



Unleashing Anti-CTLA-4 Therapy By Enhancing the Therapeutic Index

July 2023

ADAGENE

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Why Focus on Next Generation Anti-CTLA-4 Therapies?

- CTLA-4 is a proven target with a need to “troubleshoot” safety to maximize its therapeutic potential
 - Only approved checkpoint inhibitor for **both** single agent & combination use besides anti-PD-(L)1 therapies
- Treg depletion is crucial for overcoming immune suppression
 - CTLA-4 is over-expressed on Treg cells, especially in tumor microenvironment (TME) of “cold” tumors
 - Traditional CTLA-4 therapies struggle to achieve meaningful intra-tumoral Treg depletion
- To address these challenges, we target a unique epitope of CTLA-4 with enhanced Treg depletion and then add precision masking technology

A New Paradigm for Anti-CTLA-4 Therapy: Targeting CTLA-4 in the Tumor Microenvironment

Thesis for first generation anti-CTLA-4 therapies:
Efficacy is driven by T cell activation through CTLA-4 blockade.

By widening the therapeutic window, Adagene is taking anti-CTLA-4 therapy to the next level with an enhanced ratio of effector T cells (Teff) over regulatory T cells (Treg) within the TME.

“Anti-CTLA-4 Immunotherapy Does Not Deplete FOXP3+ Regulatory T Cells (Tregs) in Human Cancers”

Sharma et al. Clin Cancer Res. 2019 Feb 15;25(4):1233-1238. doi: 10.1158/1078-0432.CCR-18-0762.

Marabelle. Targets for Cancer Immunology: A deep dive into enhanced CTLA-4 targeted therapeutics. SITC webinar on Oct 5, 2022

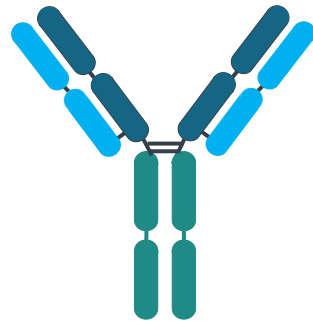
Adagene Product Candidates are Focused on Unleashing the Potential of Anti-CTLA-4 Therapy by Enhancing the Therapeutic Index (TI)

- Two unique anti-CTLA-4 candidates in phase 1b/2 studies:
 - ADG116 NEObody™ targets a unique binding site
 - ADG126 SAFEbody® is masked version of ADG116
 - Dose escalation completed for both as monotherapy and in combination with anti-PD-1
 - Dose expansion ongoing with anti-PD-1 therapies in targeted tumors, including MSS CRC
 - Roche sponsoring & conducting randomized clinical trial in 1L HCC of ADG126 + atezolizumab + bevacizumab
- Both ADG116 and ADG126 in combination with anti-PD-1 agents demonstrated fast and robust clinical responses while maintaining superior safety profiles
 - Efficacy shown in both PD-1 naïve and PD-1 resistant patients, as well as cold tumors (MSS CRC)
- Collaborations validate SAFEbody masking technology
 - Sanofi and Exelixis technology licensing agreements
 - Adagene eligible to receive ≥\$2.5B in potential milestones



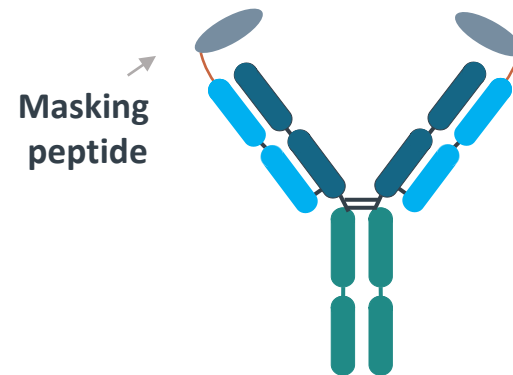
Dynamic Precision Library & Antibody Technologies Enable Wider Therapeutic Window for Anti-CTLA-4 & Other Immunotherapies

NEObody™



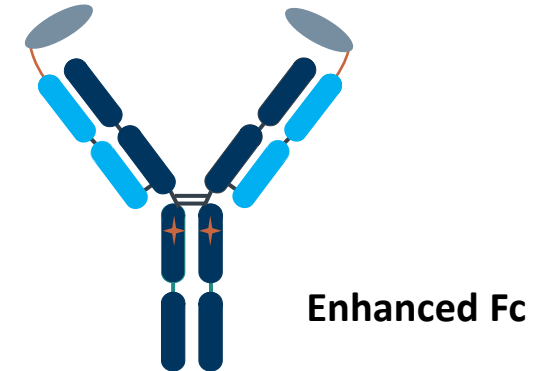
- Dynamic engagement with novel epitope of a given target
- Targets a unique epitope of CTLA-4 to widen therapeutic window

