ADAGENE

AACR 2026
Abstract Number: CT083

Ph1b evaluation of ADG126 (muzastotug, an anti-CTLA-4 masking antibody) pembrolizumab (Pembro) IO doublet in combination with fruquintinib (Fruq) in advanced and metastatic microsatellite stable colorectal cancer

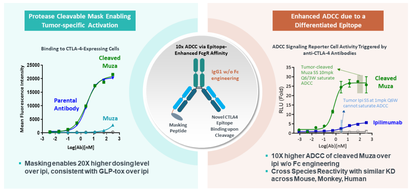
Marwan Fakih[1], Sunil Sharma[2], Manish R. Patel[3], Daneng Li[1], Yan Li[4], Luke Chung[4], Songmao Zheng[4], Xiaohong She[4], Stanley Frankel[4], Michael J. Chisamore[5], Peter Luo[4], Jiping Zha[4]

1. City of Hope Comprehensive Cancer Center, Los Angeles, CA; 2. Honor Health Research Institute, Scottsdale, AZ; 3. Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; 4. Adagene Inc., San Diego, CA 92121; 5. Merck & Co., Inc., Rahway, NJ, USA

Background

- Microsatellite Stable (MSS) CRC accounts for ~95% of all metastatic CRC[1] and remains largely unresponsive to first-generation checkpoint inhibitors. 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.

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



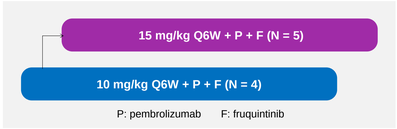
- ADG126 (muzastotug, Muza) is a masked anti–CTLA-4 IgG1 SAFEbody™ with cleavable masking peptides engineered to be preferentially activated in the TME. It binds to a unique epitope to block CTLA-4 function, primes T cells and depletes Tregs through epitope-enhanced ADCC/P (Fig. 1). The current Muza + pembrolizumab (Pembro) IO doublet focuses on non-liver metastases[2], which constitutes ~1/4 of 3L+ MSS CRC patients. The enhanced therapeutic window (safety) of Muza (e.g., 6x higher dosing compared to ipilimumab) allows for combination with standard of care (SOC) treatments, which is not possible for other CTLA-4 agents due to concerns of additive safety.
- Fruquintinib (Fruq) is an approved VEGF inhibitor for treating 3L+ MSS CRC regardless of liver metastasis status with a more pronounced efficacy in LM patients. The encouraging safety profile of Muza + Pembro provides the opportunity for combination with Fruq to potentially expand the current population for the Muza + Pembro IO doublet. As an initial proof of concept, we have tested the triple combo in NLM patients to evaluate for safety and efficacy. Tolerable combination with Fruq is one example of using the IO doublet as a backbone for combination with SOC treatment.
- We have been conducting a Phase 1b/2 trial evaluating Muza + Pembro + Fruq combination (NCT05405595) in late line MSS CRC. Here we share the first results of clinical efficacy and safety of the IO triplet across two dose levels.

References: 1, San-Román-Gil et al., Cancers (Basel). 2023;15 (3) :863 and references within. 2. Daneng Li et al., Abstract #3579, ASCO, 2025, and references within.

Method

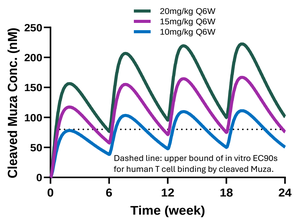
- This is a Phase 1b/2, open-label, multicenter dose escalation study of Muza (10 or 15 mg/kg Q6W IV) + Pembro (400 mg, Q6W IV) + Fruq (5 mg/day PO, 3 weeks on and 1 week off) in advanced solid tumors. All patients were without liver metastasis (NLM). Primary endpoints include safety and tolerability, ORR and DOR. Secondary endpoints include PK, ADA, PFS and OS. The study design schema for the dose escalation (DE) MSS CRC cohorts is shown.

Dose Escalation (Muza Dose Level)



- Modeled Tumor PK concentrations for cleaved Muza based on data from the Muza + Pembro IO doublet. Modeling was used to select starting doses for triplet.

