Abs #3579

Safety and Efficacy of ADG126 (an Anti-CTLA-4 Masking Antibody) in Combination with Pembrolizumab: Updated Results of Phase 1b/2 Study in Advanced MSS CRC

Poster #248

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Introduction and Background

Microsatellite Stable (MSS) CRC accounts for ~95% of all metastatic CRC and remains largely unresponsive to first-generation checkpoint inhibitors[1]. MSS CRC is characterized by an immunologically "cold" tumor microenvironment (TME), defined by high infiltration of CTLA-4$^+$ regulatory T cells (Tregs), low levels of CD8$^+$ T cells (TILs), and minimal or negative PD-L1 expression.

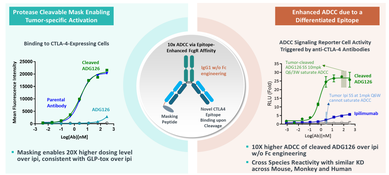
ADG126 is a masked anti–CTLA-4 IgG1 SAFEbody™ with cleavable masking peptides engineered to be preferentially activated in the TME. It binds to a unique epitope to block CTLA-4 function, primes T cells and depletes Tregs through epitope-enhanced ADCC/P (**Fig. 1**).

ADG126 can be dosed more than 6-fold higher in combination with anti-PD-1 antibodies with predicted tumor active drug exposures ≥ 10 to 20-fold higher than its unmasked parental antibody and with significantly reduced on-target/off-tumor toxicities[2].

This selective TME reprogramming of ADG126 promotes TILs and synergizes with anti-PD-1 therapies such as pembrolizumab (Pembro) to elicit anti-tumor activity.

We have been conducting a Phase 1b/2 trial evaluating ADG126 + Pembro combination (NCT05405595) in late line MSS CRC[3]. Here we share the updated results of clinical efficacy and safety of the IO doublet across several dose levels/regimens guided by quantitative PK/PD modeling.

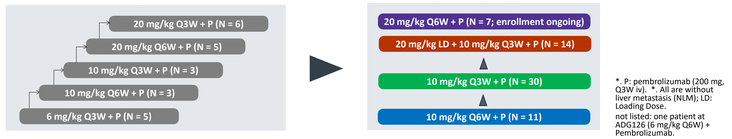
Figure 1. Unique and Effective Mechanism of Action (MOA) of ADG126



References: 1, San-Román-Gil et al., Cancers (Basel). 2023;15:863 and references within. 2, Zheng S. et al., Abstract#506, SITC Annual Meeting, 2024. 3. Daneng Li et al., Abstract#129, ASCO GI Conference, 2025, and references within.

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:

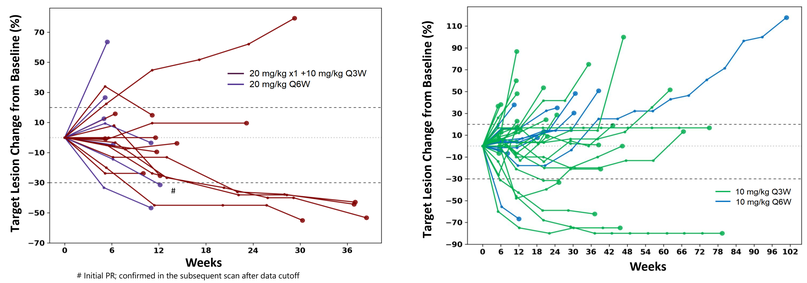


*. P: pembrolizumab (200 mg, Q3W iv). *. All are without liver metastasis (NLM); LD: Loading Dose.
not listed: one patient at ADG126 (6 mg/kg Q6W) + Pembrolizumab.

- 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 Efficacy of MSS CRC Patients

Figure 2. Time Course of Target Lesion Response MSS CRC Patients in EXP (N=60 EE)



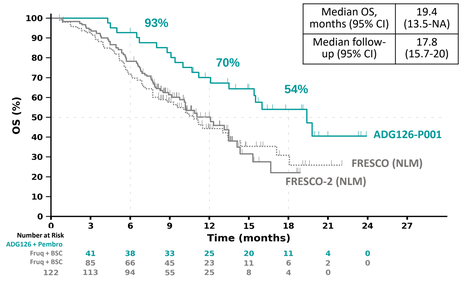
Initial PR; confirmed in the subsequent scan after data cutoff

Table 2. Summary of Clinical Activity of MSS CRC Cohorts (NLM)

