

ADG126 SAFEbody[®] :
Targeting CTLA-4+ Tregs to
Overcome MSS CRC Resistance

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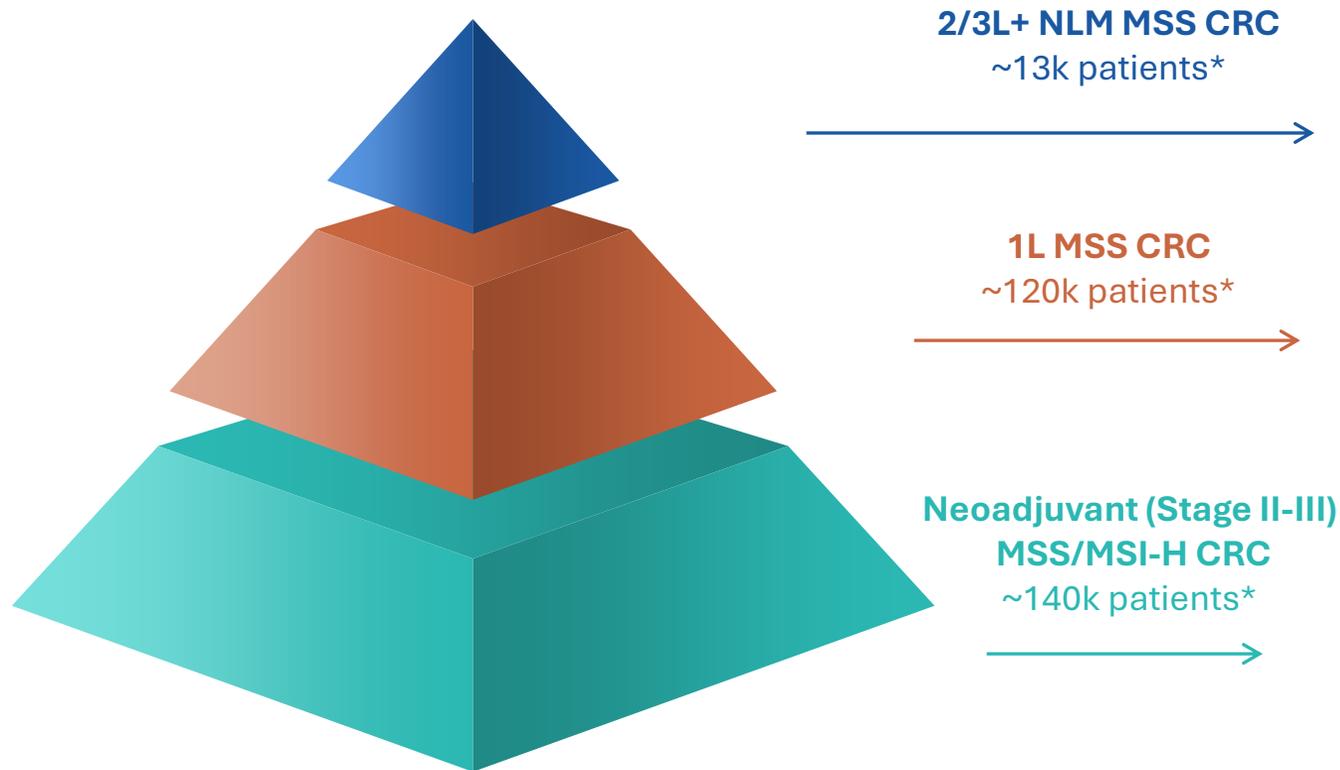
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MSS CRC is a Major Unmet Medical Need: Current Immunotherapy is Ineffective from Early to Late Stage

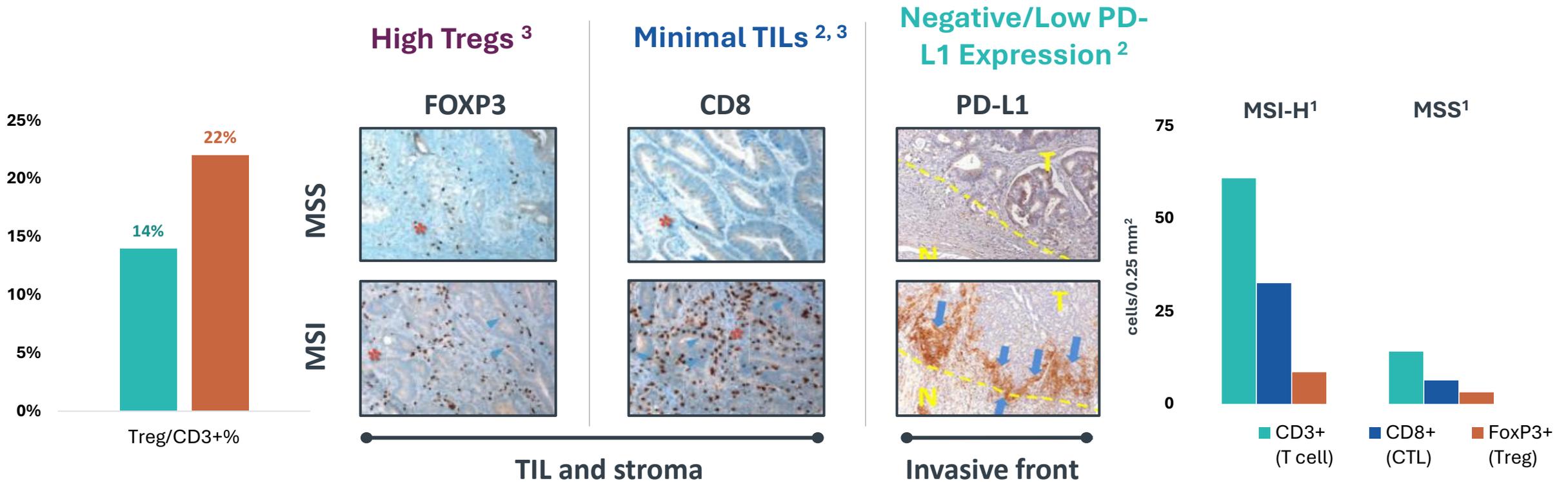
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3L+ MSS CRC Without Liver Metastases is a Substantial Initial Opportunity



- Patients with no liver metastases (NLM) show responses to IO therapy, representing ~30% of MSS mCRC patients
- Several companies are conducting registration trials in 3L+ MSS mCRC NLM
- Thanks to its safety profile, ADG126/pembrolizumab is being studied in neoadjuvant settings (NCT06846268), and in combination with the current standard of care (e.g., TAS-102 and bevacizumab)

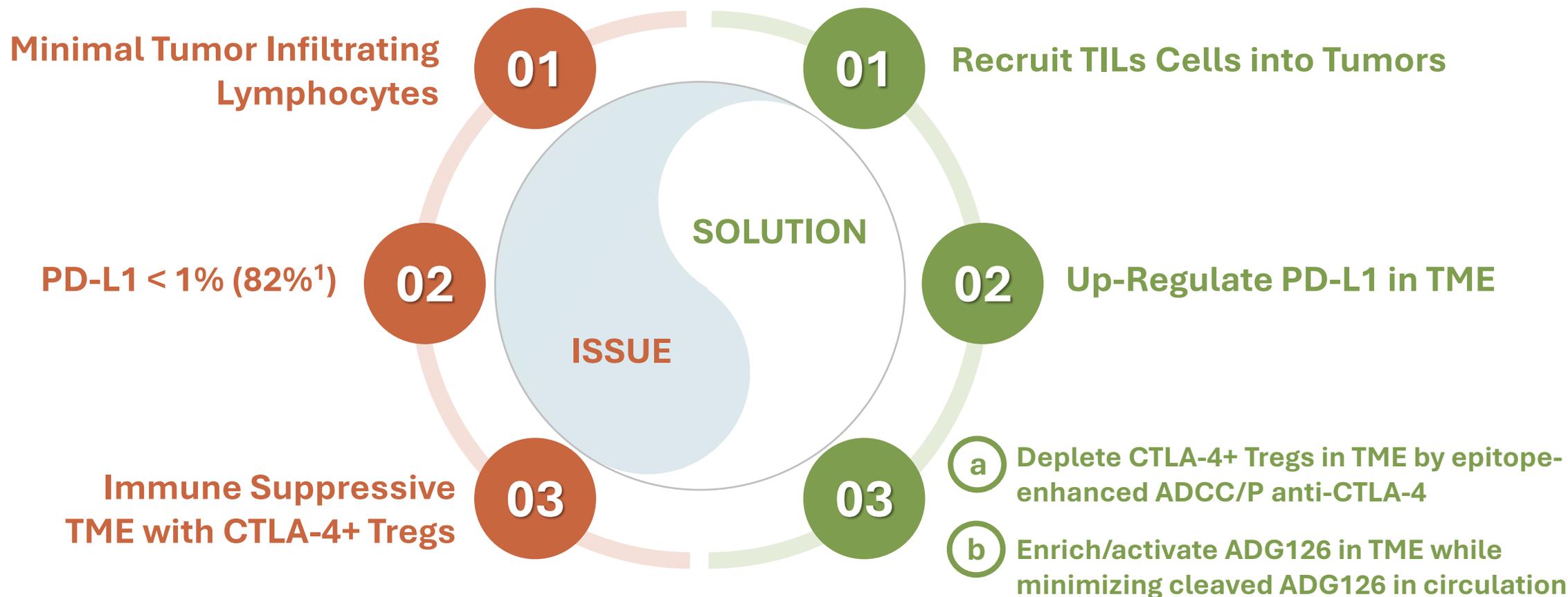
Immune-Suppressive Tumor Microenvironment in Metastatic MSS versus MSI-H mCRC: Treg, TILs, and PD-L1 Expression