SAFEbody®



- Precision masking for antibody safety
- Further expands TI by preferential targeting of CTLA-4, which is highly expressed on Treg cells in TME

POWERbody™



- Empowered SAFEbody in different modalities with FC engineering for enhanced effector function

The Challenge: Uncouple Dose-dependent Efficacy from Toxicity of Anti-CTLA-4 as Monotherapy and in Combination with Anti-PD-1 Agents

Anti-CTLA-4 Ipilimumab	Dosage (mg/kg)	m-OS (years)	≥ Gr 3 TRAEs, %	Discontinuation Rate, %
Monotherapy 1L Melanoma	10	1.3	36%	34%
	3	1	20%	19%
Combined with PD-1 1L Melanoma	3	6	55%	29%
	1	>3	34%	24%

- ✓ Greater efficacy for ipilimumab at higher doses in monotherapy and combination therapy was associated with more side effects and discontinuations
 - ✓ CTLA-4 and PD-1 combo is much more efficacious than monotherapy
 - ✓ Higher doses of anti-CTLA-4 are more efficacious, but also more toxic

Improving Safety of Anti-CTLA-4 Therapies Will Enable Improved Tolerability of Higher Effective Doses and Longer Administration

- **Safety** as monotherapy at higher effective dose
- **Safety** in combination with PD-1 at effective doses
- **Safety** that enables repeat dosing for continuous target engagement and improved duration of response

Safety is ‘The Holy Grail’* for Anti-CTLA-4 Therapy to Unleash Efficacy

Our Next Generation Anti-CTLA-4 Therapies Enhance the TI in Combination with Anti-PD-1

	Dosage	AUC _{ss, tumor ISF} fold difference	C _{max,ss,tumor ISF} fold difference
Masked	ADG126 (10 mg/kg Q3W) vs. Ipilimumab (1 mg/kg Q6W)	~27x	~9x
Unmasked	ADG116 (3 mg/kg Q3W) vs. Ipilimumab (1 mg/kg Q6W)	~4x	~3x

- ADG126 PK predicts significantly reduced active drug exposures to normal tissue with wider therapeutic window compared to ipilimumab, while ADG116 PK modelling predicts manageable drug exposures
- ADG126 enables continuous CTLA-4 target engagement in the tumor microenvironment
 - PK modelling predicts RO>90% throughout the steady state dosing cycle in TME

ADG116: Our NEObody Solution



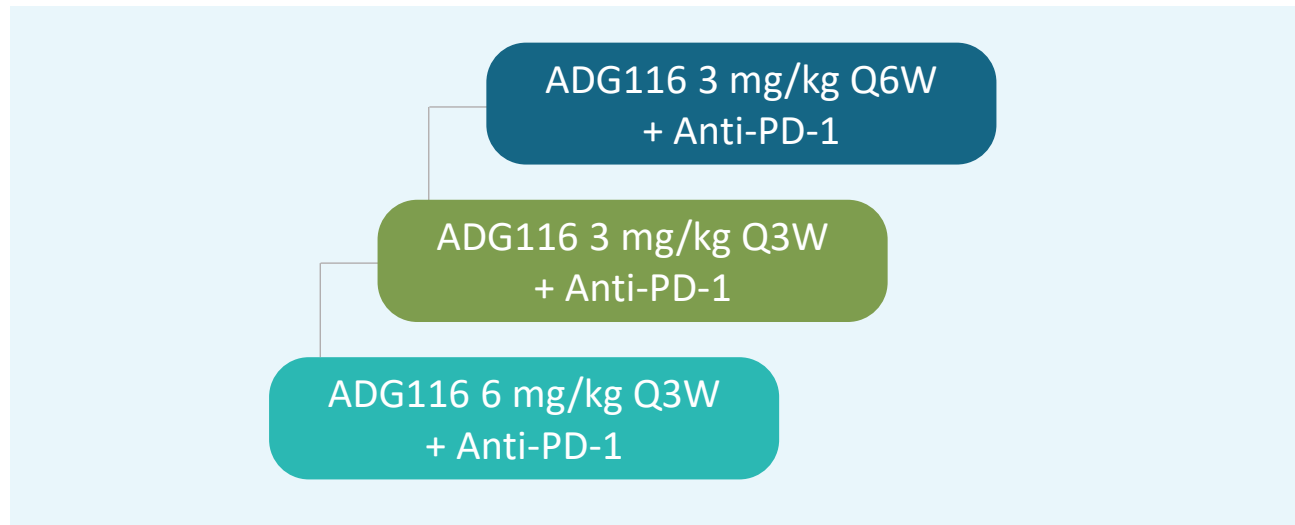
ADG116: Single Agent and PD-1 Combination Efficacy with Repeat Dosing and Enhanced TI