Muza Mean Tumor ISF Predicted PK in Patients



Tumor interstitial fluid (ISF) cleaved Muza PK in MSS CRC patients predicted based on mPBPK modeling methods as described in SITC 2023 Poster 847

Patient characteristics

- As of Feb 21, 2026, 9 Pts have been treated with Muza + Pembro + Fruq.
- 9 Pts from DE cohort are metastatic MSS CRC

Table 1. Baseline Characteristics of MSS CRC Patients

Characteristics	N = 9
Median Age, years(range)	48 (29-78)
Female, n(%)	2 (22)
Race, n(%)	
Other, n(%)	2 (22)
White, n(%)	7 (78)
ECOG 0/1, n(%)	7 (78)/2 (22)
Prior line of therapy ≥ 3, n(%)	5 (56)

Characteristics	N = 9
Prior immunotherapy, n(%)	0
Demographics	
US (n%)	9 (100)
With Liver Metastasis (NLM), n(%)	0
Peritoneal involvement, n(%)	1 (11)
Prior fruquintinib treatment, n(%)	0

Clinical efficacy

Figure 2. Waterfall (A) and Time Course (B) of Target Lesion Response MSS CRC Patients

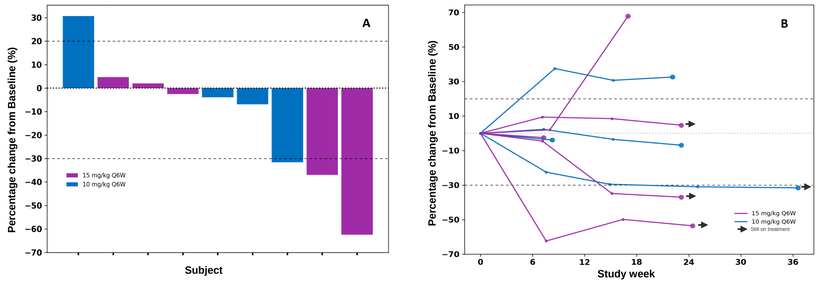


Figure 3. Swimmer Plot of Patient Response Over Time

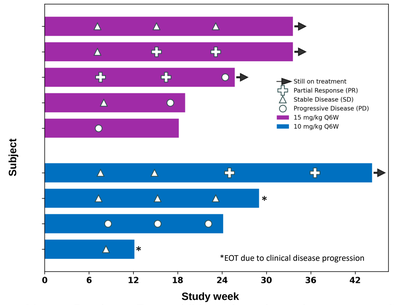


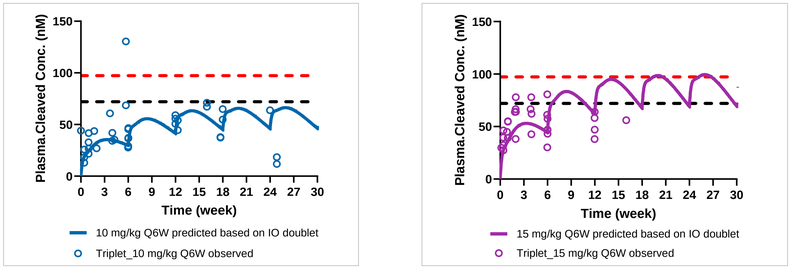
Table 2. Clinical Activity Parameters of MSS CRC Cohort

Muza Dose Level + Pembro + Fruq	10 mg/kg Q6W (N = 4)	15 mg/kg Q6W (N = 5)
ORR, % (95% CI)	25 (1-81)	40 (5-85)
BoR, N (%)		
PR	1 (25)	2 (40)
SD	2 (50)	2 (40)
CBR (CR, PR, or SD ≥6 months)	25 (1-81)	40 (5-85)
DCR (CR+PR+SD), % (95% CI)	75 (19-99)	80 (28-99)
Median PFS, months (95% CI)	NR (2-NA)	5.6 (1.7-NA)
Median follow-up, months (95% CI)	6.7 (5.6-NA)	5.9 (4.2-NA)

- Muza + Pembro + Fruq exhibits a dose-dependent response (25% and 40% ORR for 10 mg/kg and 15 mg/kg, respectively) with 3 confirmed PRs as assessed by RECIST v1.1
- The response is durable with at least one patient remaining on treatment beyond 42 weeks

Muza Plasma Cleaved (i.e., Active) Drug PK for Triplet (+Fruq) at 10 and 15 mg/kg Q6W vs. IO doublet prediction