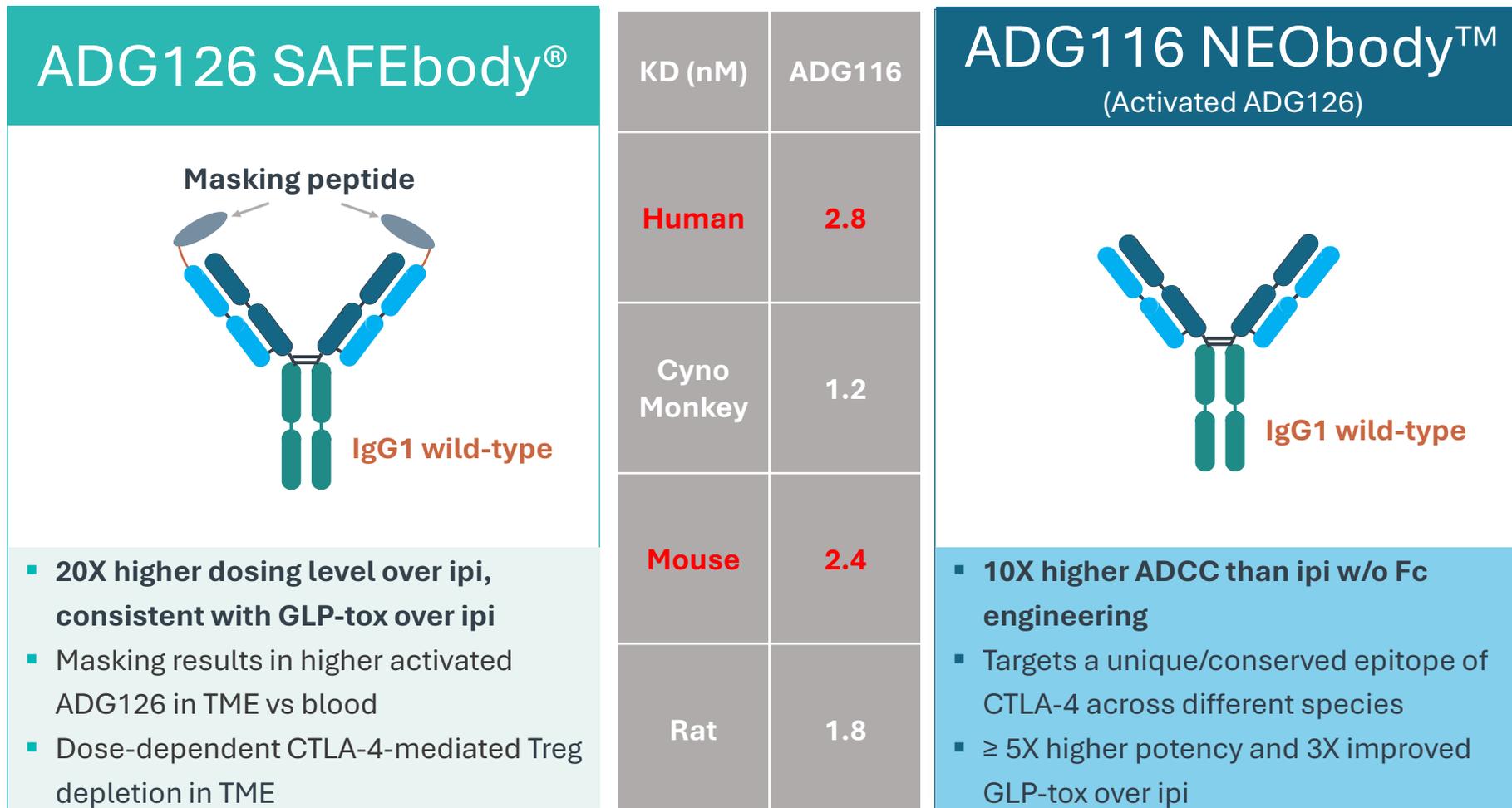
Source from: 1. S Michel et al. High density of FOXP3-positive T cells infiltrating colorectal cancers with microsatellite instability. British Journal of Cancer 2008; 99, 1867-1873. DOI: 10.1038/sj.bjc.6604756
 2. Le et al. PD-1 blockade in tumors with mismatch repair deficiency. N Engl J Med 2015; 372:2509-20. DOI: 10.1056/NEJMoa1500596
 3. NJ Llosa et al. The Vigorous Immune Microenvironment of Microsatellite Instable Colon Cancer Is Balanced by Multiple Counter-Inhibitory Checkpoints. Cancer Discov 2014; 5(1) 43-51. DOI: 10.1158/2159-8290

Targeting Intra-Tumoral CTLA-4+ Treg Depletion for Immune-Resistant MSS mCRC with Masked Anti-CTLA-4 SAFEbody, ADG126

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Dynamic Precision Library Technology Widens Therapeutic Window for Two Cross-Reactive Anti-CTLA-4 Antibodies



ADG126 Has a Higher Safety Margin Over ADG116 and Ipilimumab in Cyno Tox Study

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Cyno Tox Study	BMS CytomX			Adagene	
	Ipilimumab ^{\$}	Ipilimumab Probody (BMS-986249) ^{\$}	ADCC-enhanced Ipilimumab Probody (BMS-986288) ^{\$}	NEObody ADG116	SAFEbody ADG126
Highest Non-severely Toxic Dose (QW, 1 month)	10 mg/kg	50 mg/kg	10 mg/kg	30 mg/kg	200 mg/kg
RP2D*	1 mg/kg Q6W + Nivo Repeat dosing	/	/	3 mg/kg Q3/6W + PD-1	10 or 20 mg/kg Q6W + Pembro

