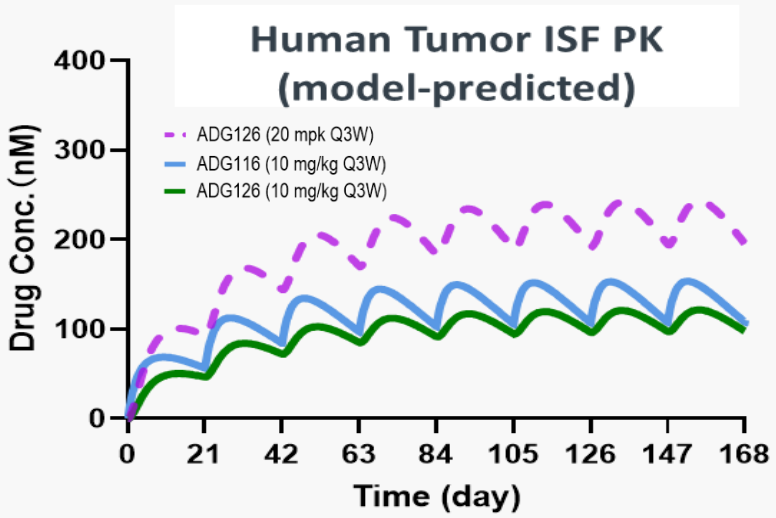
ADG116 and ADG126 Monotherapy Efficacy and Safety

ADG116 Monotherapy



ADG126 Monotherapy





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

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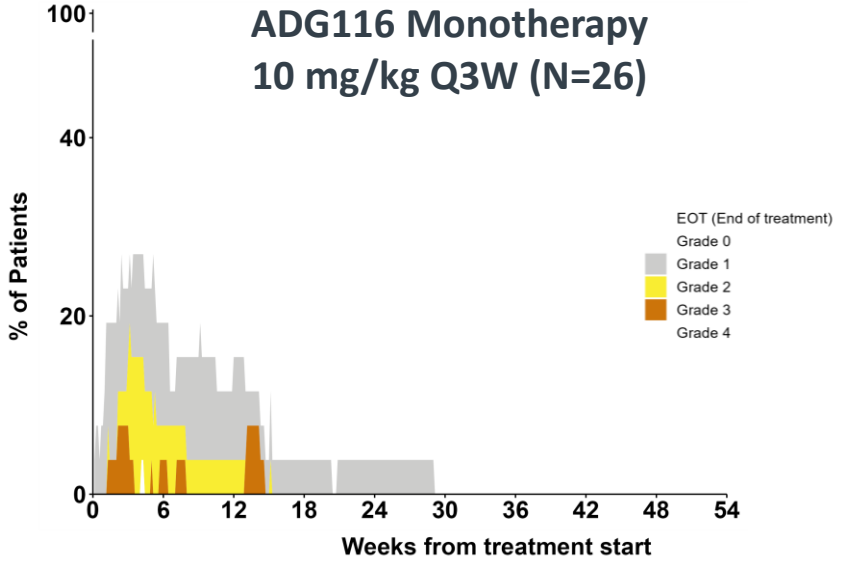
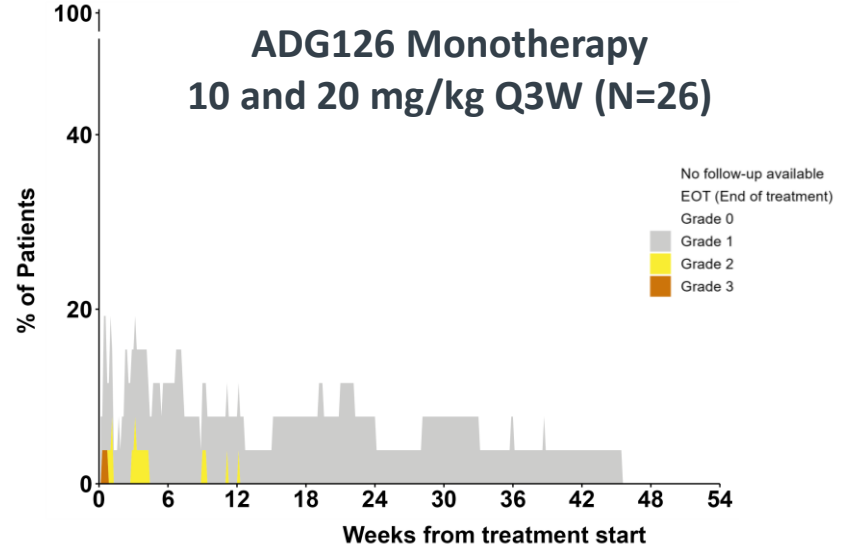
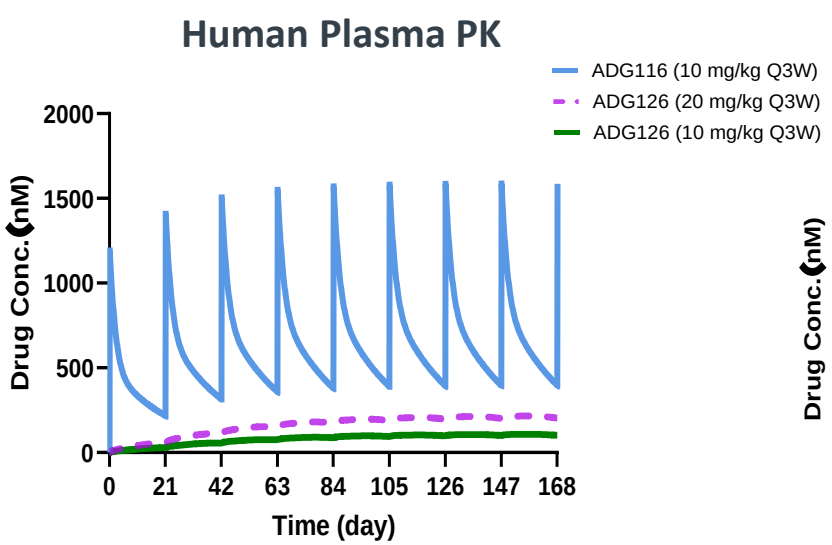
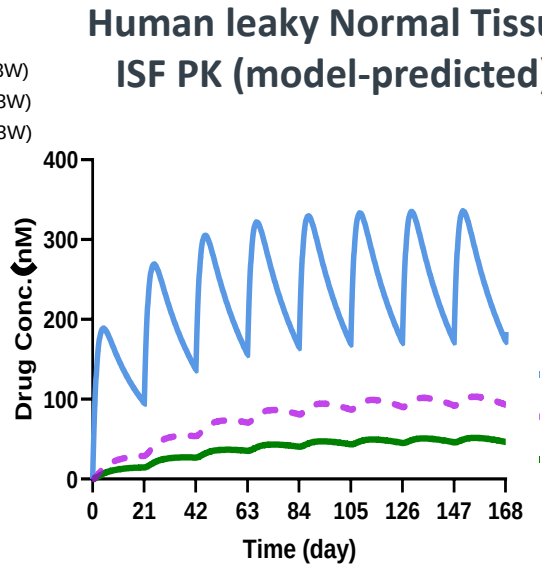
ADG116 and ADG126 Monotherapy Efficacy and Safety