- Favorable safety profile for ADG116 monotherapy at doses up to 15 mg/kg (N=59); manageable safety profile observed for ADG116 + anti-PD-1 therapy (N=22)
- ADG116 is clinically active and ready to advance into phase 2 tumor-specific cohorts:
 - Single agent activity observed with ADG116 in heavily pre-treated patients across tumors at ≥ 10 mg/kg Q3W; ORR = 13% (3/23 evaluable)
 - Confirmed PRs in RCC and MSI-H endometrial cancer
 - Initial PR in Kaposi's sarcoma
 - Encouraging efficacy profile for ADG116 + anti-PD-1 observed in dose escalation
 - ADG116 3 mg/kg Q3W + toripalimab: ORR = 20% (1/5 evaluable; sustained CR of >one year in HNSCC)
 - ADG116 3 mg/kg Q6W + toripalimab: ORR = 14% (1/7 evaluable; initial PR observed in MSS CRC)

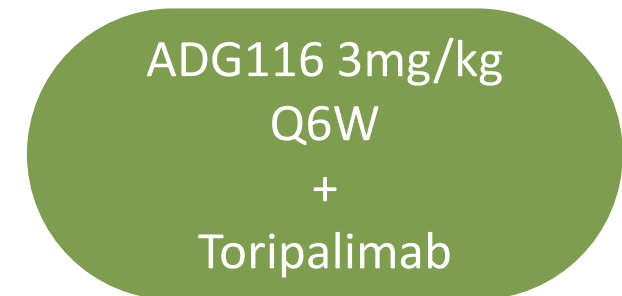
Design for ADG116 + PD-1 Combination Evaluation

- Prior monotherapy dose escalation conducted up to 15 mg/kg Q3W
- Prior combination dose escalation* conducted with either pembrolizumab (200 mg Q3W) or toripalimab (240 mg Q3W)
- Dose optimization/expansion ongoing in combination with toripalimab, including MSS CRC

Dose Optimization with Anti-PD-1



Dose Expansion



ADG116 Monotherapy: Repeat Dosing (>7 cycles) Enabled by Safety Profile Demonstrates Continuing Clinical Benefit

		Baseline	6 weeks	12 weeks	21 weeks
Target Lesion	TL1 - Lymph Node	19 mm	17 mm	10 mm	10 mm
	TL2 - Lymph Node	31 mm	27 mm	19 mm	15 mm
	Sum	50 mm	44 mm (-12%)	29 mm (-42%)	25 mm (-50%)
Non-Target Lesions	Multiple	Present	Present	Present	Present
New Lesion		N/A	No	No	No
Overall		N/A	SD	PR	PR

Subject: Female, 44 years old

Tumor Type: Endometrial carcinoma, MSI-H

Site Location: China

Dose Regimen: 10 mg/kg ADG116 (7 cycles @ Q3W)

Prior Therapies: Docetaxel + cisplatin (1st line) followed by HH2853-G101 (EZH1/EZH2 inhibitor)

Safety Profile: Only G1 TRAEs in Cycle 4 (12 weeks); rash and hyperthyroidism

ADG116 Monotherapy: Additional PR Further Reinforces Safety & Efficacy Profiles with Repeat Dosing in IO-experienced RCC Patient