Immunotherapy in Comparison with the Current SOC for 3L+ MSS CRC

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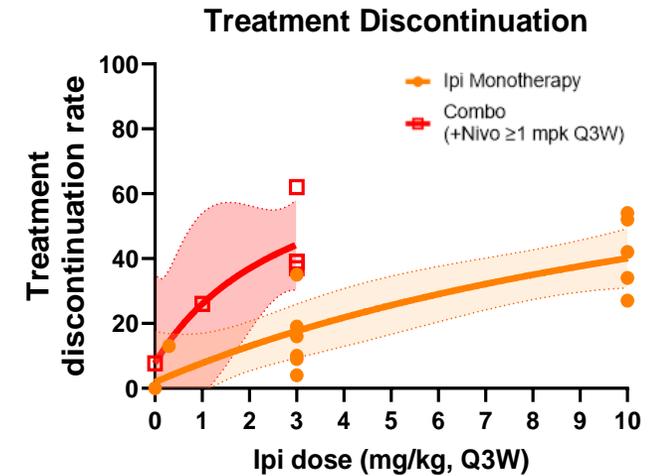
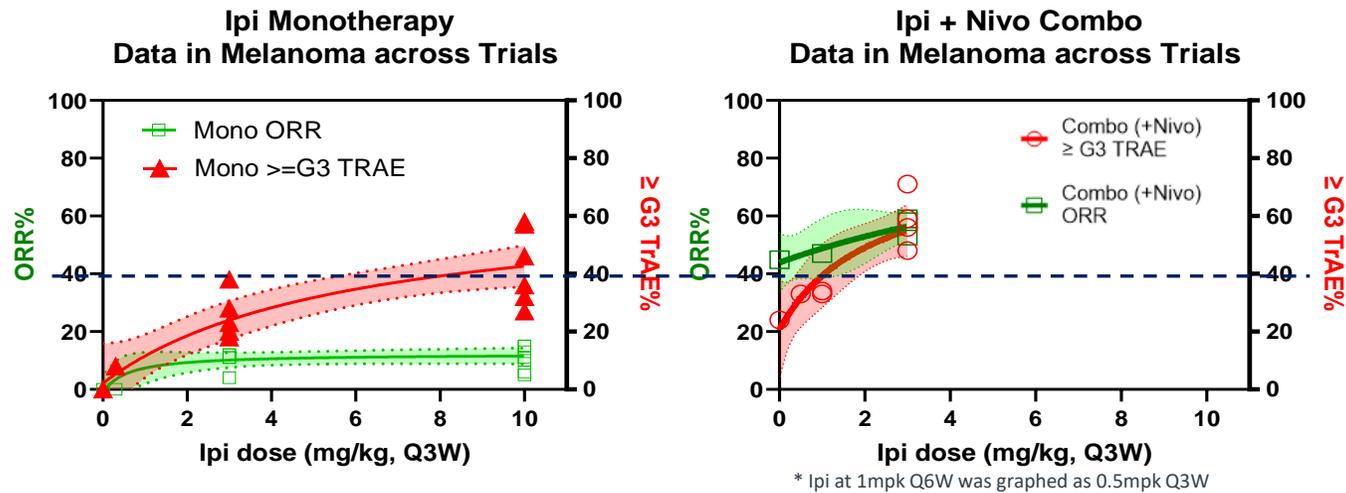
Compounds	Sunlight TAS102 plus Avastin	Fruquintinib		ADG126 Dose Level + Pembro 200mg Q3W		
		w/o Liver mets	with Liver mets	10 mg/kg Q6W	10 mg/kg Q3W	20 mg/kg x1 +10 mg/kg Q3W
ORR (%)	6.1	4.3	4.9	0 ^{*a}	23 ^{*b}	33 ^{*c}
≥G3 TRAEs	72%	36-46%		0	20%	42%
Discontinuation Rate	13%	15-20%		0	10%	0



Source from: Josep Taberero et al. 2023 ASCO Gastrointestinal; Gerald W. Prager et al. N Engl J Med 2023 May 04;388(18); Shukui Qin et al. 2019 CSCO; Jin Li et al. JAMA. 2018;319(24):2486-2496;
 * NLPM group; a, One patient with target lesion assessed as “PR”, overall assessment as “PD” due to new lesion. b. Including one unconfirmed PR (10 mg/kg Q3W). c. all PRs are confirmed.

#IO360Summit

The Addition of Ipilimumab to Nivolumab Resulted in a Disproportionate Increase in Toxicity with Limited Improvement in Response Rates



- ✓ Efficacy outcomes with ipilimumab were significantly improved when combined with anti-PD-1 (nivolumab).
- ✓ However, the incidence of severe adverse events leading to discontinuations also rose substantially, even with a threefold reduction in the dose of ipilimumab

- ✓ Combination tox is similar at >3-fold lower Ipi dose to mono
- ✓ The discontinuation rate remains low for EXP cohorts (6%) for **ADG126 + Pembro** in MSS CRC (01/15/2025 data cut across all studied cohorts).

Combining Efficacy and Safety Data with PK Modeling Drives Dosing Regimen Design – Reaching Efficacy Faster Without Sacrificing Safety

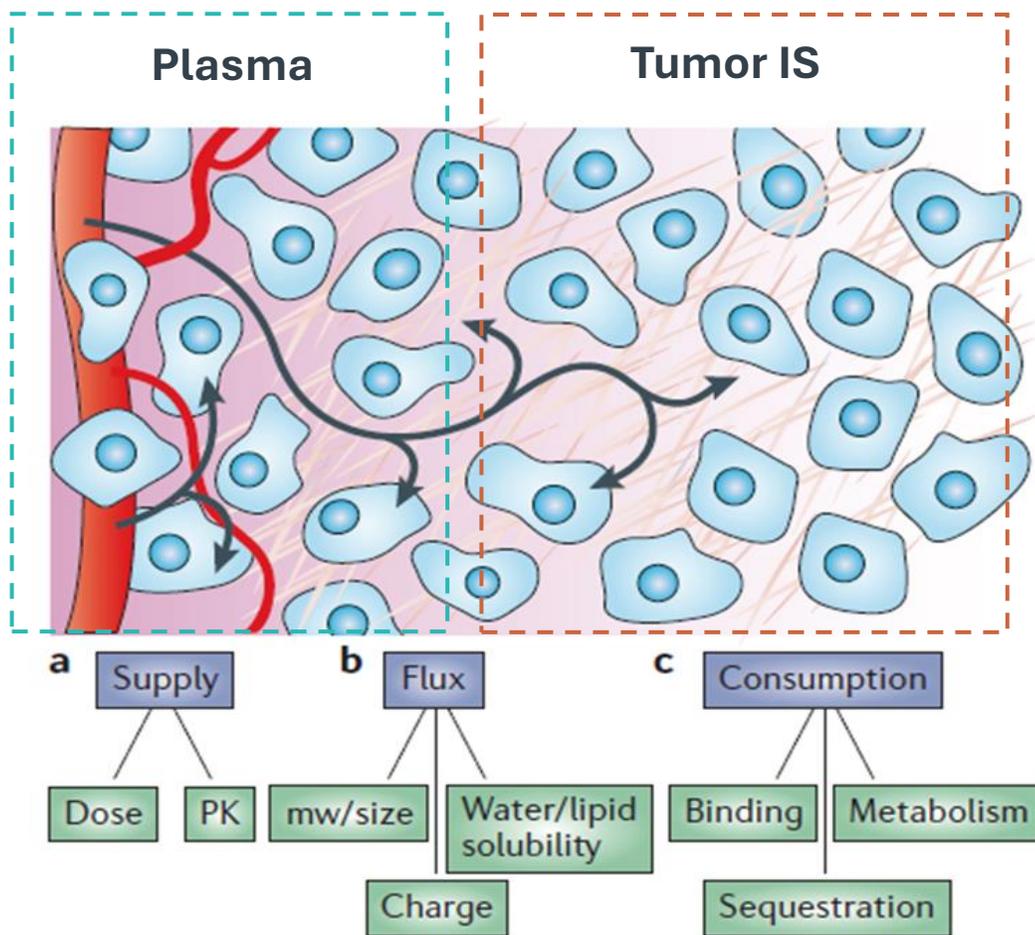
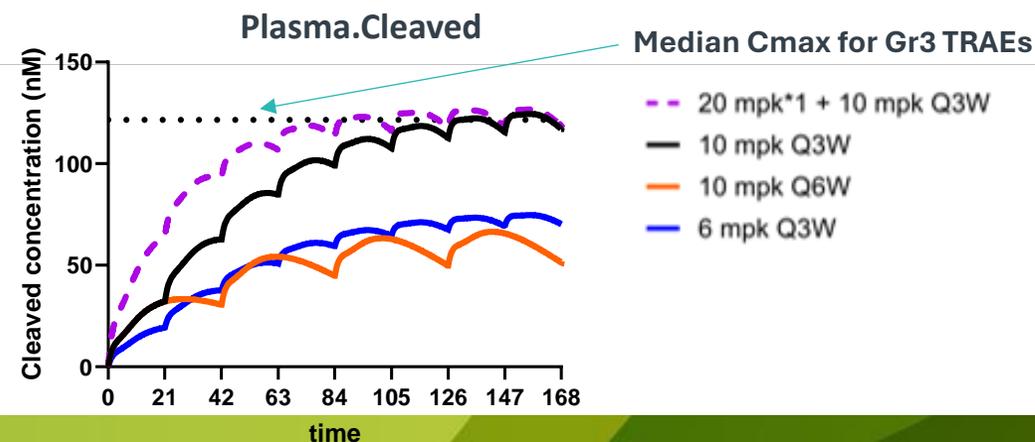
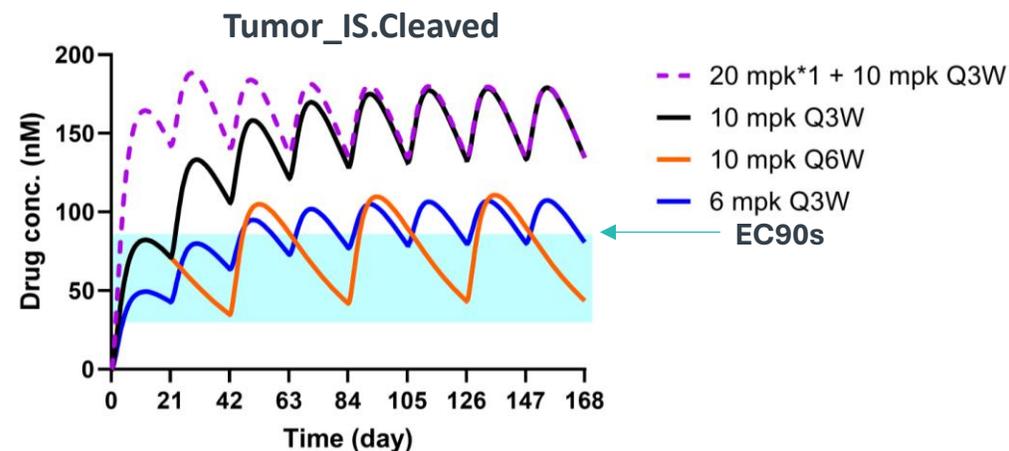


