Abs #129

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

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Background

- Microsatellite-stable colorectal cancer (MSS CRC) represents ~ 95% of advanced /metastatic CRC population[1], a highly unmet medical need group typically does not respond well to immunotherapy (IO).
- ADG126 is an anti-CTLA-4 IgG1 masked antibody with cleavable masking peptides that is preferentially activated in the tumor microenvironment, which in turn binds to a unique epitope to block CTLA-4 function, prime T cells and deplete Treg cells.
- Integrated and quantitative assessment reveals that comparing to unmasked parental mAb[2], ADG126 has higher and sustained steady-state tumor-specific engagement of CTLA-4 in the TME and reduced peripheral drug exposure through the selective cleavage of ADG126. It has been under clinical development focusing on late stage MSS CRC in combination with pembrolizumab (Pembro) (NCT05405595)[3,4]
- We employed a loading dose (LD) strategy to explore possibilities of maximizing efficacy while minimizing toxicity.
- We report an ORR of 33% by ADG126 20 mg/kg x1 LD followed by 10 mg/kg Q3W + Pembro in 3L/4L MSS CRC Pts free of liver metastasis (NLM).

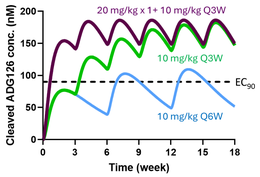


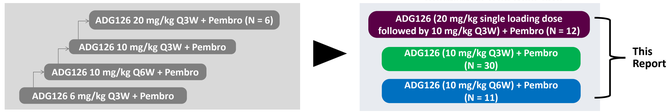
Figure 1. Model-predicted human tumor interstitial fluid (ISF) concentration of cleaved ADG126 based on clinical PK and mouse tumor tissue PK.

The 20 mg/kg x 1 Loading Dose approach (purple) is predicted to rapidly boost ISF active concentration in TME and maintain over human EC_{90} for increased efficacy compared to 10 mg/kg Q3W.[2]

References: 1, San-Román-Gil et al., Cancers (Basel). 2023;15:863 and references within. 2. Songmao Zheng et al., Abstract# 506, SITC Conference, 2024. 3, Daneng Li et al., Abstract# 6055, ESMO Congress 2024. 4. Daneng Li et al., Abstract# 744, SITC Conference, 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:

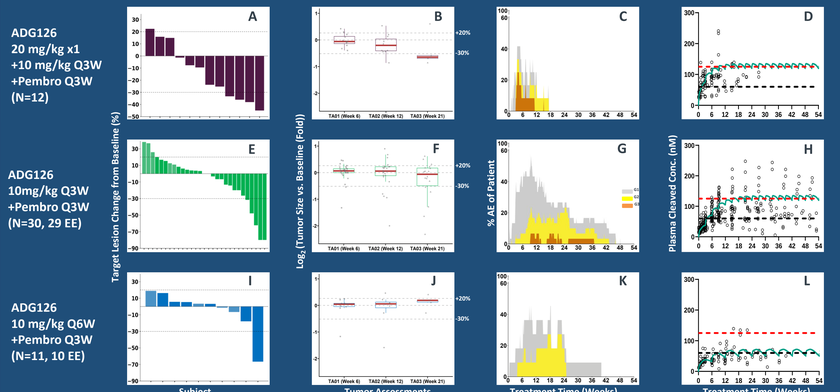


- The primary endpoints are safety and tolerability, MTD and RP2D.
- The secondary endpoints are PK, dose proportionality, immunogenicity of both agents and PK/PD relationship, and preliminary efficacy including ORR, DCR, DOR, PFS and OS etc., as assessed per RECIST 1.1 and/or iRECIST criteria.