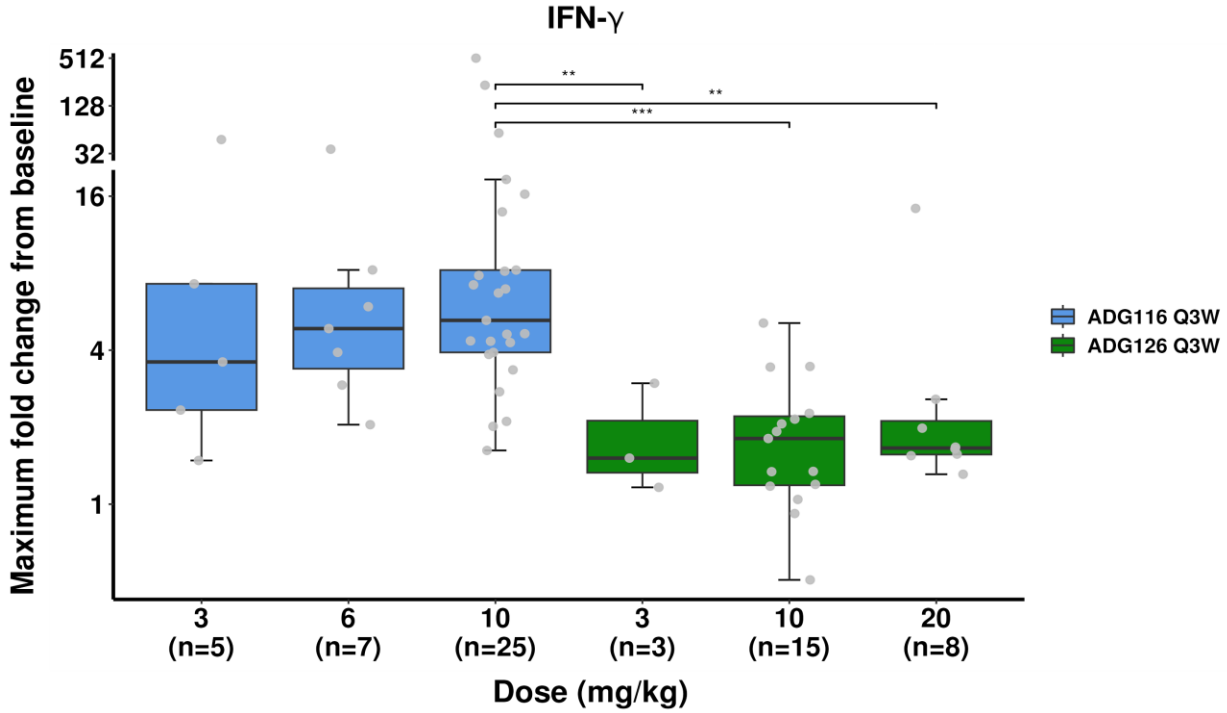






- Predicted $C_{max,SS}$ of cleaved ADG126 at 10 mg/kg Q3W in plasma and leaky normal tissue are more than 10-fold and 5-fold lower than $C_{max,SS}$ of ADG116 (10 mg/kg Q3W), respectively.
- Similarly, predicted $C_{max,SS}$ of cleaved ADG126 at 20 mg/kg Q3W in plasma ~~(B)~~ and leaky normal tissue 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.

ADG116 and ADG126 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.

Phase 1b/2, Multicenter Dose Escalation and Expansion Study of Muzastotug (ADG126, a Masked Anti-CTLA-4 SAFEbody®) in Combination with Pembrolizumab in Advanced/Metastatic MSS CRC

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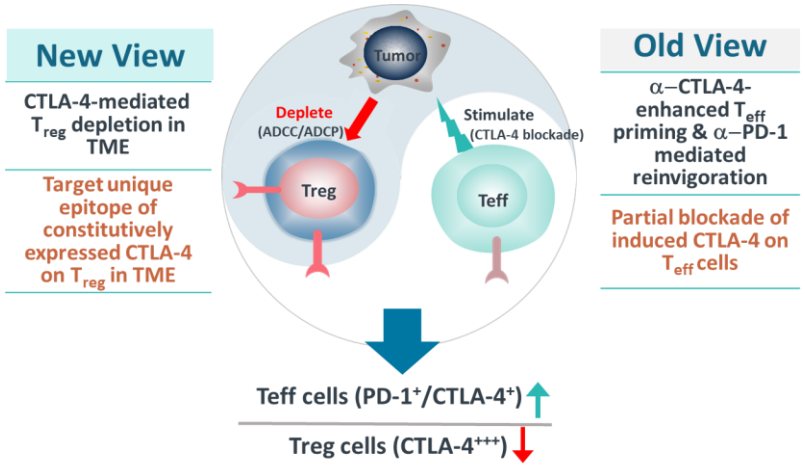
Background