		Baseline	6 weeks	12 weeks	21 weeks	30 weeks	39 weeks
Target Lesion	TL1- Lung RLL	15 mm	11 mm	11 mm	9 mm	9 mm	9 mm
	TL2 - Lung RML	16 mm	14 mm	14 mm	13 mm	13 mm	13 mm
	TL3 – Lymph Node	22 mm	14 mm	14 mm	14 mm	14 mm	14 mm
	TL4 - Right kidney	47 mm	47 mm	30 mm	27 mm	27 mm	27 mm
	TL5 - Lymph Node	15 mm	10 mm	7 mm	5 mm	5 mm	5 mm
	Sum	115 mm	96 mm (-17%)	76 mm (-34%)	68 mm (-41%)	68 mm (-41%)	68 mm (-41%)
Non-Target Lesions	Multiple	Present	Present	Present	Present	Present	Present
New Lesion		N/A	No	No	No	No	No
Overall		N/A	SD	PR	PR	PR	PR

Subject: Male, 56 years old

Tumor Type: Clear cell renal cell carcinoma

Site Location: South Korea

Dose Regimen: 10 mg/kg ADG116 (13 cycles @ Q3W)

Prior Therapies: Sunitinib (1st line) followed by INCB86550 (Oral PD-L1 inhibitor in development)

Safety Profile: No TRAEs up to 12 weeks (4 cycles); G2 adrenal insufficiency during Cycle 5

ADG116 + PD-1 Combination with Repeat Dosing: Rapid Complete Response in HNSCC Patient Sustained Beyond One Year

C1D1 (Week 1)



C2D1 (Week 3)



C4D2 (Week 10)



Photos of external lesions (right mandibular and right submandibular) at C1D1, C2D1 and C4D2

		Baseline	Week 6	Week 18	Week 50
Target Lesion	TL1 - Right mandibular	32 mm	Disappeared	Disappeared	Disappeared
	TL2 - Right submandibular	18 mm	Disappeared	Disappeared	Disappeared
	TL3 - Lymph node	15 mm	8 mm	5 mm	5 mm
	Sum	65 mm	8 mm	5 mm	5 mm
Non-target Lesions	3	Present	Disappeared	Disappeared	Disappeared
New Lesion			No	No	No
Overall			CR	CR	CR

Subject: Male, 64 years old, ECOG PS 1

Tumor Type: HPV negative recurrent head and neck squamous cell carcinoma (HNSCC)

Site Location: Singapore

Dose Level: 3 mg/kg ADG116 (initially Q3W; then Q6W) + Tori 240 mg

Prior Therapies: Right modified cervical lymph node dissection followed by adjuvant radiotherapy (local therapy); concurrent chemoradiotherapy, including weekly cisplatin

Safety Profile: TRAEs include G3 lipase increase, G2 amylase increase, G2 arthralgia and G1 pyrexia

ADG116 + PD-1 Combination with Repeat Dosing: Initial Partial Response in MSS CRC Observed Within Two Cycles

		Baseline	6 weeks
Target Lesion	TL1- LN (right paraaortic)	25 mm	15 mm
	TL2 -LN (common iliac)	20 mm	15 mm
	Sum (percent change)	45 mm	30 mm (-33%)
Non-Target Lesions	NTL1- LN (right lower paratracheal)	Present	Present
	NTL2- LN (right upper paratracheal)	Present	Present
New Lesion		N/A	No
Overall		N/A	PR

- Subject:** Female, 50 years old
- Tumor type:** MSS CRC with lung, kidneys and lymph node metastasis
- Site Location:** Singapore
- Dose Regimen:** 3 mg/kg ADG116 Q6W + Tori 240 mg
- Prior Therapies:** Curative surgery followed by three lines of therapy (MFOLFOXIRI + bevacizumab; Encorafenib + Cetuximab; TAS102 + bevacizumab)
- Safety Profile:** TRAEs include G3 AST elevated, G2 ALT elevated, G1 (e.g., rash)