Clinical Summary of ADG126 + Pembro in Advanced Metastatic MSS CRC

- **ADG126 20 mg/kg single LD + 10 mg/kg Q3W regimen further enhanced clinical efficacy (33% ORR; 4/12) compared to 10 mg/kg Q3W while maintaining a manageable safety profile. No G4/G5 TRAEs and no discontinuation were observed to date.**
- **Results from dose optimization demonstrated dose-dependent efficacy and clear concordance between ADG126 cleaved exposure in plasma vs. efficacy or safety.**
- **The totality of the data supports that the IO doublet has a therapeutic window that offers an effective and potentially best-in-class treatment option of anti-CTLA-4 + anti-PD-1 combination in hard-to-treat late stage MSS CRC and beyond.**

Figure 2. ADG126+Pembro Efficacy-Safety-Dose/Exposure Correlation in MSS CRC (NLM)

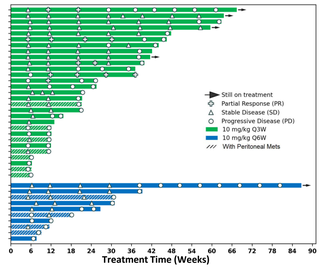


E and I: ▨ **represents patients with** peritoneal metastasis. TA: Tumor Assessment. **D, H, L: symbols are** measured individual plasma cleaved PK; **Solid lines:** PK simulation using mPBPK population parameters. **Black and red dashed lines:** reference plasma cleaved conc. associated with SD/PR and G3 TRAE, respectively.

A, E, I: Waterfall plots showing Best of Response of target lesions to ADG126 + Pembro; **B, F, J:** Box plots showing continuous target lesion size reduction for 20 mg/kg LD cohort but less obvious for the other two dose levels; **C, G, K:** Stacked area plots of TRAEs illustrating the cumulative incidence and severity of AEs over treatment time; **D, H, L:** Measured plasma exposure of cleaved ADG126 over treatment time.

Clinical Efficacy of MSS CRC Patients Treated by ADG126 + Pembro Combination

Figure 4. Duration of Treatment (MSS CRC)*



Data based on December 6, 2024 data-cut; *Excluding 20 mg/kg x1 +10 mg/kg Q3W (data not yet mature).

Table 3. Clinical Activity Parameters of MSS CRC Cohorts

ADG126 Dose Level + Pembro 200mg Q3W	10 mg/kg Q6W		10 mg/kg Q3W		20 mg/kg x1 +10 mg/kg Q3W
Subpopulation (N)	NLM (10)	NLPM (6)	NLM (29)	NLPM (22)	NLPM (12)
ORR, % (95% CI)	0[a] (0-31)	0[a] (0-46)	17[b] (6-36)	23[b] (8-45)	33[c] (10-65)
BoR, N (%)					
PR	0	0	5[b] (17)	5[b] (23)	4[c] (33)
SD	7 (70)	4 (67)	17 (59)	14 (64)	5 (42)
DCR (CR+PR+SD), %, (95% CI)	70 (35-93)	67 (22-96)	76 (56-90)	86 (65-97)	75 (43-95)
6-month CBR, %, (95% CI)	20 (3-56)	33 (4-78)	41 (24-61)	55 (32-76)	Data not mature
Median PFS, months (95%CI)	4.5 (1.4-7.1)	5.9 (1.4-NA)	4.8 (2.6-6.7)	6.7 (4.6-9)	Data not mature

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.

Figure 5. Schematics of Dosing and Safety Management Enabled Clinical Benefits (PR) in 20 mg/kg LD Cohort

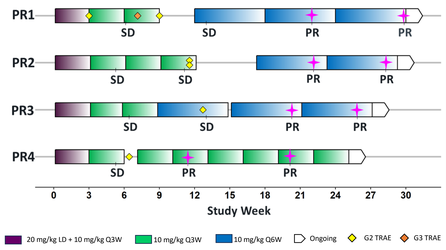
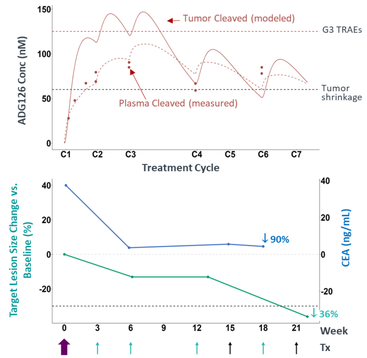


Figure 6. Case Study: Correlation of ADG126 PK, CEA and Efficacy



Patient Information for Figure 6

Male, 68 years old
Tumor Type: MSS CRC (NLPM)
Prior Therapies: XELOX in adjuvant followed with FOLFIRI+Bev and 5-FU/LV+Bev.
Baseline Total Target Lesion Size: 61 mm
Dose Regimen: ADG126 20 mg/kg x1 + 10 mg/kg Q3W + Pembro 200 mg Q3W; then ADG126 10 mg/kg Q6W + Pembro 200 mg Q3W
G2/G3 AEs: G3 Diarrhea, G2 Adrenal Insufficiency
Efficacy: Initial PR; 36% target lesion reduction at last assessment.