- Approximately > 1.9 million individuals are diagnosed with colorectal cancers (CRC) each year; it is a leading cause of death worldwide and 3rd leading cause of cancer related death in the US. The 5-year overall survival (OS) of advanced/metastatic CRC is merely ~ 15%.[1]
- The majority of mCRC are microsatellite stable (MSS) CRC, which is associated with distinct molecular pathogenesis. Unlike MSI-H CRC, MSS CRC typically does not respond to immune checkpoint inhibitors.[2]



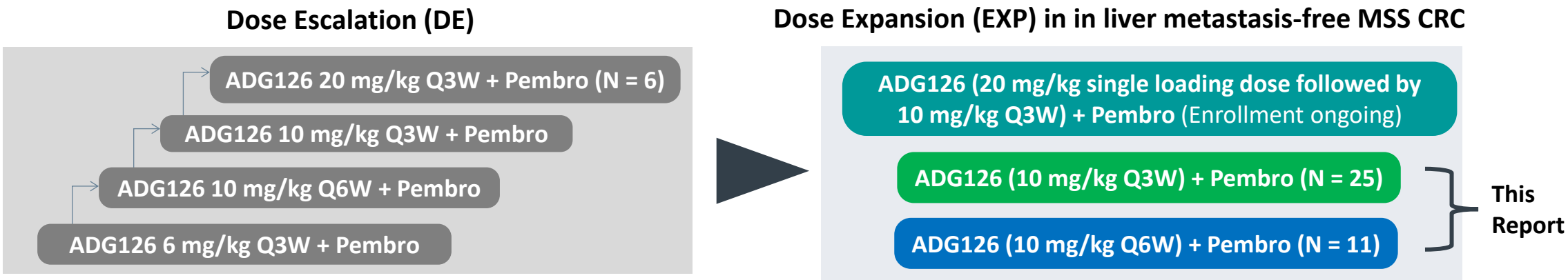
- ✓ ADG126 is a masked anti-CTLA-4 prodrug designed to improve therapeutic index (TI) by targeting a unique epitope of CTLA-4 on T regulatory cells (Treg) in the tumor microenvironment (TME).
- ✓ Over expression of CTLA-4 on Treg in TME helps to recruit ADG126 locally, where masking peptide is cleaved by upregulated enzymes in TME.
- ✓ The cleaved ADG126 in TME has a 10-fold higher ADCC activity over ipilimumab (Ipi) due to an epitope shift, resulting in potent intra-tumoral Treg depletion without Fc engineering.

- Early clinical result of this study (NCT05405595) was reported elsewhere.[3,4] Here we report detailed safety and efficacy data from 10 mg/kg Q3W and Q6W ADG126 + Pembrolizumab (Pembro) treatment of MSS CRC patients who were free of liver metastasis (NLM), and a case study that demonstrates correlation between efficacy, plasma exposure and biomarker modulation.

References: 1, Ferlay J. et al, Global Cancer Observatory: Cancer Today, 2024; 2, Gandini A. et al, Frontiers in Oncology, 2023; 3, Daneng Li et al., Abstract# 434536, ASCO GI Conference, 2024; 4. Daneng Li et al., Abstract# 6055, ESMO Congress 2024.

Methods and Study Design Schema

This is a Phase 1b/2, open-label, multicenter dose escalation and expansion combination study of ADG126 + Pembrolizumab (200 mg, Q3W) in advanced solid tumors. The study design schema for the dose escalation (DE) and dose expansion (EXP) MSS CRC cohorts is shown below:



- The primary endpoints are safety and tolerability, MTD and RP2D
- The secondary endpoints are PK, dose proportionality, immunogenicity of both agents and PK/PD relationship, and early sign of efficacy parameters (ORR, DCR, DOR, PFS and OS) associated with the combination treatment as assessed per RECIST 1.1 and/or iRECIST criteria.

MSS CRC Patients Baseline Characteristics

- As of September 16, 2024, 36 patients with MSS CRC were treated with ADG126 + pembrolizumab IO doublet combination therapy at ADG126 dose of either 10 mg/kg Q6W (n=11) or 10 mg/kg Q3W (n=25).
- Of the 36 patients, 10 were from US and 26 were from the Republic of Korea.
- All 36 patients were liver metastasis-free (NLM), a cancer subtype considered immunologically “cold” tumors.
- 34 of these patients are efficacy evaluable.
- The baseline characteristics of the patients reported here are summarized in table.

Baseline Characteristics	N=36
Age (Years old), Median (range)	59.5 (26-75)
Female n(%)	19 (53%)
Race n(%)	
Asian (n%)	27 (75%)
White n(%)	9 (25%)
ECOG 0/1 n(%)	12 (33%)/24 (67%)
w/ Peritoneal involvement	12 (33%)
Prior line of therapy ≥ 3	12 (33%)
Prior immunotherapy, n(%)	0

Clinical Summary in Advanced Metastatic MSS CRC

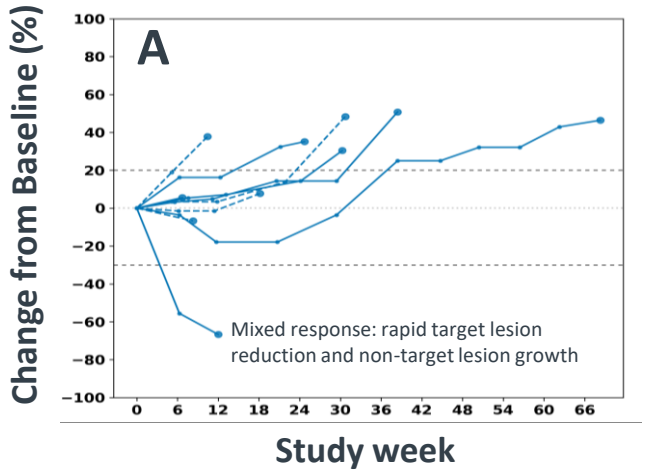
10 mg/kg repeat doses of ADG126 in combination with pembrolizumab shows striking dose dependent clinical efficacy and well-tolerated safety in accordance with plasma cleaved ADG126 concentrations. Data supports ADG126 may be a potential best-in-class anti-CTLA-4 and may be considered as a backbone therapy by itself and in combination with SOCs.