ADG126: Our SAFEbody Solution



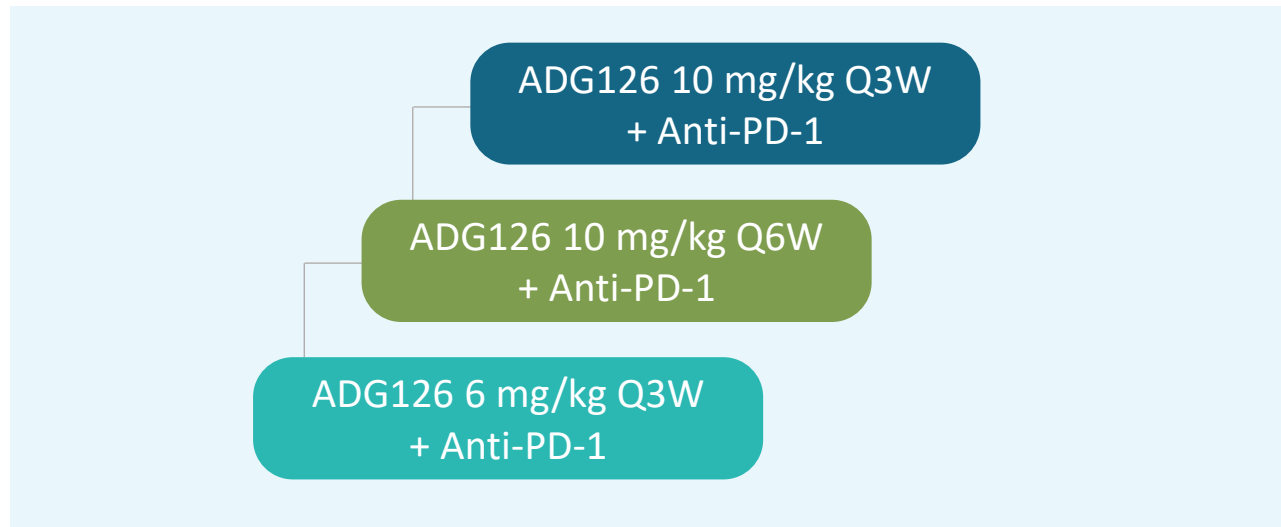
ADG126: Encouraging Efficacy Profile Observed with Anti-PD-1 at High Dose Levels with Repeat Dosing and Further Enhanced TI

- No DLT or \geq G3 TRAEs observed for ADG126 monotherapy up to 20 mg/kg Q3W (N=30)
- Safety profile of ADG126 + PD-1 dose escalation demonstrates best-in-class potential (N=31)
 - Continuous dosing beyond 4 cycles may enable combination with agents beyond anti-PD-1
 - TI enables novel dosing regimens for double and triple combinations:
 - Roche sponsoring triple combination study of ADG126 + atezolizumab + bevacizumab (NCT04524871)
- Efficacy profile observed for ADG126 10 mg/kg Q3W + PD-1: ORR = 40% (4/10 evaluable)
 - Confirmed PR in a cervical cancer patient who previously progressed on pembrolizumab
 - Three confirmed PRs in previously treated patients with anal SCC, penile SCC and MSI-H endometrial cancer
 - Significant tumor shrinkage (\geq 20% reduction in target lesion) and prolonged stable disease observed in cold tumors, including MSS CRC

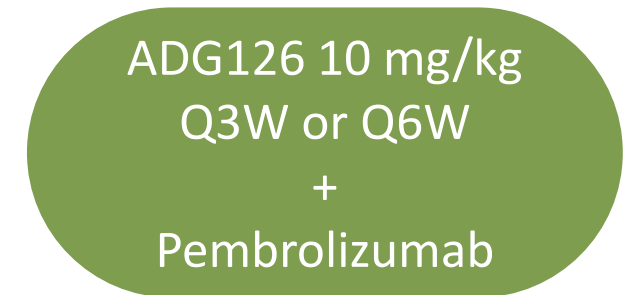
Design for ADG126 + Anti-PD-1 Combination Evaluation

- Prior monotherapy dose escalation conducted up to 20 mg/kg Q3W
- Prior combination dose escalation* with either pembrolizumab (200 mg Q3W) or toripalimab (240 mg Q3W)
- Dose expansion ongoing, primarily with pembrolizumab in ~20 patients with advanced/metastatic MSS CRC

Dose Escalation with Anti-PD-1



Dose Expansion in MSS CRC



Uncoupling Efficacy from Safety: ADG126 + PD-1 Combination Unleashes Efficacy with Enhanced TI

ADG126 Dosing Regimen	Patients Dosed (N)	Safety	Efficacy
6 mg/kg Q3W	11 (10 evaluable for efficacy)	<ul style="list-style-type: none"> No DLT or >G3 TRAEs reported 27% G3 TRAEs 	DCR = 30%
10 mg/kg Q6W	10 (9 evaluable for efficacy)	<ul style="list-style-type: none"> No DLT or >G3 TRAEs reported 30% G3 TRAEs 	DCR = 56%
10 mg/kg Q3W*	10 (from 2 different studies)	<ul style="list-style-type: none"> No DLT or >G3 TRAEs reported 10% G3 TRAEs 	ORR = 40% (4 partial responses) DCR= 60%

Emerging data show higher & more frequent doses of ADG126 in combination with anti-PD-1 therapy increase efficacy without increasing G3 TRAEs

* Early data cut from patients dosed by ADG126 + anti-PD-1 therapies in ADG126-1001 study (data cutoff: Mar 14, 2023) and ADG126-P001 study (data cutoff: Mar 9, 2023) as reported in [poster presentations](#) at AACR 2023.