Figure 4. Muza measured plasma cleaved PK for triplet (+Fruq) at 10 and 15 mg/kg Q6W vs. IO doublet-based prediction



- Triplet combo does not change the plasma cleaved PK of Muza vs. IO doublet (Muza + Pembro)
- 10 and 15 mg/kg Q6W observed data (triplet, symbols) are generally within the prediction range of IO doublet PK modeling (dashed reference lines represent cleaved concentrations associated with any reduction in target lesion(s) measurement [black] and Gr3 TRAEs [red] from E-R analysis of IO doublet)
- Predictable PK behavior in the triplet setting combined with safety and efficacy can be used to guide development of further tailored dosing regimen (e.g., with induction and maintenance phases)

Safety parameters

Table 3. Treatment Emergent Adverse Events

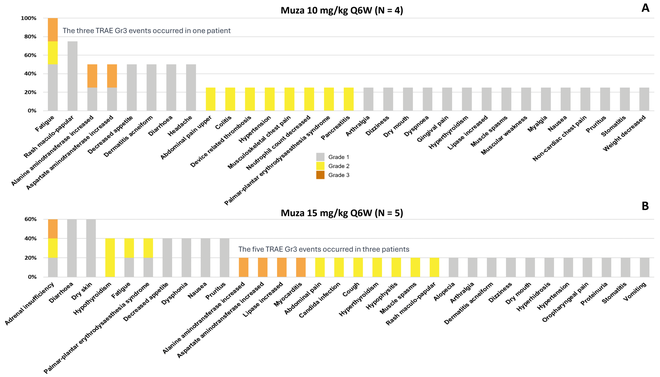
Dose levels (Muza mg/kg)	N	All G: N (%)	G1: N (%)	G2: N (%)	G3: N (%)	Discont. Rate (%)
All	9	9 (100)	0	4 (44)	5 (56)	0
10 mg/kg Q6W	4	4 (100)	0	2 (50)	2 (50)	0
15 mg/kg Q6W	5	5 (100)	0	2 (40)	3 (60)	0

Table 4. Treatment Related Adverse Events

Dose levels (Muza mg/kg)	N	All G: N (%)	G1: N (%)	G2: N (%)	G3: N (%)	Discont. Rate (%)
All	9	9 (100)	0	5 (56)	4 (44)	0
10 mg/kg Q6W	4	4 (100)	0	3 (75)	1 (25)	0
15 mg/kg Q6W	5	5 (100)	0	2 (40)	3 (60)	0

- **Safety & Tolerability:** No DLTs or Grade 4/5 TEAEs/TRAEs, and no new safety signals at studied dosages relative to known CTLA-4, PD-L1, and Fruq monotherapy and combination safety signals. Fruq was dose modified for 3/4 and 5/5 patients in 10 mg/kg and 15 mg/kg cohorts, respectively.
- **Discontinuation Rate:** 0% for the combination regimen, compared to 15-20% historical discontinuation rate for Fruq monotherapy (FRESCO/FRESCO-2).
- **Overall Profile:** Manageable and transient, demonstrating safety comparable to Fruq monotherapy (historical Gr3+ TEAEs of 61-63%; Gr3+ TRAEs of 36-46%) despite the addition of dual immunotherapy.

Figure 5. TRAE frequencies by type



Conclusions

- The Muza + Pembro + Fruq combination treatment shows promising dose-dependent efficacy in 3L+ MSS CRC NLM patients with ORR of 25% and 40% at 10 mg/kg and 15 mg/kg Muza, respectively
- The enhanced therapeutic window of Muza + Pembro doublet enables its combination with Fruq, with no DLT, 25-60% Grade 3 TRAEs and no Grade 4/5 TRAEs, compared to that (36-46%) of Fruq
- Given Fruq is active in MSS CRC patients with liver mets, the triple combo may have therapeutic benefit beyond NLM population
- The safety profile of this triplet suggests that it is possible to combine with other anti-VEGF therapies in late and early line settings of MSS CRC

This study ADG126-P001 (NCT05405595) is sponsored by Adagene Inc. and is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

We would like to acknowledge all patients, PIs and medical staff involved in ADG126-P001 trial; Jack Skinner and Zhining Wan for review and critical input. Authors would like to thank Ying Wu for graphics support.