- Confirmed ORR at 10 mg/kg Q3W including tumor shrinkage at 10 mg/kg Q6W; CBR, mPFS and maturing OS compare favorably with historical SOCs and other benchmarks in 3L+ MSS CRC (Fig. 1A & B, Table 3 & 4).

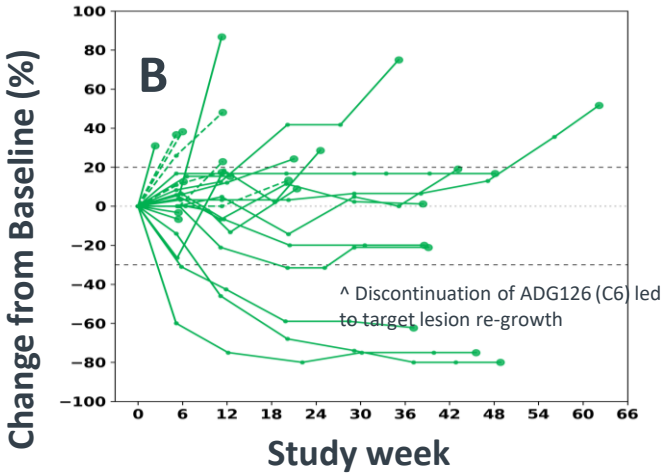
- No long term (>1 year) and late onset G3 TRAEs for ADG126 Q6W vs Q3W with <20% G3 TRAEs (Fig. 1C & D, Table 2) in comparison with other anti-CTLA-4 therapies, and superior safety profile to SOCs (Fig. 2).

ADG126+Pembro Efficacy-Safety-Dose/Exposure Correlation in MSS CRC

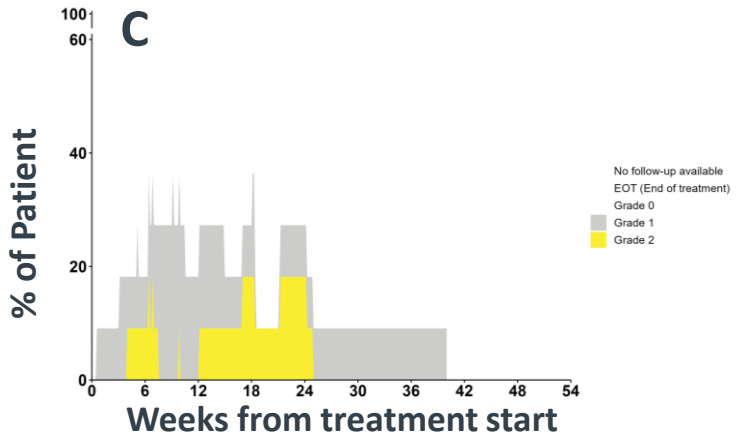
ADG126 10 mg/kg Q6W

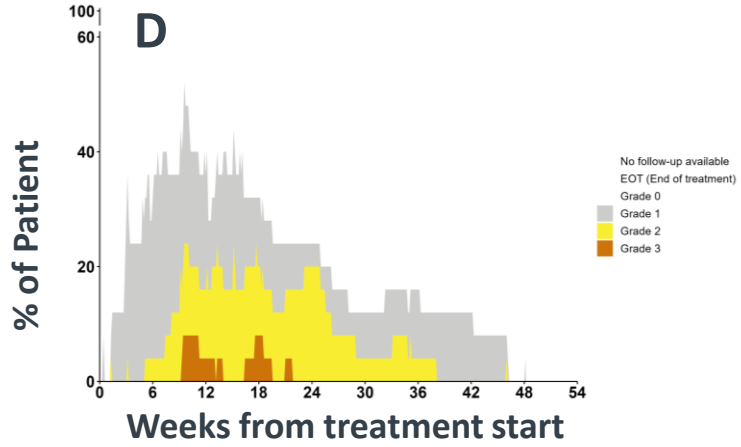


ADG126 10 mg/kg Q3W

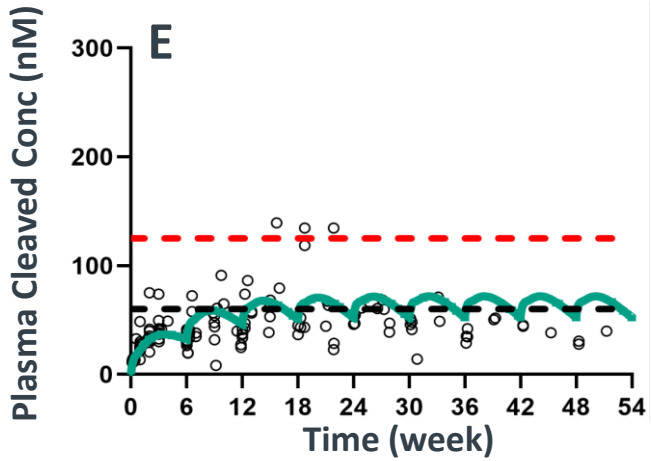


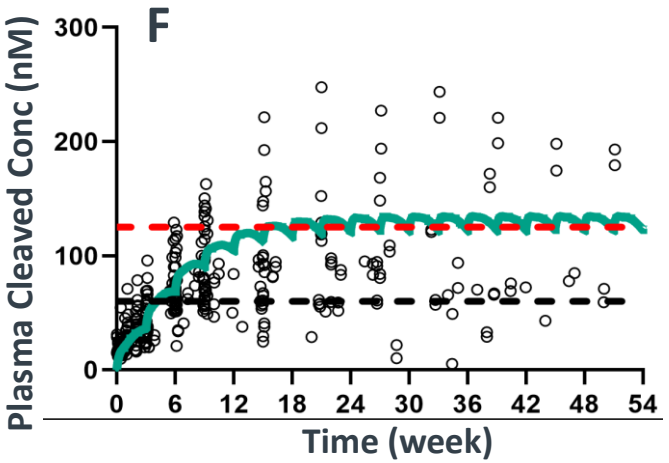
Dotted line: with peritoneal mets;
Solid line: w/o peritoneal mets





The total area corresponds to the overall occurrence of TRAEs during treatment; the different segments(color) highlight the distribution of adverse event grades.