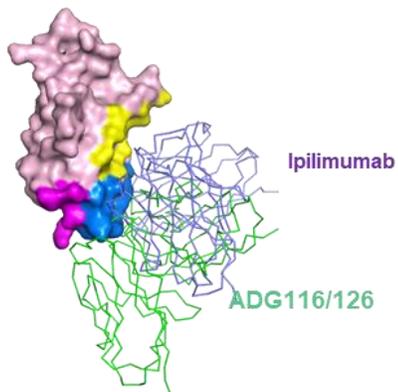
Figure 2 | Drug distribution in tissue.

The percentage of patients who reach the target concentration at a given dosing regimen

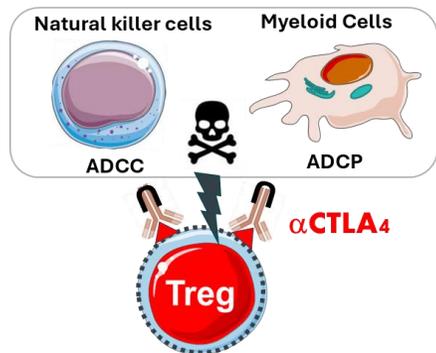
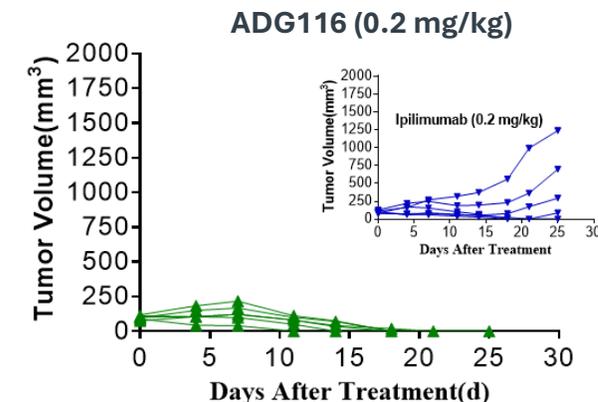
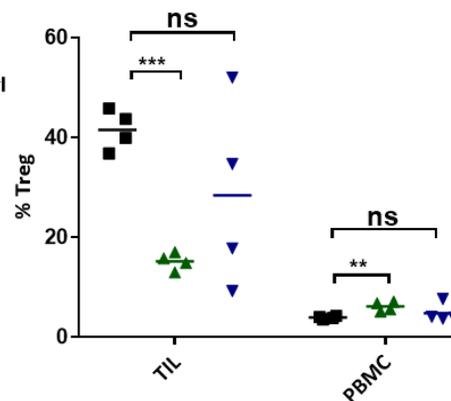
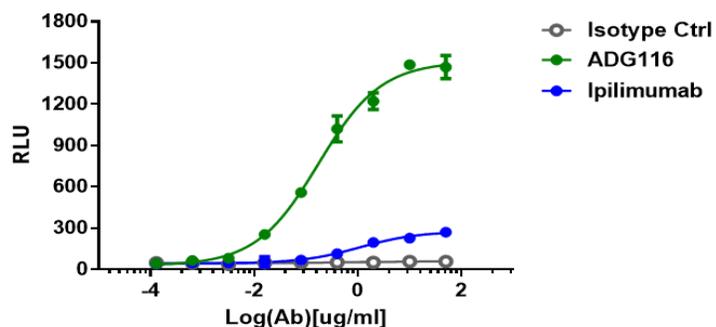


Epitope-Enhanced ADCC/P for Treg Depletion in TME

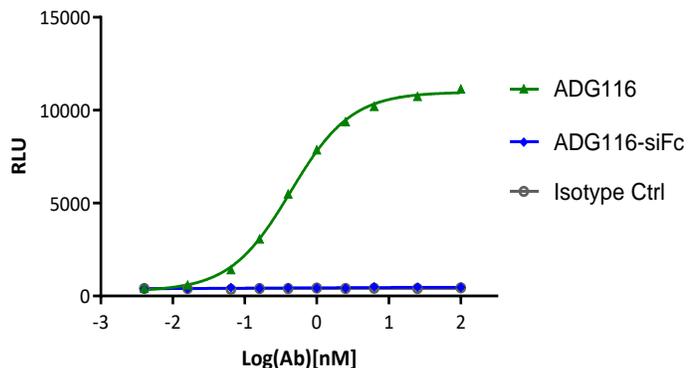
CTLA-4+ Treg depletion via epitope-enhanced ADCC/P of ADG116 vs ipilimumab



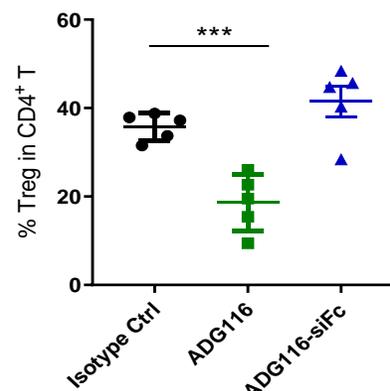
Enhanced ADCC Activity by ADG116



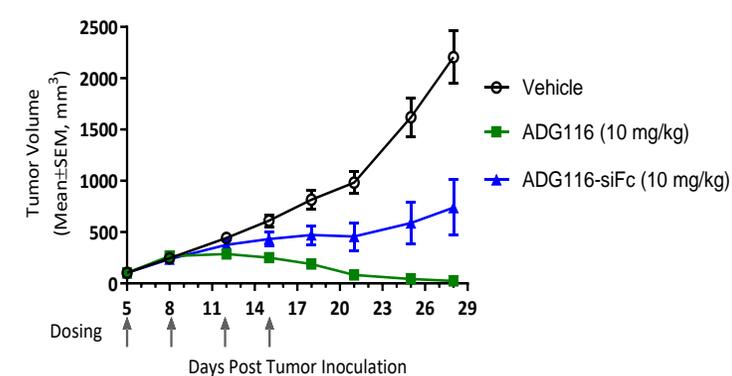
ADCC Reporter Cell Signaling Activity



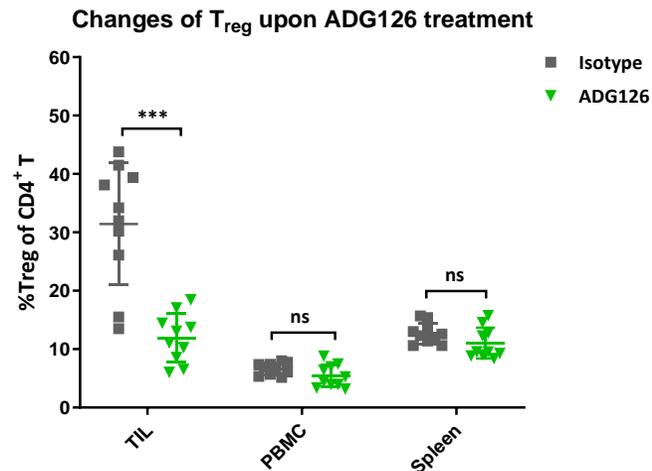
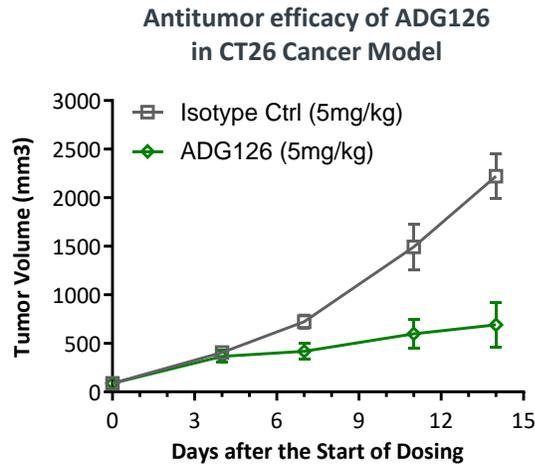
Changes of Intramural Treg