ADG126 Dose Level + Pembro 200mg Q3W	10 mg/kg Q3W (N=29)	20 mg/kg Combined (N=21)
ORR% (95% CI)	17 (6-36)	29 (11-52)
BoR, N (%)		
PR	5[a] (17)	6[b] (29)
SD	17 (59)	11 (52)
DCR (CR+PR+SD)%, (95% CI)	76 (56-90)	81 (58-95)
6-month CBR%, (95% CI)	38 (21-58)	Data not mature
Median PFS, months (95%CI)	4.8 (2.6-6.7)	NR (2.7-NA)
6-month PFS%, (95% CI)	39.5 (21.8-56.7)	50.4 (20.7-74.2)
Median DoR, months (95%CI)	6.2 (4.2-NA)	NR (all PRs are ongoing)

a. Including one unconfirmed PR (10 mg/kg Q3W). b. all PRs are confirmed.
NR: Not reached; NA: not available

Figure 3. OS of MSS CRC NLM Patients Treated with ADG126 10 mg/kg (Q3W + Q6W) + Pembro vs. Fruquintinib Historical Controls



Median OS, months (95% CI)	19.4 (13.5-NA)
Median follow-up (95% CI)	17.8 (15.7-20)

Source FRESCO: Li J.et al. JAMA. 2018;319(24):2486–2496; FRESCO-2: Garcia-Carbonero, R. et al .Annals of Oncology, Volume 35, S439. Fruq: fruquintinib. BSC: Best Standard of Care (used in trial)

MSS CRC Cohorts Safety and AE Summary

Table 3. Summary of Percent of TRAEs from ADG126 + Pembro Treatments in MSS CRC Patients

Dose levels (mg/kg)	N	All G n (%)	G1 n (%)	G2 n (%)	G3 n (%)	Discont. Rate (%)
All	**67**	**55 (82)**	**20 (30)**	**22 (33)**	**13 (19)**	**3 (4)**
10 mg/kg Cohorts	**41**	**34 (83)**	**10 (24)**	**18 (44)**	**6 (15)**	**3 (7)**
10 mg/kg Q6W	11	8 (73)	2 (18)	6 (55)	0	0
10 mg/kg Q3W	30	26 (87)	8 (27)	12 (40)	6 (20)	3 (10%)
20 mg/kg Cohorts	**26**	**21 (81)**	**10 (38)**	**4 (15)**	**7 (27)**	**0**
20 mg/kg Q6W	12	10 (83)	6 (50)	2 (17)	2 (17)	0
20 mg/kg x1 +10 mg/kg Q3W	14	11 (79)	4 (29)	2 (14)	5 (36)	0

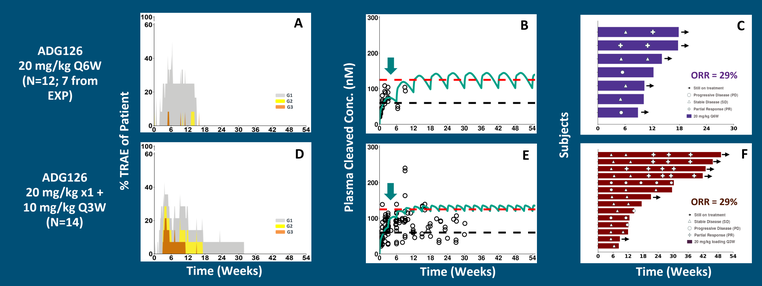
Table 4. Summary of >=10% TRAEs from ADG126 + Pembro Treatments in MSS CRC Patients

Preferred Term (≥10%)	All G n (%)	G1 n (%)	G2 n (%)	G3 n (%)
Any TRAE	55 (82.1)	20 (29.9)	22 (32.8)	13 (19.4)
Pruritus	23 (34.3)	19 (28.4)	4 (6)	0
Diarrhea	9 (13.4)	3 (4.5)	4 (6)	2 (3)
Hypothyroidism	9 (13.4)	3 (4.5)	6 (9)	0
Fatigue	8 (11.9)	6 (9)	2 (3)	0
Adrenal insufficiency	7 (10.4)	2 (3)	5 (7.5)	0

- **Overall:** No dose-limiting toxicities (DLT) or G4/5 TRAEs; low discontinuation rate (4%).
- **10 mg/kg Q3W:** Average follow-up time of 13.2 months; manageable safety profile consistent with previous reports.
- **20 mg/kg Q6W:** Lower G3 TRAE% than that from 20 mg/kg x1 +10 mg/kg Q3W cohort.
- **20 mg/kg x1 +10 mg/kg Q3W:** Manageable AE/safety profile. Infrequent use of infliximab.

Integrative View: Identification of "Induction Phase" for ADG126 + Pembrolizumab

Figure 5. Safety Kinetics, Plasma Cleaved ADG126 and ORR of 20 mg/kg Cohorts



Stacked area plots of TRAEs illustrating the cumulative incidence and severity of AEs over treatment time (**A, D**), the corresponding plasma cleaved ADG126 concentration over time (**B, E**) and treatment time course (**C, F**). **B & E**: symbol represents measured individual plasma cleaved PK; solid lines represent mean PK simulation using mPBPK population parameters; black and red dashed lines represents reference plasma cleaved conc. associated with SD/PR and G3 TRAE through E-R analysis, respectively, based on previously reported values when both cohorts' data were not included (ESMO 2024 Poster No. 578P).

