Abs #744

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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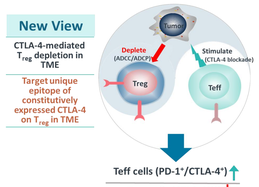
Background

- 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]



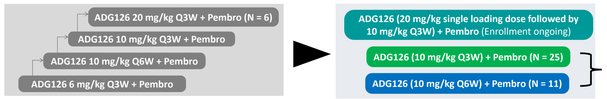
- ✓ ADG126 is a masked anti-CTLA-4 prodrug designed to improve therapeutic index (TI) by targeting a unique epitope of CTLA-4 on T regulatory cells (Treg) in the tumor microenvironment (TME).
- ✓ Over expression of CTLA-4 on Treg in TME helps to recruit ADG126 locally, where masking peptide is cleaved 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 Included in This Report

- 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 1**.

Table 1. Baseline Characteristics

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

Trial Safety and AE Summary

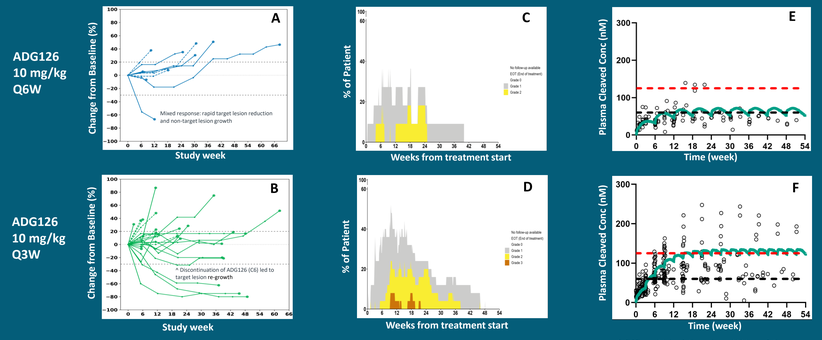
(MSS CRC Patients treated with ADG126 of 10 mg/kg Q3W or Q6W + Pembrolizumab 200 mg Q3W)

- 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 (Table 2).**
- **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 (Figure 2).**

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).

Figure 1. ADG126+Pembro Efficacy-Safety-Dose/Exposure Correlation in MSS CRC



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.[3]

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.

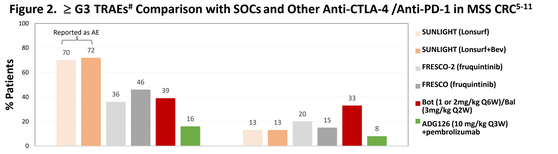
Highlights of Safety and TRAEs of MSS CRC Patients*

Table 2. 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[11]	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

Figure 2. ≥ G3 TRAEs# Comparison with SOCs and Other Anti-CTLA-4 /Anti-PD-1 in MSS CRC[5-11]



#. TRAEs unless otherwise noted

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

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

Table 3. Key Efficacy Parameters Summary

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

NLPM: no liver and peritoneal metastasis; ^ Mixed response: rapid target lesion reduction and non-target lesion growth

Figure 3. Duration of Treatment (MSS CRC)

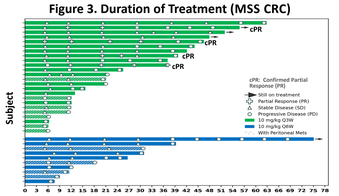


Table 4. Efficacy vs Benchmark SOCs in MSS CRC (NLM)

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**	

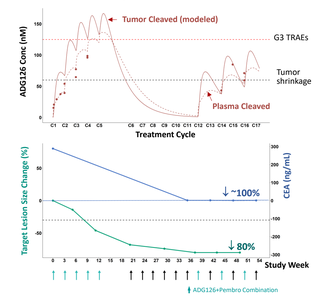
* All are without liver metastasis unless specified; **: No liver and no peritoneal metastasis. Source information: see References next to Figure 2.

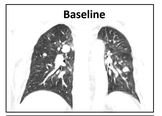
Case Study

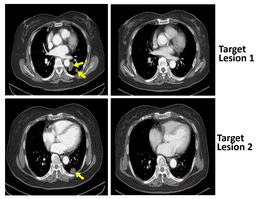
Tumor Type: Female, 64 years old, MSS CRC (liver metastasis-free)
Prior Therapies: 2 lines of prior therapies:
- Bevacizumab + Oxaliplatin + Leucovorin + 5-Fluorouracil
- Anti-TGF-β + Bevacizumab + Irinotecan HCL + 5-Fluorouracil + Leucovorin

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 **(images below)**
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 (**Fig. 4**)

Figure 4. Correlation between Tumor Shrinkage, CEA and Plasma Exposure







Images curtesy of Dr. Sun Young Kim

Summary:
- 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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