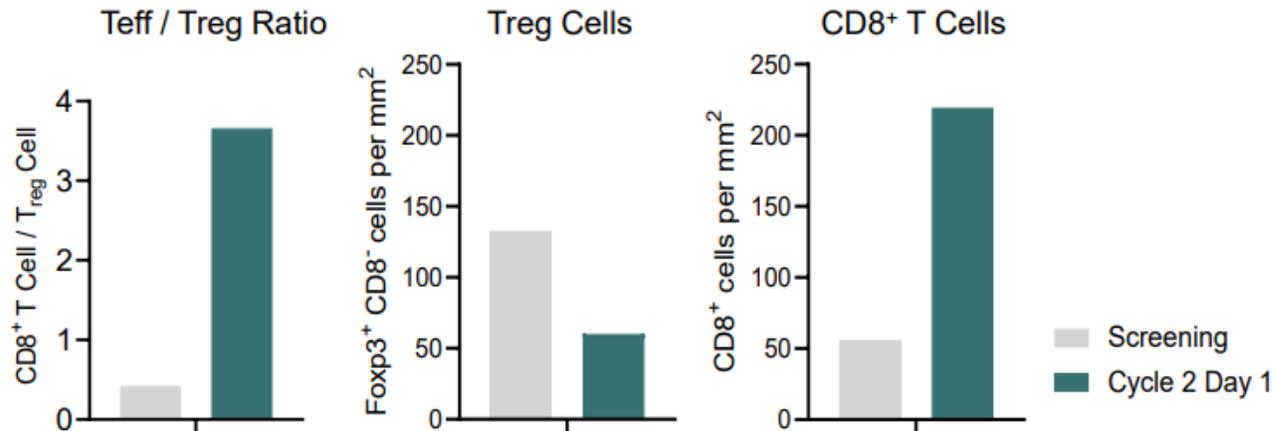
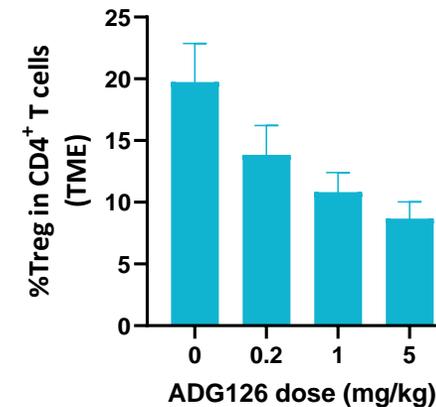
MC38 Colon Cancer Model



ADG126 SAFEbody Shows Robust Anti-Tumor Efficacy and CTLA-4+ Treg Depletion in TME via Strong ADCC/P in both Mouse and Human



Treg depletion dose response upon ADG126 treatment



- An HCC patient progressed on 1L Atezolizumab + Bevacizumab and 2L Lenvatinib, ~21-cm tumor size
- Stable disease for ~6 months with no TRAEs by ADG126 monotherapy @10 mg/kg Q3W
- Increased Teff / Treg, with Treg depletion and increased CD8+ T cells in paired tumor biopsies

Update of Phase 1b/2 Study of Muzastotug (ADG126, an Anti-CTLA-4 SAFEbody[®]) in Combination with Pembrolizumab in Advanced/Metastatic MSS CRC

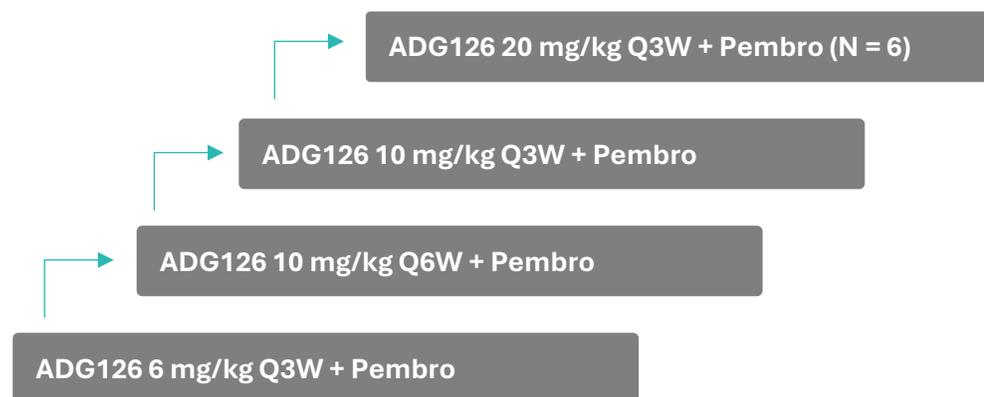
Daneng Li^{1*}, Sun Young Kim^{2*}, Hee Kyung Kim³, Sunil Sharma⁴, Sang Joon Shin⁵, Jeeyun Lee⁶, Sae Won Han⁷, Marwan Fakhri¹, Luke Chung⁸, Yan Li⁸, Ping Xiao⁸, Songmao Zheng⁸, Kristine She⁸, Dana Hu-Lowe⁸, Jiangchun Xu⁸, Stanley Frankel⁸, Michael J. Chisamore⁹, Peter Luo⁸, Jiping Zha⁸, Manish R. Patel¹⁰

Methods and Study Design Schema: ADG126-P001 Study

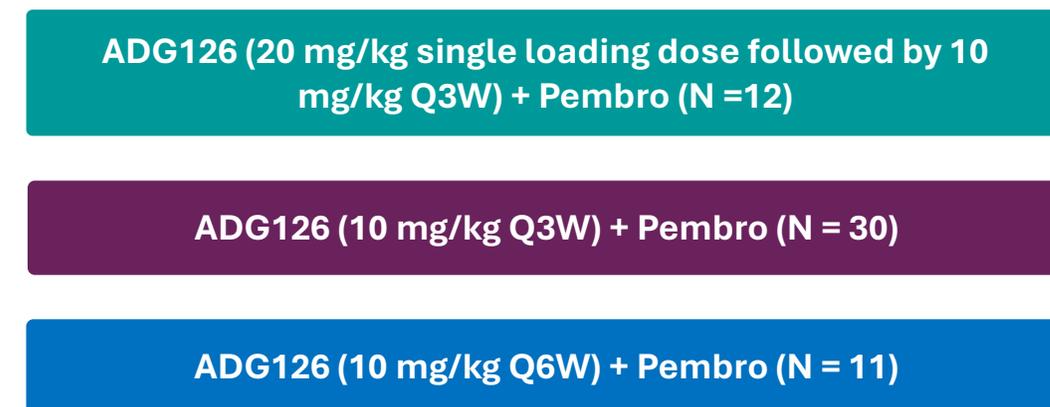
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This is a Phase 1b/2, open-label, multicenter dose escalation and expansion combination study of ADG126 + Pembrolizumab (200 mg, Q3W) in advanced solid tumors. The study design schema for the dose escalation (DE) and dose expansion (EXP) MSS CRC cohorts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

Dose Escalation (DE)



Dose Expansion (EXP) in liver metastasis-free MSS CRC

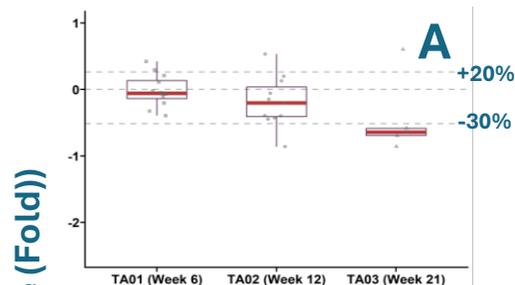


The primary endpoints are safety and tolerability, MTD and RP2D.

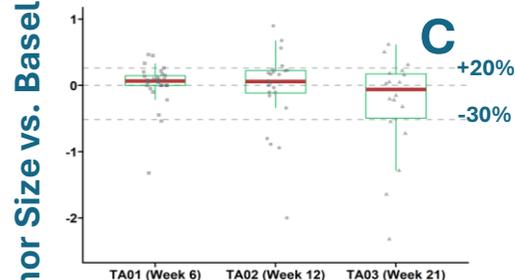
The secondary endpoints are PK, dose proportionality, immunogenicity of both agents and PK/PD relationship, as well as early sign of antitumor activity parameters (ORR, DCR, DOR, PFS and OS) associated with the ADG126/Pembro combination as assessed per RECIST 1.1 and/or iRECIST criteria.