Solid lines: PK simulation using mPBPK population parameters. Black and Red dotted lines: Reference plasma cleaved conc. Of ADG126 associated with SD/PR and G3 TRAE, respectively.[4]

A and B: Spider plots showing target lesion response to ADG126 + Pembro; C and D: Stacked area plots of treatment-related TRAEs illustrating the cumulative incidence and severity of TRAEs over the trial course; E and F: Measured plasma exposure of cleaved ADG126 over treatment time. A, C, E: 10 mg/kg Q6W ADG126; B, D, F: 10 mg/kg Q3W ADG126.

Trial Safety and AE Summary
(MSS CRC Patients treated with ADG126 of 10 mg/kg Q3W or Q6W + Pembrolizumab 200 mg Q3W)

- No dose-limiting toxicities (DLT) or G4/5 TRAEs.
- For 10 mg/kg Q3W, only 16% G3 TRAEs (4/25) was observed with an average follow-up time of 9.8 months, indicating a safe and manageable safety profile.
- Eleven (11) patients developed SAEs (6 are treatment related), however discontinuation rate remains low (6%).
- There was no G3 diarrhea/colitis, pneumonitis or hepatitis for any of the two dose levels of ADG126.
- Three (8%; 3/36) patients received infliximab to treat their diarrhea/colitis.
- Significantly less G3 TRAEs rate and discontinuation rate than those of current SOCs being used in the same patient population.

Summary of Key TRAEs of ADG126 (10 mg/kg Q6W or Q3W) + Pembrolizumab in MSS CRC Patients*

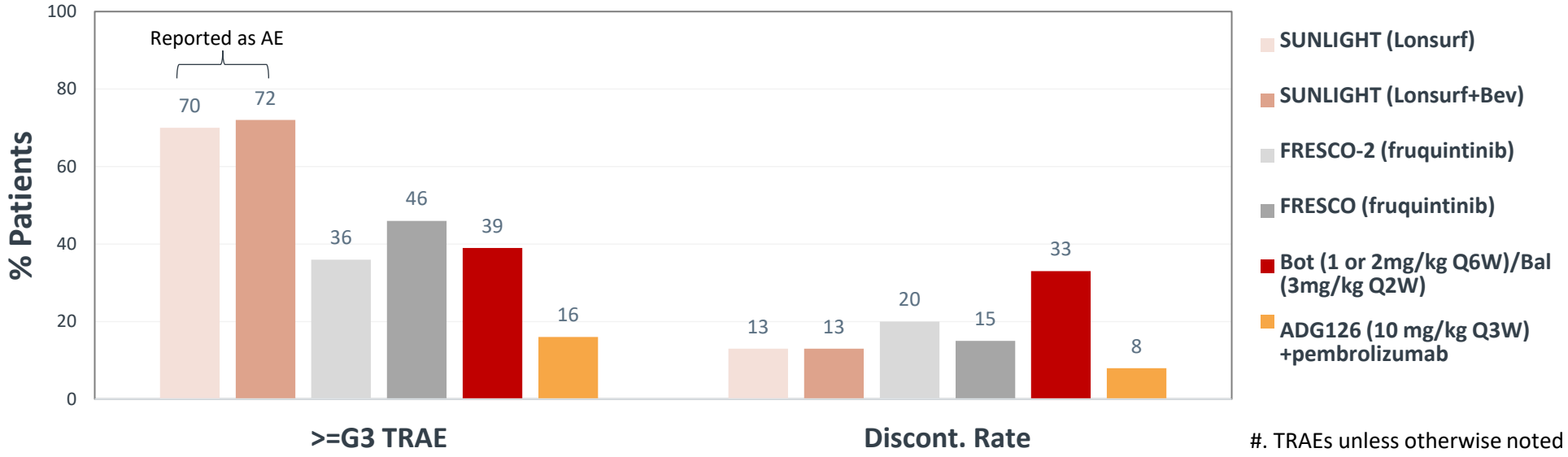
Group	Dose levels (mg/kg)	Safety (TRAEs), n (%)									
		Patients Dosed	Diarrhea/Colitis/ Immune-mediated enterocolitis			Pneumonitis			Hepatitis (Hepatitis/LFT/AST/ALT)			Discontinuation Rate (%)
			G1	G2	≥G3	G1	G2	≥G3	G1	G2	≥G3	
ADG126/ Pembrolizumab	All*	36	1 (3)	5 (14)	**0**	1 (3)	2 (6)	**0**	0	0	**0**	**2 (6)**
	10 mg/kg Q6W	11	0	1 (9)	**0**	1 (9)	0	**0**	0	0	**0**	**0**
	10 mg/kg Q3W	25	1 (4)	4 (16)	**0**	0	2 (8)	**0**	0	0	**0**	**2 (8)**
Botensilimab/ Balstilimab[1]	1 or 2 mg/kg Q6W /3 mg/kg Q2W	101	**23**		**16**	N/A						**33**

* Ten (10) patients were from US and 26 were from the Republic of Korea. N/A: not available

1. Bullock AJ et al., Presentation at ESMO GI 2023.

Highlights of Safety and TRAEs of MSS CRC Patients

≥ G3 TRAEs# Comparison with SOCs and Other Anti-CTLA-4 /Anti-PD-1 in MSS CRC[1-7]



#. TRAEs unless otherwise noted

References: 1.Tabernero J. et al, Poster at ASCO 2024;2.Fernandez M. et al, Poster at ESMO 2024.3.Qin S. et al, Presentation at CSCO 2019. 4.Prager GW. et al, N Engl J Med 2023; 388:1657-67. 5.Arvind Dasari, et al, Lancet 2023; 402: 41–53. 6. Li J. et al, JAMA. 2018; 319:2486-2496. 7. Bullock AJ et al., Presentation at ESMO GI 2023.