ADG126 at 10 mg/kg Q3W Enables Repeat Dosing with Anti-PD-1 to Achieve Efficacy Profile

- 4 PRs (4/29) have been observed in the dose escalations of ADG126 in combination with anti-PD-1 therapy
 - ORR of 40% (4/10) in the ADG126 10 mg/kg Q3W cohort
 - One PR each for anal SCC, penile SCC, endometrial (MSI-H) and cervical cancer
 - 3 IO-naïve patients and **one patient w/ cervical cancer who progressed on 9 cycles of pembrolizumab monotherapy**
- Prolonged stable disease with reduced target lesions in patients with “cold” tumors (MSS CRC)

ADG126 with anti-PD-1 therapy correlates with observed response in PD-1 resistant patients and tumor reduction in MSS CRC, the primary tumor type selected for cohort expansion

ADG126 + PD-1 Combination: Confirmed PR with Continuous Tumor Shrinkage in a PD-1 Resistant Patient with Low PD-L1 Expression

	Lesion #	Location	Baseline	6 Weeks	12 Weeks	18 Weeks	24 Weeks	30 Weeks
Target lesion	TL#1	Lymph node (Subcarinal)	25 mm	25 mm	21mm	17 mm	13 mm	9 mm
	TL#2	Lymph node (Pre-carinal)	29 mm	29 mm	30 mm	30 mm	25 mm	17 mm
	Sum		54 mm	54 mm	51 mm	47 mm	38 mm	26 mm
Non target lesion		Lymph node (Right Supra-clavicular)	Present	Present	Present	Present	Present	Present
New lesion				No	No	No	No	No
Overall response				SD (+0%)	SD (-5.6%)	SD (-13%)	PR (-30%)	PR (-52%)

Tumor Type:

Female, 70 years old, advanced cervical cancer (stage IV squamous carcinoma)

- PD-L1 CPS score = 1, TMB high: 24 Muts/Mb
- Concurrent clear cell renal cancer

Site Location:

United States

Prior Therapies:

Previously received 2 lines of therapies:

- Carboplatin/paclitaxel/bevacizumab x 6 cycles
- Pembrolizumab monotherapy x 9 cycles

Dose Regimen:

ADG126 10 mg/kg Q3W + Pembro 200 mg Q3W (10 cycles)

Safety Profile:

Only G2 TRAEs

ADG126 + PD-1 Combination: 58% Reduction in Target Lesions in a Mixed Response in MSS CRC

Tumor assessment on study		Baseline	Week 7	Week 13	Week 17
Target Lesion	TL1 – Lung	15 mm	14 mm	13 mm	16 mm
	TL2 – Lymph Node	22 mm	12 mm	12 mm	Disappeared
	TL3 – Lymph Node	18 mm	10 mm	6 mm	Disappeared
	TL4 – Lymph Node	19 mm	14 mm	15 mm	Disappeared
	TL5 – Liver	17 mm	20 mm	22 mm	22 mm
	Sum	91 mm	70 mm (-23%)	68 mm (-25%)	38 mm (-58%)
Non-Target Lesion	NTL1 – Lung	Present	Present	Present	Disappeared
	NTL2 – Bone	Present	Present	Present	Present
New Lesion		NA	No	No	Yes
Overall Response		NA	SD	SD	PD (iuPD)

Tumor Type: Male, 53 years old, ECOG PS 0, MSS rectosigmoid adenocarcinoma with liver metastasis at baseline

Site Location: Singapore

Prior Therapies: Previously received curative & palliative surgery for liver metastasis and 3 lines of therapies (Leucovorin + 5FU + irinotecan + oxaliplatin; bevacizumab + TAS102; regorafenib)


Dose Regimen: ADG126 10 mg/kg Q6W + Toripalimab 240 mg Q3W

Safety Profile: TRAEs include G3 lipase increase and G2 amylase increase

The Case for ADG126 in MSS CRC: Evidence of Activity in Cold & Difficult-to-Treat Tumors