Dose-dependent Efficacy with Manageable Safety for the ADG126/Pembro Combo in MSS CRC with No Liver Metastasis

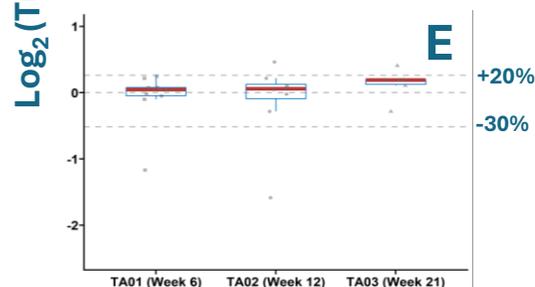
ADG126
20 mg/kg x1
+10 mg/kg Q3W
+ Pembro Q3W
(N=12)



ADG126
10mg/kg Q3W
+ Pembro Q3W
(N=30, 29 EE)

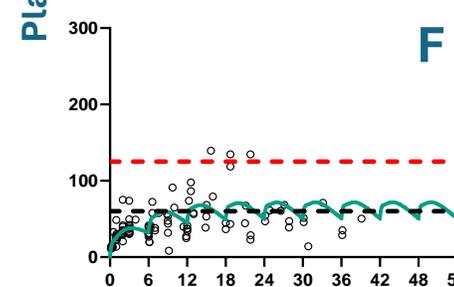
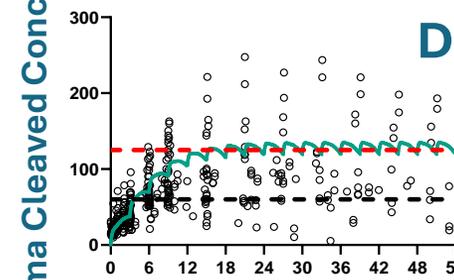
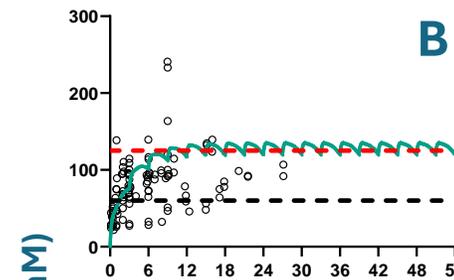


ADG126
10 mg/kg Q6W
+Pembro Q3W
(N=11, 10 EE)



Box plots of first 3 tumor assessments (TA) across different dose levels

Tumor Assessments



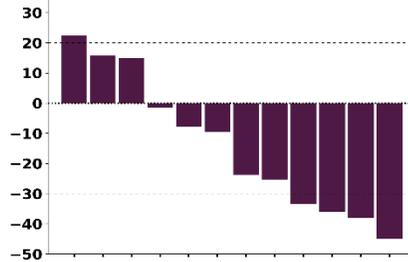
Treatment Time (Weeks)

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.

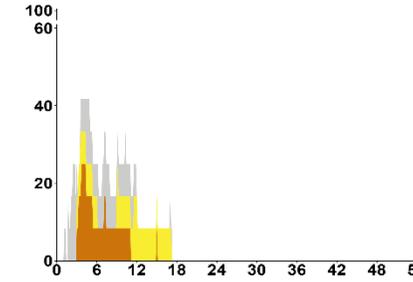
Dose-dependent Efficacy with Manageable Safety

ADAGENE

ADG126
20 mg/kg x1
+10 mg/kg Q3W
+ Pembro Q3W
(N=12)



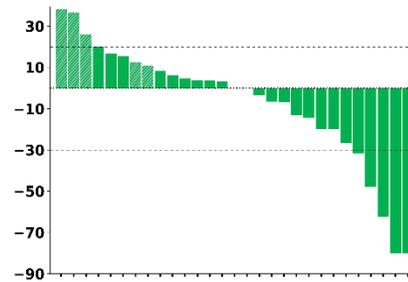
ORR
33%



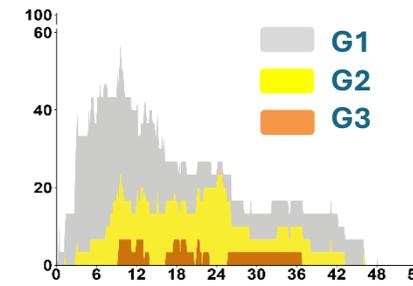
G3
42%

Discont. Rate
0%

ADG126
10mg/kg Q3W
+ Pembro Q3W
(N=30, 29 EE)



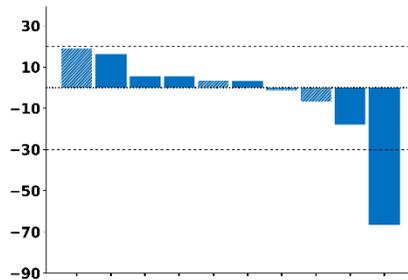
17%



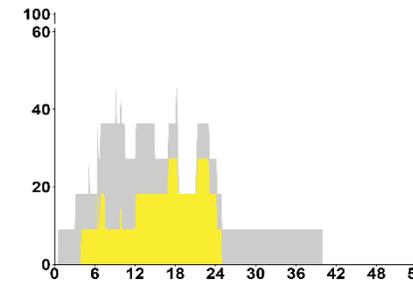
20%

10%

ADG126
10 mg/kg Q6W
+Pembro Q3W
(N=11, 10 EE)



0%



0%

0%

Subject

Waterfall plots

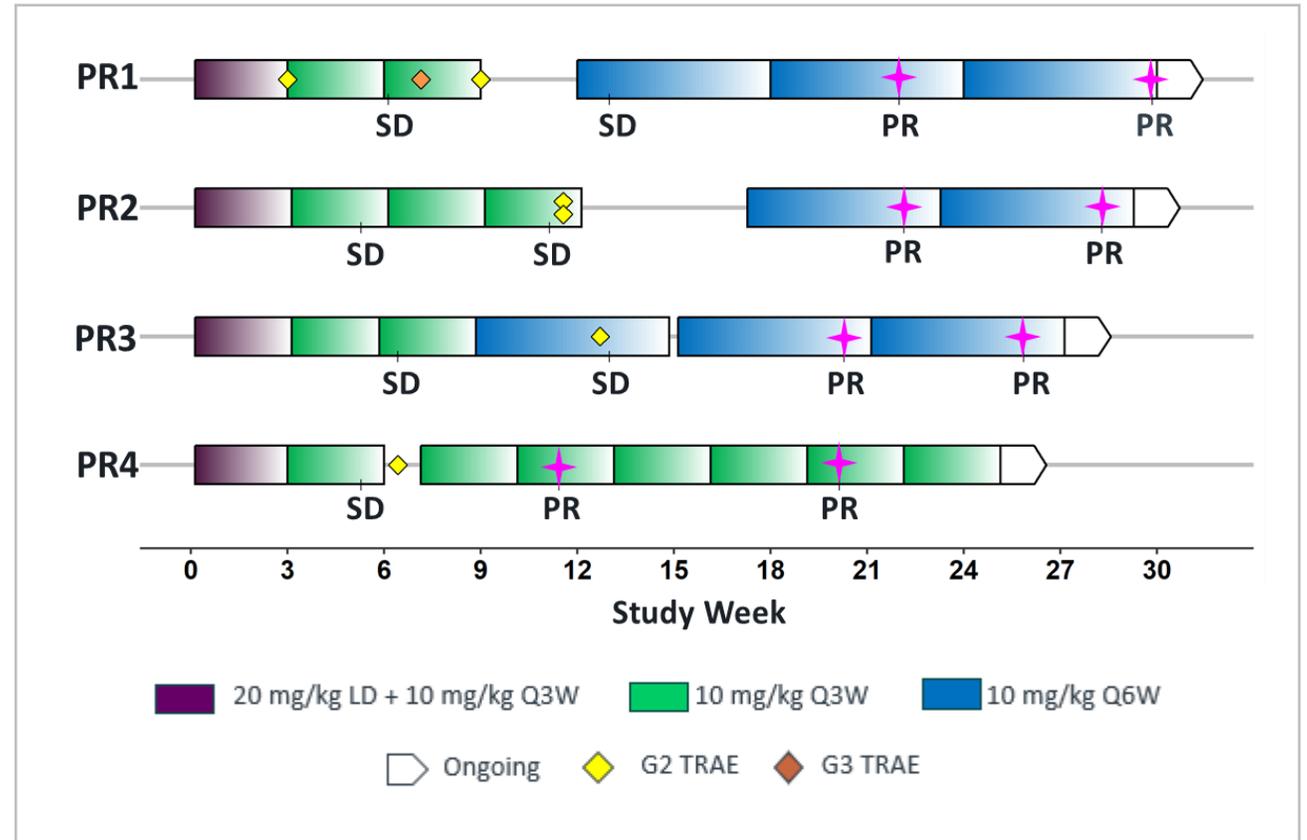
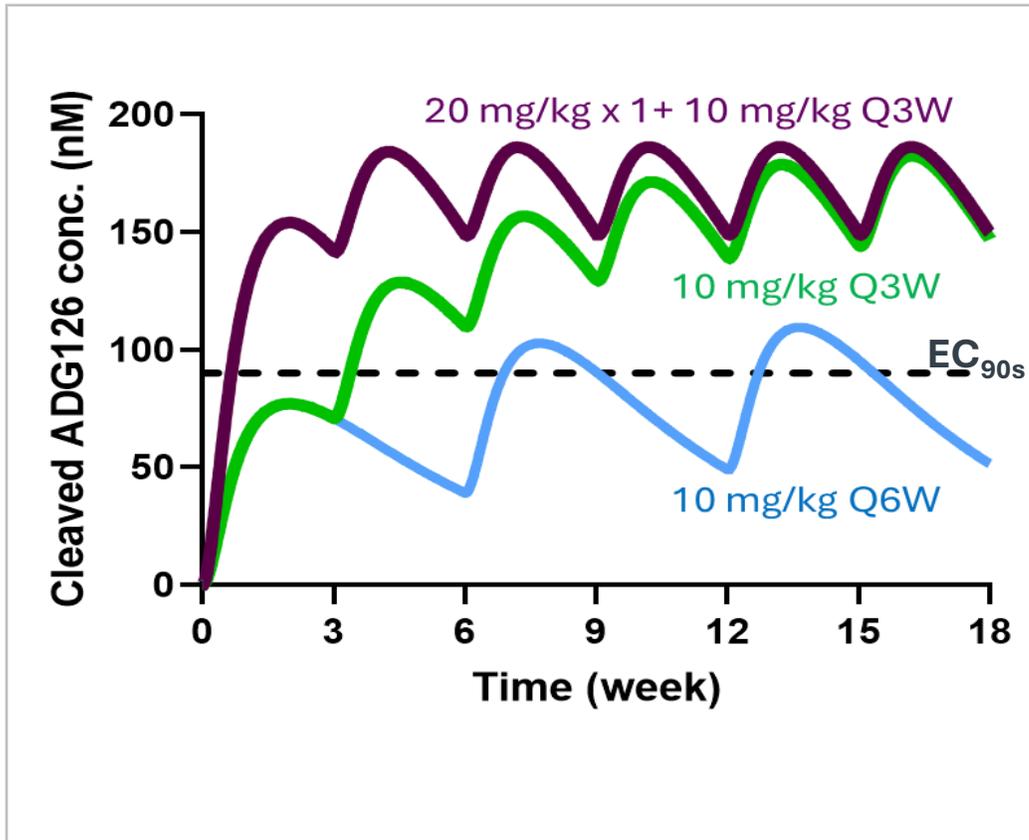
across different dose levels