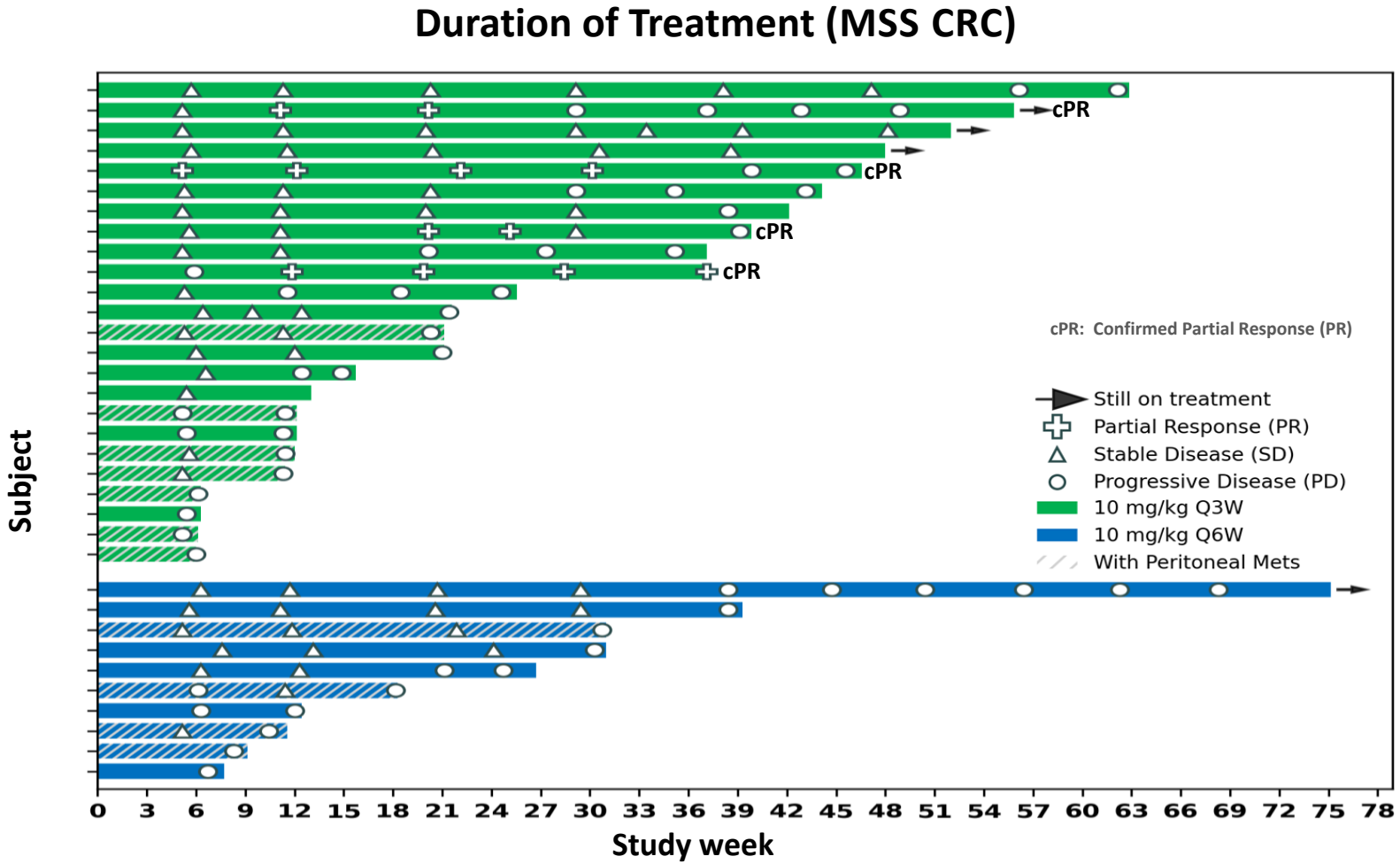
Clinical Efficacy of MSS CRC Patients
(10 mg/kg ADG126/ Pembrolizumab)

Efficacy vs Benchmark SOCs in MSS CRC (NLM)

ADG126 Dose and Subpopulation (N = 34 Efficacy Evaluable Patients)	10 mg/kg Q6W		10 mg/kg Q3W	
	All NLM (n=10)	NLPM (n=6)	All NLM (n=24)	NLPM (n=17)
ORR, % (95% CI)	0^ (0-31)	0^ (0-46)	**17** (5-37)	**24** (7-50)
BoR, N (%)				
PR	0	0	**4 (17)**	**4 (24)**
SD	7 (70)	4 (67)	14 (58)	11 (65)
DCR (CR+PR+SD), %, (95% CI)	**70** (35-93)	**67** (22-96)	**75** (53-90)	**88** (64-99)
6-month CBR, %, (95% CI)	20 (3-56)	**33** (4-78)	**33** (16-55)	**47** (23-72)
Median PFS, months (95%CI)	**4.5** (1.4-7.1)	**5.9** (1.4-NA)	**4.7** (2.6-8.5)	**8.5** (2.9-9.2)
Median Duration of Drug Exposure (Days) of ADG126	88.5	108.5	127	223

^ Mixed response: rapid target lesion reduction and non-target lesion growth

Clinical Efficacy of MSS CRC Patients
(10 mg/kg ADG126/ Pembrolizumab)



Clinical Efficacy of MSS CRC Patients
(10 mg/kg ADG126/ Pembrolizumab)

Key Efficacy Parameters Summary

Efficacy of SOCs for late stage MSS CRC*	ORR(%)	mPFS (mon)	mOS (mon)
SUNLIGHT: LONSURF® + Bevacizumab	7.7	8	Not Estimable
SUNLIGHT: LONSURF®	3.4	3.8	10.9
FRESCO-2: Fruquintinib	4.1	4.5	12.1
FRESCO: Fruquintinib	4.3	3.9	10.8
ADG126 (10 mg/kg Q3W) + Pembrolizumab	**17**	**4.7**	**Not Reached**
	24**	**8.5****	

* All are without liver metastasis unless specified; **. No liver and no peritoneal metastasis. Source information: see References next to Figure 2.