- The E-R illustration focuses on the **"Induction Phase"** cohorts: 20 mg/kg x1 + 10 mg/kg Q3W and 20 mg/kg Q6W.
- 20 mg/kg Q6W resulted in better longitudinal safety profile (**A**) vs. 20 mg/kg x1 + 10 mg/kg Q3W (**D**), consistent with the differential plasma cleaved PK profile (**B** and **E**).
- After the initial loading dose at 20 mg/kg, the 2nd dose of 10 mg/kg dose resulted in the plasma cleaved ADG126 concentration to approach G3 TRAE threshold (red dash line) between week 3-6 (**arrow in E**), while 20 mg/kg Q6W did not (**arrow in B**). Both regimens reached the target plasma efficacious concentration (black dash line) in cycle 1, which correlated to a similar and meaningful ORRs (29%; **C and F**) .
- Dose optimization guided by PK-PD modeling revealed that 20 mg/kg Q6W is a more desirable loading dose during the Induction Phase.

Patients Characteristics

- As of April 22, 2025, 97 Pts have been treated in ADG126-P001: 22 Pts in DE (all comers) and 75 Pts in EXP (primarily MSS CRC).
- 67 Pts (5 from DE, 62 from EXP) are metastatic MSS CRC.

Table 1. Baseline Characteristics of MSS CRC Patients

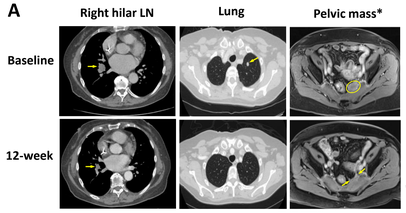
Characteristics	N=67
Median Age (Years), (range)	58 (24-75)
Female, n(%)	35 (52)
Race, n(%)	
Asian, (n%)	46 (69)
White, n(%)	21 (31)
ECOG 0/1, n(%)	24 (36%)/43 (64)
Prior line of therapy ≥ 3, n(%)	23 (34)
Prior immunotherapy, n(%)	0
Demographics	
US, n	24
SK, n	36
CHN/HK, n	7 (CHN=5; HK=2)
Without Liver Metastasis (NLM), n(%)	66 (99)
Peritoneal involvement, n(%)	15 (22)

Case Study: Tumor Reduction and CEA Reduction

Patient Information:

75 years old female; MSS CRC (NLM), p53 and APC mutation, RAS WT
Prior Therapies: FOLFOX; FOLFIRI +panitumumab → maintenance 5-FU + bevacizumab
Baseline Total Target Lesion Size: 59 mm (sum of three).
Dose Regimen: ADG126 20 mg/kg Q6W + Pembro 200 mg Q3W;
AE Profile: G2 lipase increase, G1 amylase increase and G1 fatigue
Efficacy: Partial response (-31%) at week-12 with corresponding decrease in CEA

Figure 4. Radiology View of Target Lesion Reduction (A) and Concurrent CEA Reduction (B)

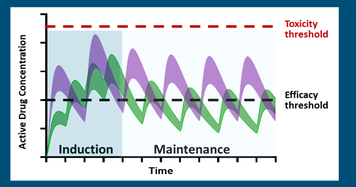


* With peritoneal involvement

Conclusions

- **The ADG126 + pembrolizumab treatment shows an ORR of 29% with an acceptable safety profile that allows for repeated dosing. Early evaluation of OS shows promising results that justify further clinical development of this combination.**
- **A predictive framework based on the quantitative PK/PD/E-R modeling has been developed that informs dosing regimens of ADG126 + pembrolizumab for treating MSS CRC (NLM).**
- **An induction phase (higher ADG126 dose/more frequent dosing schedule) followed by maintenance phase (lower ADG126 dose/less frequent dosing schedule) holds the potential to maximize efficacy and minimize accumulative treatment related toxicities for long-term clinical benefits.**
- **A randomized study is planned for further dose optimization to meet Project Optimus requirements.**

Figure 6. Conceptual Framework for the Induction Phase and Maintenance Phase Dosing Approach for ADG126



- Implementing an induction phase with either less frequent administration of a higher dose (e.g., 20 mg/kg Q6W) or more frequent administration of a lower dose (e.g., 10 mg/kg Q3W), followed by a maintenance phase with less frequent, lower dosing (e.g., 10 mg/kg Q6W), can optimize clinical efficacy—such as objective response rate (ORR) and duration of response (DoR), while minimizing cumulative treatment-related toxicities.
- A randomized clinical study evaluating two regimens leveraging this framework can allow for the determination of a most optimal regimen that can be used in future clinical studies.

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