/// represents patients with peritoneal metastasis.

Treatment Time (Weeks)

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

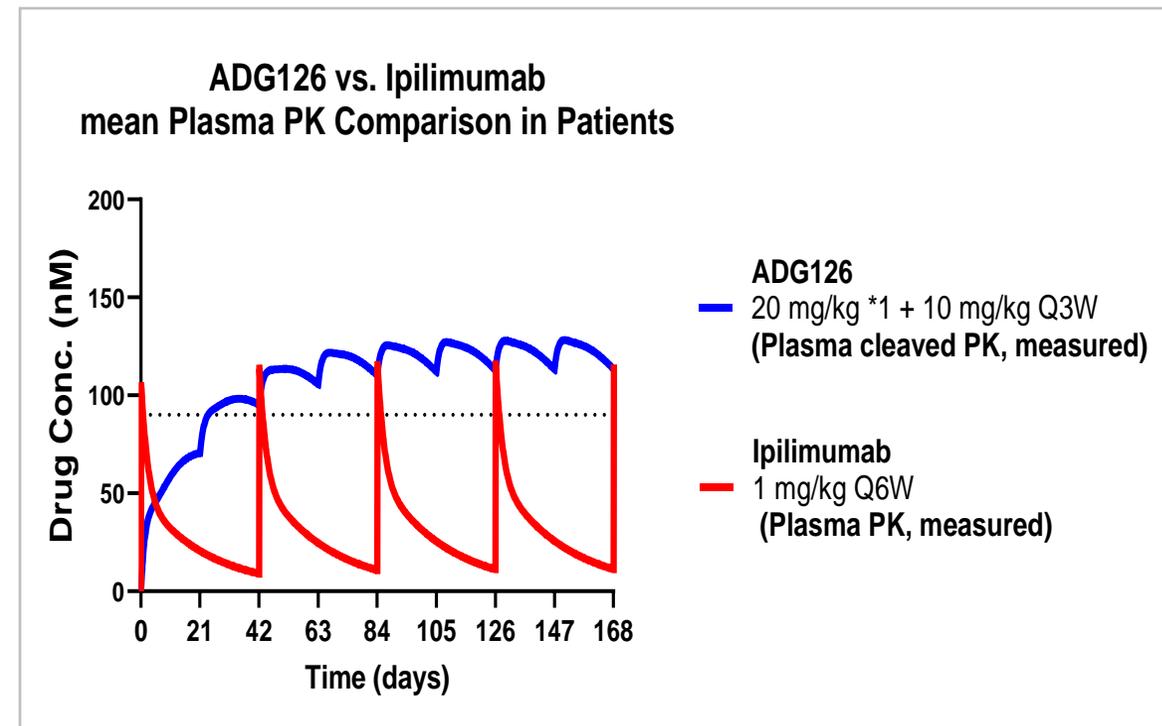
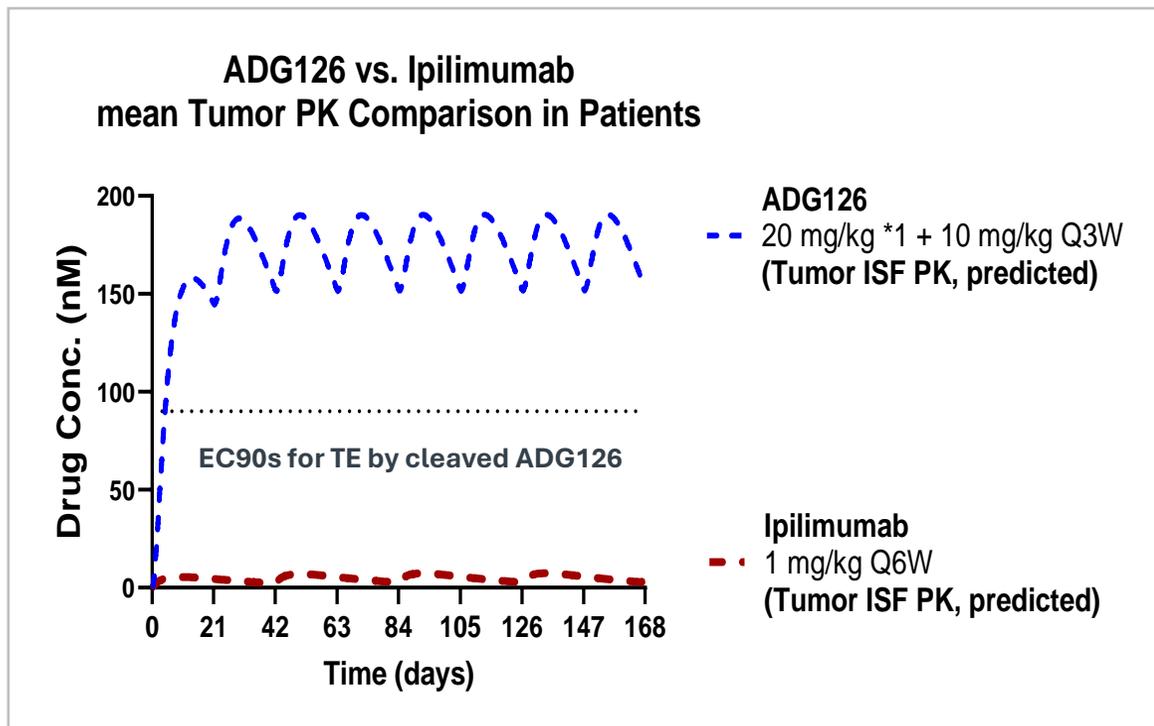
Loading Dose (20 mg/kg) of ADG126 Increases Drug Exposure in Tumor During Early Cycles and Led to a Higher Objective Response Rate ADAGENE



- Optimal steady-state levels of activated ADG126 are achieved sooner with the loading dose of 20 mg/kg
 - All 4 responses were ongoing as of the latest data cut-off date
 - Patients were maintained on treatment thanks to slight dose modifications