Case Study: Confirmed Partial Response in MSS CRC Patient w/out Liver Metastases

Tumor Type: Female, 64 years old, MSS CRC (liver metastasis-free)

Prior Therapies: 2 lines of prior therapies:

- Bevacizumab + Oxaliplatin + Leucovorin + 5-Fluorouracil
- Anti-TGF-β + Bevacizumab + Irinotecan HCL + 5-Fluorouracil + Leucovorin

Baseline Total Target Lesion Size: 50 mm

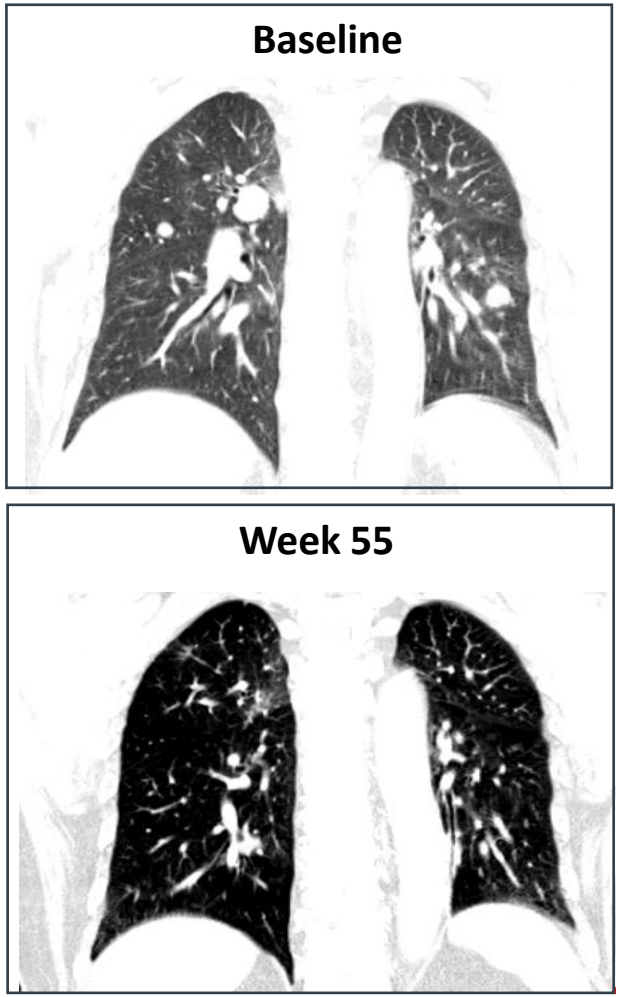
Dose Regimen: ADG126 10 mg/kg Q3W+Pembro 200 mg Q3W initiated Aug 2023.

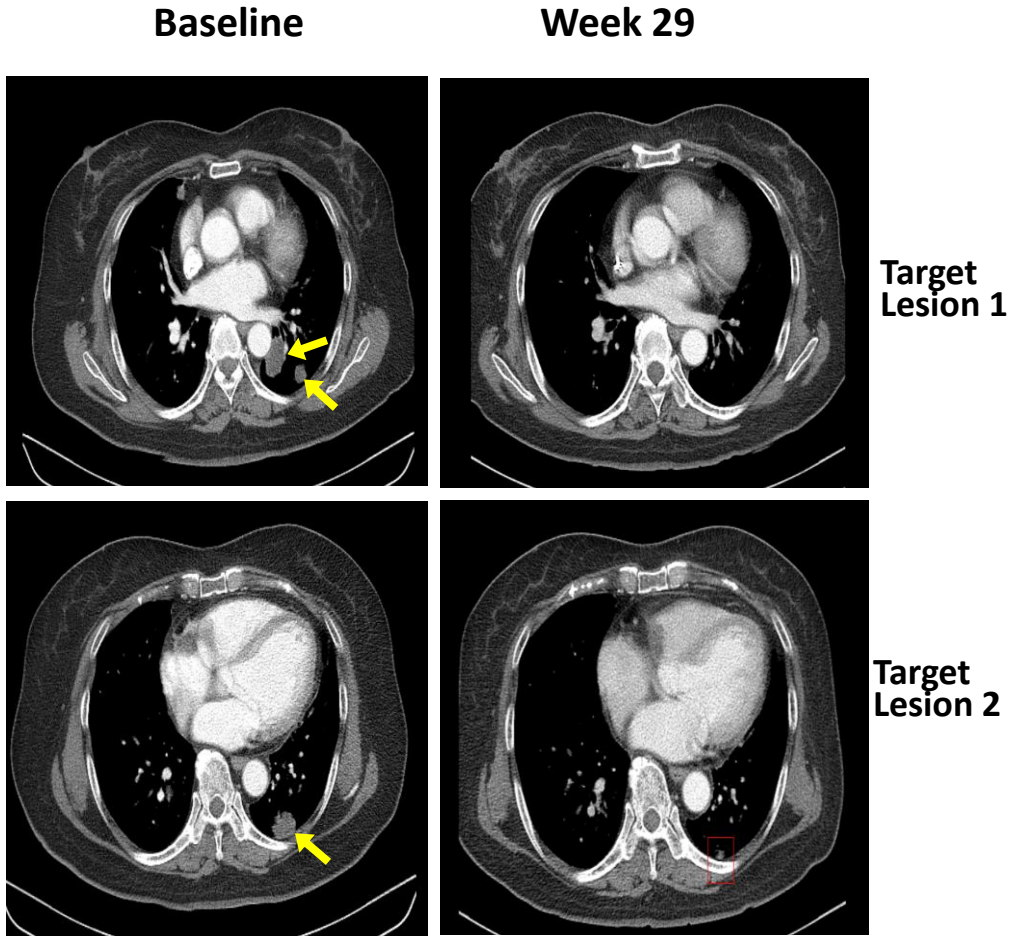
Efficacy: confirmed PR; 80% target lesion reduction at last assessment

