Results of a Phase 1b/2 Study of ADG126 (a Masked Anti-CTLA-4 SAFEbody®) in Combination with Pembrolizumab (Pembro) in Patients with Metastatic Microsatellite-stable (MSS) Colorectal Cancer (CRC)

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Background

ADG126 (muzastotug) is a fully human masked anti-CTLA-4 IgG1 SAFEbody® that is designed to allow preferential activation in the tumor microenvironment (TME) which enables prolonged on-tumor drug exposure and limited systemic toxicity, affording enhanced therapeutic index (TI). Activated ADG126 binds to a unique CTLA-4 epitope to prime T cells and deplete immunosuppressive Tregs through strong antibody-dependent cellular cytotoxicity (ADCC)/phagocytosis (ADCP). Preclinical studies showed that ADG126/anti-PD-1 combination effectively increases Teff/Treg ratio[1]. In early Phase 1b/2 studies, ADG126 demonstrated a favorable safety profile and clinical efficacy as monotherapy and in combination with anti-PD-1 therapy[2-4].

Here we report the interim results of study ADG126-P001 (a combination study of ADG126 with pembrolizumab (Pembro), NCT05405595). Specifically,

- The safety profile of patients (Pts) in dose escalation (all comers, N=11) and the dose expansion (n=35).
- Clinical activity summary of the dose escalation cohort and an in-depth efficacy analysis of MSS CRC Pts in dose expansion cohorts.

1: A novel anti-CTLA-4 checkpoint inhibitor prodrug to address on-target off-tumor toxicity for cancer immunotherapy. Liu GZ, et al., *Abstract 1853, AACR 2021*

2: Phase 1 Results Demonstrate Highly Differentiated Safety and PK Profile of ADG126, a Masked anti-CTLA-4 SAFEbody® in Patients with Advanced Solid Tumors. Richardson G. et al., *Abstract 741P, ESMO, 2022*

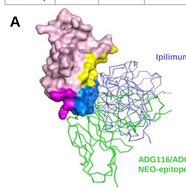
3. Interim Results of a Phase 1b/2 Study of ADG126 (a Masked anti-CTLA-4 SAFEbody®) Monotherapy and in Combination with Toripalimab (an anti-PD-1 Antibody) in Patients (pts) with Advanced / Metastatic Solid Tumors. Ariyapperuma M. et al., *Abstract CT227, AACR, April 2023*

4. Initial Results of a Phase 1b/2 Study of ADG126 (a Masked anti-CTLA-4 SAFEbody®) in Combination with Pembrolizumab (an anti-PD-1 Antibody) in Patients with Advanced/ Metastatic Solid Tumors. Daneng Li et al., *Abstract CT233, AACR, 2023*

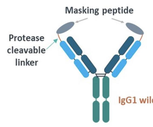
ADG126 Targets a Distinct Epitope of CTLA-4 Compared to Ipilimumab Resulting in Unique MOAs

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

A

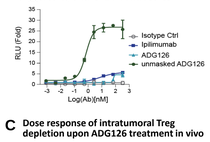


ADG126 SAFEbody®



- 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

B **ADCC signaling reporter cell activity triggered by anti-CTLA-4 antibodies**



C **Dose response of intratumoral Treg depletion upon ADG126 treatment in vivo**

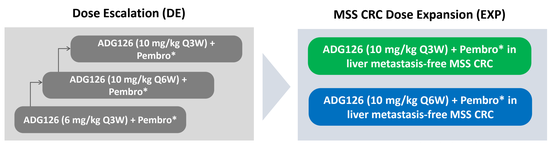
Figure 1. Binding Epitopes and Activities of ADG126 vs. Ipilimumab. The unique binding epitope of ADG126 and its parental antibody ADG116 with species cross-reactivity (A), results in stronger ADCC activity compared with ipilimumab (B), and dose-dependent intratumoral Treg depletion in vivo in CT26 model by ADG126 anti-CTLA-4 SAFEbody (C).