- Objective responses and/or tumor shrinkage, and prolonged stable disease by ADG116 (unmasked parental antibody) and ADG126 in MSS CRC patients
- Correlation of clinical activities with the reduction in carcinoembryonic antigen (CEA) levels
- Efficacy correlated with dosing schedule of ADG126 10 mg/kg Q3W with anti-PD-1 (ORR = 40%; N=10) in heavily pre-treated patients across multiple tumors during dose escalation
- CTLA-4 is over-expressed in Treg cells, therefore enhancing Teff/Treg in TME of “cold” tumors

A Path Forward for ADG126 in MSS CRC

- **95%** of metastatic CRC patients are microsatellite stable (MSS)
 - **\$18.6B** growing CRC global market*
 - **Limited clinical benefit** from SoC:
 - No immunotherapy approved
 - Approved therapies include regorafenib (TKI) or TAS-102 (trifluridine/tipiracil)
 - mPFS = ~2 months; ORR = <5%
 - Recent progress for trifluridine/tipiracil +/- bevacizumab (from Sunlight Trial)
 - mPFS = 2.4 – 5.6 months; ORR = <7%
- 

- ADG126 SAFEbody is the **most advanced clinical stage anti-CTLA-4 candidate**⁺ that integrates masking technology and Treg depletion for superior safety & efficacy profiles
- Dose expansion cohort of ADG126 plus pembrolizumab enrolling ~20 MSS CRC patients, with **preliminary efficacy readout end of 2023**

* [the insight partners 2022](#)

+ Based on review of publicly available data as of May 2023 for anti-CTLA-4 candidates in clinical trials.

Next Steps & Takeaways



Status & Next Steps

	Status	Next Steps
ADG116	<ul style="list-style-type: none">• Confirming dosing regimens for future trials	<ul style="list-style-type: none">• Advance into Ph 2 tumor-specific cohorts
ADG126	<ul style="list-style-type: none">• Ongoing dose expansion at 10 mg/kg Q3W & Q6W• Randomized trial with novel triple combination in HCC	<ul style="list-style-type: none">• Ph 2 MSS CRC and HCC efficacy readouts

Establishing registration path and strategy (e.g., RP2D, indication and design) for pivotal trial of anti-CTLA-4 with anti-PD-1 therapy in targeted tumors

Key Takeaways

- **Adagene's next-generation CTLA-4 candidates are designed to widen the therapeutic window by targeting a unique epitope of CTLA-4 and then combining it with precision masking technology:**
 - Enhanced Treg depletion in TME
 - Repeat dosing for sustained target engagement
- **ADG116 & ADG126 demonstrate ability to unleash the full potential of anti-CTLA-4 therapy in multiple patient populations:**
 - Efficacy profile in cold tumors
 - Activity in PD-1 resistant/refractory patients
 - Ability for novel dosing regimens and combinations across modalities

Additional Information



Both Masked and Unmasked Anti-CTLA-4 Candidates Show Favorable Safety Profiles Compared to Historical Controls

		Dose	TRAE \geq Grade 3	Safety (HNSTD, mg/kg)
Masked	ADG126* (SAFEbody)	10 and 20 mg/kg Q3W (n=17) With repeat dosing	0%	200
	BMS 986249 (Ipi-Probody)	20 mg/kg** Q4W (n=10)	60%	50#
Unmasked	ADG116	\leq 6 mg/kg Q3W (n=30) 10 & 15 mg/kg Q3W (n=29)	0% 14%	30
	Ipilimumab+	3 mg/kg Q3W 10 mg/kg Q3W	20-27% 36%	10#

This slide contains information from various clinical trials which are not head-to-head comparisons. Data on file.

* ADG126 data from ADG126-1001 study (March 14, 2023 datacut). ADG116 data from ADG116-1002 and ADG116-1003 study (May 2023 datacut).

** Dosing of 10 & 20 mg/kg is calculated from 800 mg and 1600 mg, assuming 80kg body weight from ESMO 2022, 740P, NCT03369223

+ Clinical data for Ipilimumab from trials in melanoma. Reference on file.

John Engelhardt, et al. Preclinical characterization of novel anti-CTLA-4 prodrug antibodies with an enhanced therapeutic index. AACR 2020. Poster 4551.

HNSTD = highest non-severely toxic dose. From preclinical GLP toxicology studies.

Reference List for Slide 7

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