⬆ ADG126 20mg/kg x1 + Pembro
↑ ADG126 10mg/kg Q3W+Pembro
↑ Pembro mono dose

Patients Characteristics

- As of Dec 6, 2024, 83 Pts have been treated in ADG126-P001.
- There are 17 Pts in Dose Escalation (DE, all comers) and 66 Pts in Dose Expansion (EXP), among which, 53 Pts are advanced MSS CRC (**Table 1**).

Table 1. Baseline Characteristics of MSS CRC Patients in EXP Phase

Characteristics	N=53
Age (Years), Median(range)	59 (26-75)
Female, n(%)	28 (53%)
Race, n(%)	
Asian, (n%)	38 (72%)
White, n(%)	15 (28%)
ECOG 0/1, n(%)	16 (30%)/37 (70%)
Prior line of therapy ≥ 3	18 (34)
Prior immunotherapy, n(%)	0
Demographics	
US	16
SK	36
CHN/HK	1
Without Liver Metastasis (NLM)	100%
Peritoneal involvement	12 (23%)

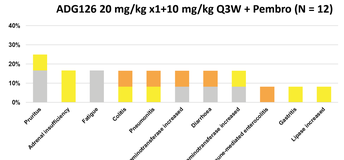
MSS CRC Cohorts Safety and AE Summary

- **Overall (Table 2):**
  - No dose-limiting toxicities (DLT) or G4/5 TRAEs.
  - 10 TRSAEs (19 SAEs); discontinuation rate due to TRAE remains low (6%).
  - 6% (3/53) Pts received infliximab for diarrhea/colitis
- **10 mg/kg Q3W:** 20% G3 TRAEs with an average follow-up time of 11 months, indicating a manageable safety profile, consistent with previous reports.
- **20 mg/kg LD:** Higher G2/G3 TRAEs but manageable through dose modification and infrequent use of infliximab/medical intervention, affording no treatment discontinuation and clinical benefits (Table 2, Figure 3).

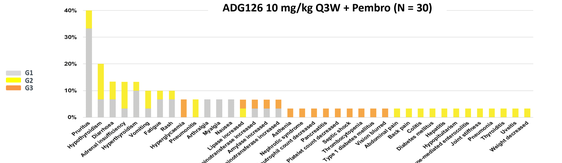
Table 2. Summary of Key TRAEs of ADG126 + Pembrolizumab in MSS CRC Patients (EXP)

Dose levels (mg/kg)	N	All G n (%)	G1 n (%)	G2 n (%)	G3 n (%)	G4/G5 n (%)	Discont. Rate
All	53	44 (83)	13 (25)	20 (38)	11 (21)	0	3 (6%)
10 mg/kg Q6W	11	8 (73)	2 (18)	6 (55)	0	0	0
10 mg/kg Q3W	30	26 (87)	8 (27)	12 (40)	6 (20)	0	3 (10%)
20 mg/kg x1 +10 mg/kg Q3W	12	10 (83)	3 (25)	2 (17)	5 (42)	0	0

Figure 3. TRAE Profile of 20 mg/kg LD and 10 mg/kg Q3W cohorts ADG126 + Pembro in Dose Expansion MSS CRC Patients.



Excluding Preferred Term with G1 TRAE that occurred only once.



Conclusions

- The ADG126 loading dose strategy at 20 mg/kg coupled with dose modification (when necessary) can improve efficacy while maintaining manageable safety in late stage MSS CRC patients. This strategy delivered a higher ORR than SOCs and other investigational anti-CTLA-4 plus anti-PD1 combination therapies tested in advanced MSS CRC.
- Clinically confirmed safe doses of ADG126 in combination with Pembro should enable tailored and robust development plans targeting specific lines of therapy/populations/diseases. Studies that further investigate clinical benefits of ADG126 + Pembro as IO doublet in advanced MSS CRC and/or as an IO backbone therapy in combination with line/disease-specific SOCs are being initiated/planned.

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