Methods and Study Design Schema

This is a Phase 1b/2, open-label, multicenter dose escalation (DE) and expansion (EXP) study of ADG126 in combination with Pembrolizumab. Key inclusion criteria are:

- DE Phase: advanced/metastatic solid tumors who have progressed after all standard therapies, or for whom no further standard therapy exists.
- EXP Phase (CRC indication): advanced CRC not amenable to curative surgery, with MSS status, who has received at least 2 and no more than 3 prior systemic therapies, free of liver metastasis and no prior immunotherapy.

The study design schema for the dose escalation (DE) and dose expansion (EXP) MSS CRC cohorts is shown below:



*Pembrolizumab: 200 mg Q3W

- 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 and PFS) associated with the ADG126/Pembro combination as assessed per RECIST 1.1 and/or iRECIST criteria.

Baseline Characteristics of Patients in DE and EXP

- We report results of 46 Pts who participated in study ADG126-P001 (Data cutoff: Nov 30, 2023)
- Three dose levels were evaluated in dose escalation phase (N = 11). The cancer types consisted of ovarian (N=1), colorectal (N=6), pancreatic (N=1), endometrial (n=1), cervical (N=1) and neuroendocrine tumor (N=1).
- Two dose schedules of ADG126 10 mg/kg were evaluated in dose expansion phase (N = 35). The tumor types are advanced MSS CRC (free of liver metastasis; N = 24) and other cancer types (I/O naïve and experienced; N=11).
- Majority of Pts (74.5%) have what are generally considered immunologically "cold" tumors.
- The baseline characteristics of the patients reported here are summarized in **Table 1** (Right).
- The median follow-ups (month) for DE and EXP patients included in this report are 10.9 (8.6-NR) and 6.7 (4.6-NR), respectively.

Table 1. Baseline Characteristics

Characteristics	N=46
Dose Escalation (# of pts)	11
Dose Expansion (# of Pts)	35
Age (Years), Median (Range)	60 (26-75)
Female, n (%)	21 (46%)
Race, n (%)	
Caucasian, n (%)	19 (41%)
Asian, n (%)	23 (50%)
Black or African American, n (%)	1 (2%)
Other, n (%)	3 (7%)
ECOG, n (%)	
0	20 (43%)
1	26 (56%)
Prior treatment regimens ≥3	17 (37%)
Prior immunotherapy, n (%)	6 (13%)

Clinical Safety (TRAEs, N = 46)

- Highly manageable safety and tolerability profile; no dose-limiting toxicities.
- Most TRAEs are G1 and G2, with no G4/5 TRAEs. A total of 5 Pts developed Grade 3 TRAEs (10.8%).
- Three Pts with TRAEs (G2 pneumonitis, G3 pancreatitis and G2 Diarrhea) led to study discontinuation (6.5%).
- Twelve Pts developed SAEs and 5 are treatment related, which are diarrhea (G2), secondary adrenocortical insufficiency, pancreatitis, asthenia and type 1 diabetes mellitus and hyperglycemia (G3).

Fig 2A. ADG126 6 mg/kg Q3W (N = 5)

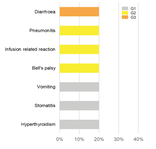


Fig 2B. ADG126 10 mg/kg Q6W (N = 17)

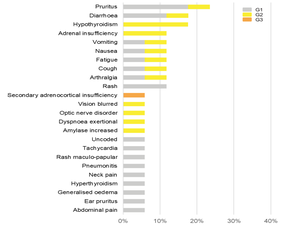


Fig 2C. ADG126 10 mg/kg Q3W (N = 24)

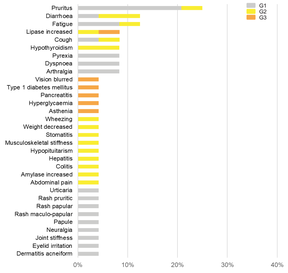


Table 2. TRAEs By Grade and Dose Level

ADG126 Dose Level	N	All Grades (%)	G1 (%)	G2 (%)	G3 (%)	G4-5 (%)	Discont. Rate
6 mg/kg Q3W	5	3 (60%)	1 (20%)	1 (20%)	1 (20%)	0	20%
10 mg/kg Q6W	17	12 (71%)	3 (18%)	8 (47%)	1 (6%)	0	0
10 mg/kg Q3W	24	16 (67%)	5 (21%)	8 (33%)	3 (13%)	0	8%

Figure 2. TRAEs in 46 pts in dose escalation and expansion cohorts across three dose levels/schedule of ADG126. Pembrolizumab was dosed at 200mg, Q3W throughout.