Enhanced Therapeutic Index Resulting from Increase of Cleaved ADG126 over Ipilimumab in Tumor vs Blood

At 20mpk single LD + 10mpk Q3W regimen for ADG126, the predicted mean tumor active drug conc. is > 25-fold of Ipi at 1 mpk Q6W (range: 26-70X)

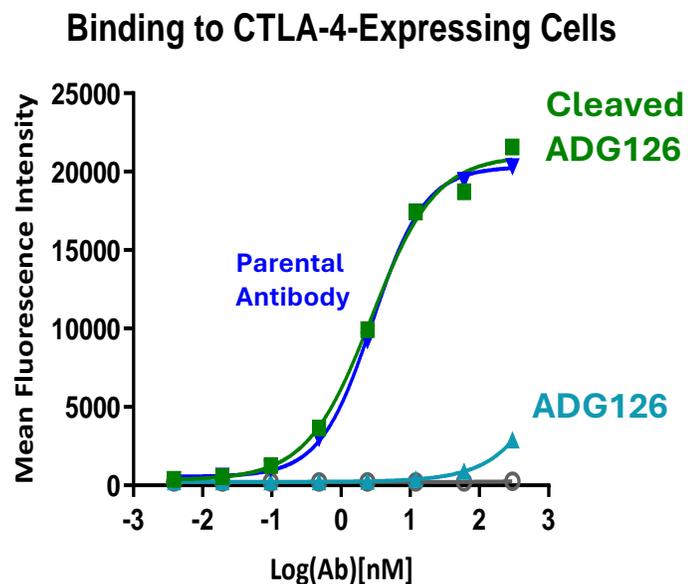


- Adagene will evaluate neoadjuvant high-dose ADG126 + KEYTRUDA® in up to 20 patients (Apr 2025 enrollment) with Major Pathologic Response as primary endpoint. (NCT06846268, Led by Singapore's National University Cancer Institute)
- Confirm Key MoA : ADG126/pembrolizumab effects on tumor immune profile and tissue pharmacokinetics to confirm mechanism and therapeutic efficacy.

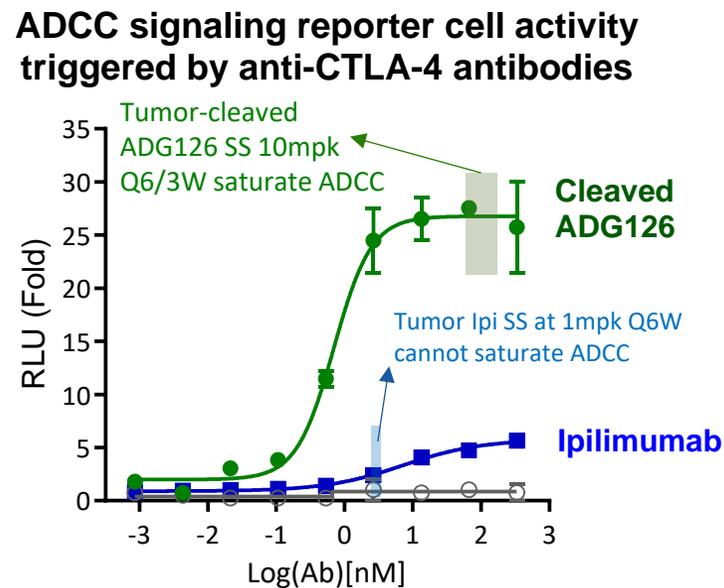
ADG126: A Novel Anti-CTLA-4 Incorporating a Protease Cleavable Mask, and Offering a Broad Therapeutic Index

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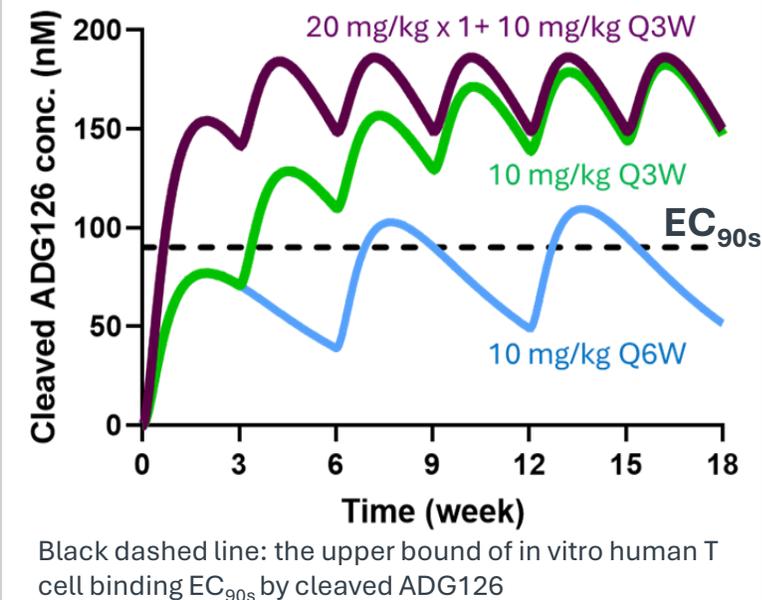
Protease cleavable mask enabling tumor-specific activation



Enhanced ADCC thanks to a differentiated epitope

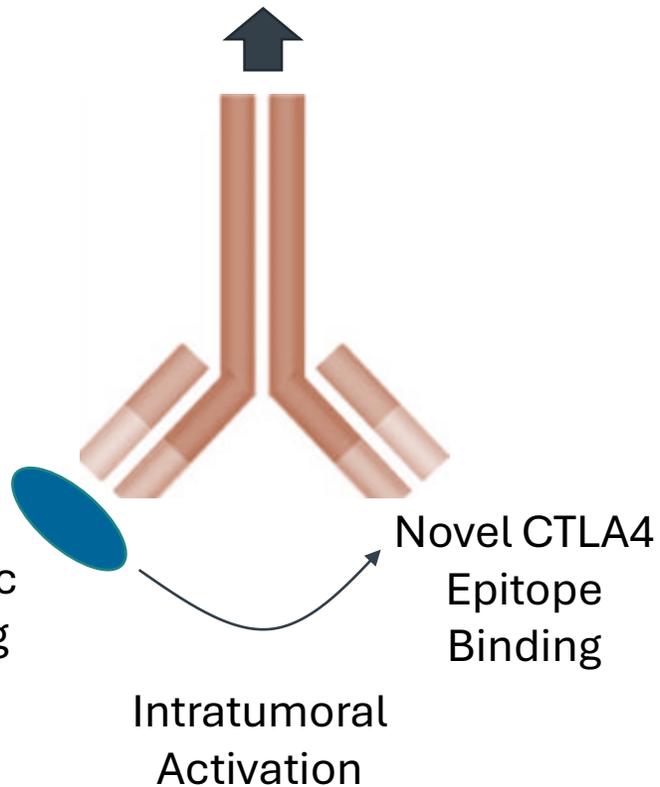


Dose/Efficacy/Safety



At approved Ipi combo dose level (1mpk Q6W) with Nivo across multiple indications, tumor PK analysis by MC38 mice tumor and clinical PK of Ipi and ADG126 showed that **the projected ADCC by Ipi at 1mpk Q6W in patients is > 10X lower than that by ADG126 at 10mpk Q6W in TME**

Epitope-Enhanced
ADCC/P Due to Higher
FcγR Affinity



- ADG126 combines enhanced CTLA4 inhibition AND a favorable safety profile due to peptide masking and intracellular activation with controlled release in peripheral circulation, leading to an improved therapeutic index
- The combination of ADG126 and pembrolizumab is associated with a high, dose-dependent ORR, and durable clinical benefits in non-liver metastatic colorectal cancer, supporting its development in this indication in chemotherapy-resistant settings and its development in neoadjuvant settings.
- The favorable safety profile of ADG126 combined with pembrolizumab may allow for the integration of this regimen with trifluridine bevacizumab, or fruquintinib, in 3rd line settings

2025 Milestones

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- Provide longer-term time-to-event data from the existing Ph 1b/2 study of ADG126 + pembrolizumab in 3L+ MSS CRC
- Update 20 mg/kg loading dose cohort for durability of response (DOR and other time-to-event endpoints)
- Conduct EOP1 meeting with FDA by Q3 to obtain their endorsement on the proposed dose regimens, trial design and patient population
- Initiate evaluation of ADG126 + pembrolizumab in combination with standard of care in MSS CRC patients including those with liver metastases, beginning Q2
- Provide initial clinical data from investigator-initiated Phase 2 trial for neoadjuvant ADG126 in colorectal cancer
- Establish additional collaboration/licensing agreements

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Thank You!