Safety Profile and management:

- Developed TRAEs of septic shock, hyperglycaemia, nephrotic syndrome and thrombocytopenia 5 cycles into treatment, resulting in dose interruption
- Treatment resumed 6 weeks later: pembrolizumab monotherapy for 6 cycles followed by 10 mg/kg Q6W ADG126+Pembro combo (ongoing)
- Target lesions decreased by 80%, CEA reduced by nearly 100% vs. baseline

Case Study: PR in MSS CRC Demonstrates Significant Tumor Reduction at 10 mg/kg Q3W Dosing in Combination with Pembrolizumab

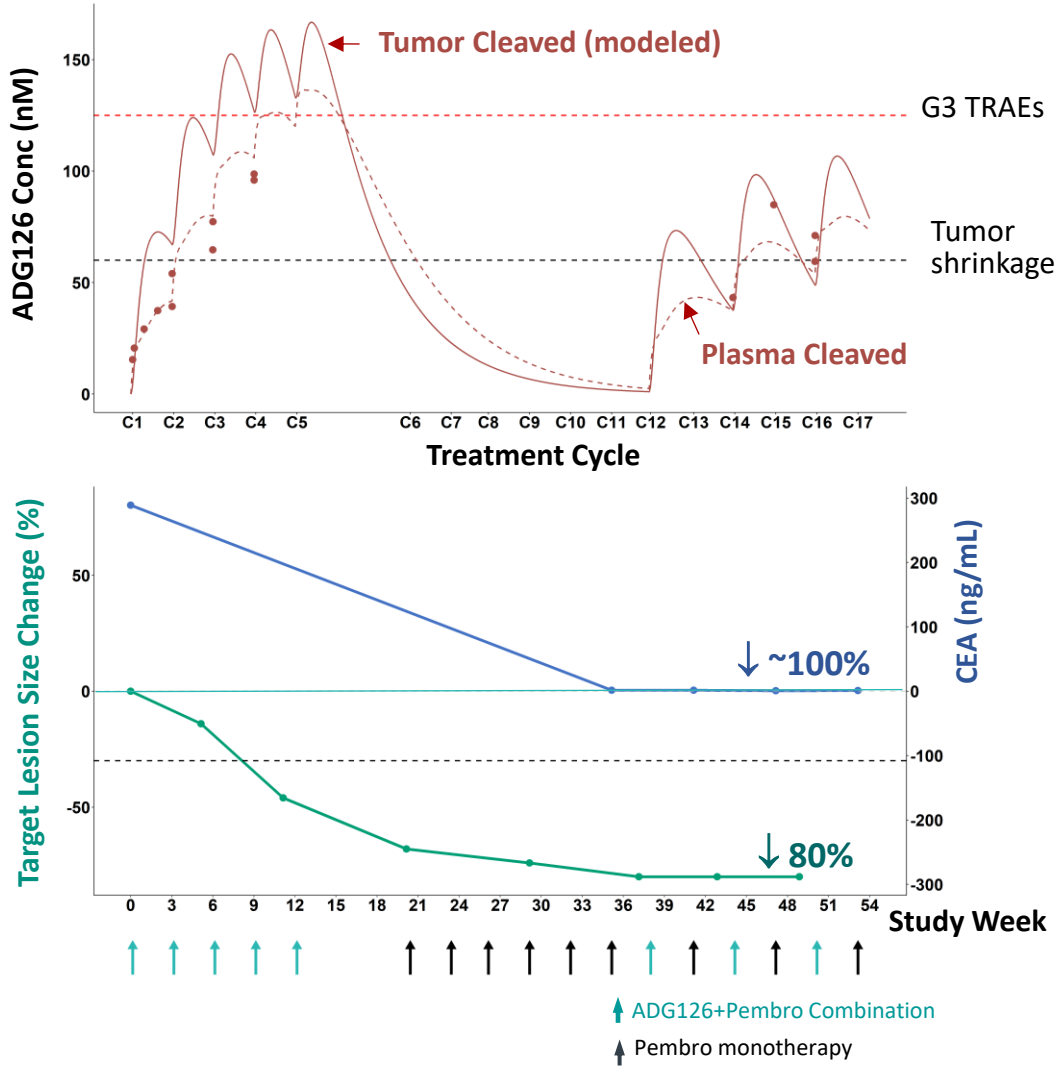




Images curtesy of Dr. Sun Young Kim

Case Study: Individualized PK & Biomarker Data Shows Strong Correlation of Tumor Response with CEA Levels

Correlation between Tumor Shrinkage, CEA and Plasma Exposure



- Appropriate AE management and dose modification enabled the patient to stay with the study to-date.
- Patient was successfully rechallenged with combo without recurrent toxicities while receiving durable clinical benefits for over 12 months.

Conclusions

- The therapeutic index of ADG126+pembrolizumab supports further clinical testing in MSS CRC patient free of liver metastasis, as well as exploration of the utility of the IO doublet in combination with SOCs and other modalities in broader MSS CRC, such as those with liver metastasis, and in additional cancer types with unmet medical needs.

- Further investigation of ADG126+pembrolizumab IO doublet in MSS CRC and in combination with SOC studies are planned.

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