Clinical Activity of Evaluable Patients

Fig 3A. Dose Escalation Cohort (N = 11)

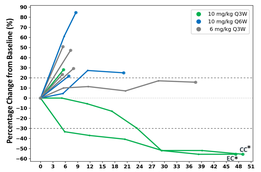


Fig 3B. Dose Escalation and Dose Expansion Cohorts (N = 43)

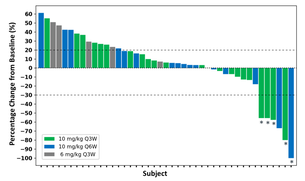


Figure 3. A, Spider plot of 11 Pts in dose escalation cohort. The 10 mg/kg Q3W ADG126/Pembro combination therapy resulted in 2 confirmed and durable PRs (1 EC and 1 CC who progressed on prior anti-PD-1). **B,** Waterfall plot of all 43 efficacy evaluable patients from both dose escalation and expansion cohorts (multiple cancer types). A total of 5 confirmed PRs were observed. * PR: partial response; CC: cervical cancer; EC: Endometrial cancer.

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Clinical Efficacy of Patients with MSS CRC (Free of Liver Mets) in Dose Expansion

Table 3. MSS CRC Patients Baseline Characteristics

CRC Patients Characteristics	N=24
Age (Years; median range)	60 (41-75)
Female, n (%)	12 (50%)
Race, n (%)	
Caucasian, n (%)	9 (38%)
Asian, n (%)	15 (62%)
Other	-
ECOG, n (%)	
0	9 (38%)
1	15 (62%)
With peritoneal metastasis, n (%)	8 (33%)
Prior Treatment ≥3	10 (42%)
Prior immunotherapy, n (%)	0

Fig 4A. Duration of Treatment of MSS CRC Pts by 10mg/kg Q6W and Q3W of ADG126/pembrolizumab
(N=22 efficacy evaluable pts with at least one CT scan)

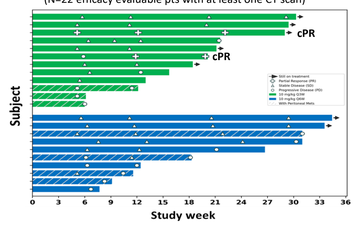


Fig 4B. Spider plot of evaluable MSS CRC Pts treated by 10 mg/kg Q3W ADG126/Pembrolizumab (N = 12)

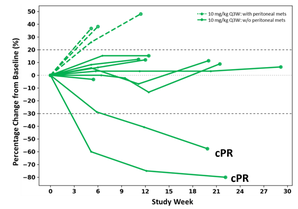


Table 5. PFS Subpopulation Analysis of Evaluable MSS CRC Patients with and without Peritoneal Metastasis

Progression-free Survival of MSS CRC				
ADG126 Dose/schedule	10mpk Q6W and Q3W	10mpk Q3W	10mpk Q6W and Q3W	10mpk Q3W
Including Pts with Peritoneal Mets? (N)	YES (22)	YES (12)	NO (15)	NO (9)
Median PFS, months (95% CI)	4.9 (2.4 - NR)	4.9 (1.2 - NR)	7.0 (2.9 - NR)	NR (2.9 - NR)
6-month PFS, % (95% CI)	42 (19 - 63)	41 (8 - 74)	55 (22 - 79)	56 (7 - 88)

Fig 4C. Overlay of PFS plots of MSS CRC subgroups with and without peritoneal metastasis

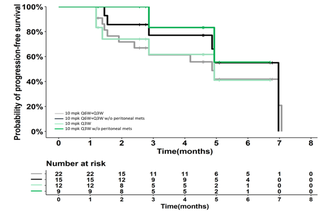


Table 4. Summary of Response Rate of Evaluable MSS CRC Pts (10 mg/kg Q3W)

Response Rate of MSS CRC		
ADG126 Dose and subset (N)	10mpk Q3W (12)	10mpk Q3W w/o peritoneal metastasis (9)
Confirmed ORR, % (95% CI)	17 (2-48)	22 (3-60)
BoR, N (%)		
PR	2 (17)	2 (22)
SD	7 (58)	7 (78)
DCR (CR+PR+SD), % (95% CI)	75 (43-95)	100 (66-100)

cPR: confirmed partial response. PFS: Progression-free survival. BoR: Best of Response. DCR: Disease control rate. NR: Not reached

Data cutoff date: 11/30/2023

Case Study: Confirmed Partial Response and Shrinkage of New Liver Lesions in a 3L MSS CRC Patient

Tumor Type: Female, 66 years old, advanced rectal adenocarcinoma stage IV with lung and lymph node metastasis.
- KRAS WT, BRAF normal, MSS, TMB 11.07muts/mb

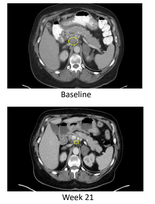
Prior Therapies: Previously received 2 lines of therapies:
- FOLFIRI + Vectibix
- Clinical trial G1290 with rivoceranib + Lonsurf

Dose Regimen: ADG126 10 mg/kg Q3W/Pembro 200 mg Q3W (5 cycles)

	Lesion #	Location	Baseline (mm)	6 weeks (mm)	12 weeks (mm)	21 weeks (mm)
Target lesion	TLR#1	Right lung	14	10	8	8
	TLR#2	Right lung	8	8	6	0
	TLR#3	LN	22	14	13	9
	TLR#4	LN	15	10	8	8
	Total		59	42 (-28.8%)	35 (-40.7%)	25 (-57%)
Non target lesions			Present	Present	Present	Present
New lesion	#1	Liver		16	8	0
	#2	Liver		12	7	6
	#3	Other		9	3	0
	Total			37	18 (-51%)	6 (-84%)
Overall response				uPD	PR*	PR*

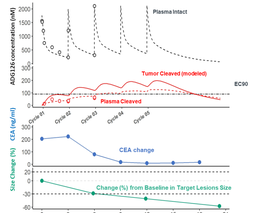
*Based on iRECIST assessment

Fig 5A. Treatment-induced change in the perihepatic lymph node



Courtesy of Dr Tammy Lamb, Florida Cancer Specialists

Fig 5B. Correlation of PK, CEA and Tumor Response



Conclusions

- The masked anti-CTLA-4 SAFEbody ADG126 (muzastotug) is designed to widen the therapeutic index by targeting a unique epitope of CTLA-4, precision masking for enhanced intra-tumoral Treg depletion.
- ADG126 administered at up to 10 mg/kg Q3W with repeat dosing in combination with pembrolizumab is well tolerated with 13% G3 TRAEs, 8% discontinuation rate and no G4/5 TRAEs or DLT.
- In dose escalation, 2 confirmed PR were observed among 3 subjects treated with 10 mg/kg Q3W ADG126/Pembro, which triggered dose expansion at this dose level.
- In dose expansion, 10 mg/kg Q3W ADG126/Pembro treatment in 12 subjects with MSS CRC resulted in 2 confirmed PR, and reduction of new liver lesions. This triggered further expansion into Stage 2 of the Simon's 2-stage design at this dose level.
- The favorable safety profile of ADG126/Pembro allows for continued treatment with repeated dosing, resulting in a long PFS (≥ 7 mons), especially in MSS CRC patients without liver and peritoneal metastasis.
- These promising data support further evaluation of this potential best-in-class anti-CTLA-4 antibody ADG126 (muzastotug) in combination with pembrolizumab in MSS CRC.