Results from the phase 1b/2 Morpheus Liver study in patients with unresectable locally advanced or metastatic hepatocellular carcinoma (HCC): muzastotug (ADG126: masked anti-CTLA-4 Ab) combination arm

ADAGENE

AACR 2026
Abstract Number: CT054

Daneng Li[1], Edward Gane[2], Chih-Hung Hsu[3], Adam Burgoyne[4], Peter Luo[5], Songmao Zheng[5], Yan Li[5], Xiaohong She[5], Stanley Frankel[5], Jiping Zha[5], Ann-Lii Cheng[3]

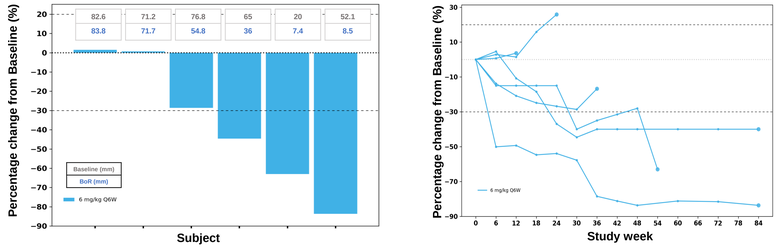
1. City of Hope Comprehensive Cancer Center, Los Angeles, 2. Auckland City Hospital, Auckland, New Zealand, 3. National Taiwan University Cancer Center, Taipei, 4. University of California, San Diego Medical Center, 5. Adagene Inc., San Diego, CA 92121

Introduction and background

- Hepatocellular carcinoma (HCC) accounts for ~90% of primary liver cancers. Current treatment options including atezolizumab (Atezo) + bevacizumab (Bev), durvalumab + tremelimumab (Treme), nivolumab + ipilimumab (Ipi) and tyrosine kinase inhibitors offer modest long-term survival benefit and the majority of patients fail to achieve significant tumor shrinkage.
- The HCC tumor microenvironment (TME) is immunosuppresive, characterized by heavy infiltration of Tregs and low PD-L1 expression. Overcoming Treg burden requires intense, high-dose CTLA-4 blockade. Legacy unmasked therapies require mandatory cycle limits due to systemic toxicities. For example, 3 mg/kg Ipi is capped at 4 cycles and Treme is restricted to a single 300 mg priming dose. Forced discontinuation prevents sustained, continuous administration to maintain long-term Treg suppression.
- Muzastotug (Muza, ADG126) is a masked anti-CTLA-4 IgG1 SAFEbody™ with cleavable masking peptide preferentially activated in the TME. Upon cleavage, Muza binds to a unique epitope to potentially block CTLA-4 function, primes T cells and forcefully depletes Tregs via epitope-enhanced antibody-dependent cellular cytotoxicity/phagocytosis (ADCC/P).
- Here we report the interim safety and efficacy results for the randomized Muza + Atezo + Bev triplet compared directly against the active control cohort (Atezo + Bev) in the 1L setting for the MORPHEUS-Liver trial (NCT04524871).

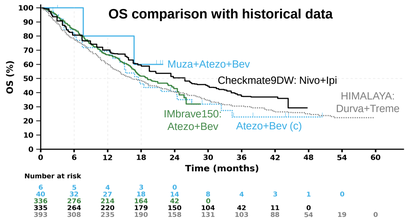
Clinical efficacy

Waterfall and spider plots: efficacy for Muza + Atezo + Bev treatment arm



- Muza + Atezo + Bev resulted in higher ORR compared to the Atezo + Bev control arm (66.7% vs 32.5% based on HCC-specified modified RECIST v1.1 and 50% vs. 17.5% based on RECIST v1.1)
- Muza + Atezo + Bev similarly outperformed control in terms of DoR, PFS, and OS, though interpretation is limited by sample size. OS for the Atezo + Bev control arm is essentially overlapping with that reported for IMbrave150 and largely overlapping with PD-1 (Sinti, Tori) + Bev (data not shown).

OS comparison with historical data



	Median OS, months (95% CI)
Muza 6 mg/kg Q6W + Atezo + Bev (n=6)	NR (7.66-NA)
Atez+Bev (c) (n=40)	17.51 (12.98-27.07)
IMbrave150: Atezo + Bev (n=336)	19.2 (17.0-23.7)
Checkmate9DW: Nivo + Ipi (n=335)	23.7 (18.8-29.4)
HIMALAYA: Durva + Treme (n=393)	16.43 (14.16-19.58)

RECIST v1.1

	Atezo+Bev (c) (N=40)	Muza 6 mg/kg Q6W Atezo+Bev (N=6)
ORR, % (95% CI)	17.5 (7.3-32.8)	50.0 (11.8-88.2)
BoR, N (%)		
CR	1 (2.5)	0
PR	6 (15.0)	3 (50.0)
SD*	19 (47.5)	2 (33.3)
DCR# %, (95% CI)	52.5 (36.1-68.5)	83.3 (35.9-99.6)
Median DoR, months (95%CI)	NR (NA-NA)	NR (>16 months) (4.2-NA)
Median PFS, months (95%CI)	4.3 (2.8-11.4)	8.2 (5.6-NA)
Median OS, months (95%CI)	17.5 (13.0-27.1)	NR (>22 months) (7.7-NA)
Median duration of follow-up (months)	17.2	18.8

HCC-specified modified RECIST v1.1

	Atezo+Bev (c) (N=40)	Muza 6 mg/kg Q6W Atezo+Bev (N=6)
ORR, % (95% CI)	32.5 (18.6-49.1)	66.7 (22.3-95.7)
BoR, N (%)		
CR	5 (12.5)	0
PR	8 (20.0)	4 (66.7)
SD*	15 (37.5)	1 (16.7)
DCR# %, (95% CI)	57.5 (40.9-73.0)	83.3 (35.9-99.6)
Median DoR, months (95%CI)	14.4 (4.2-NA)	NR (>16 months) (2.7-NA)
Median PFS, months (95%CI)	5.5 (4.2-11.4)	8.2 (5.6-NA)
Median OS, months (95%CI)	17.5 (13.0-27.1)	NR (>22 months) (7.7-NA)
Median duration of follow-up (months)	17.2	18.8

Criteria for disease control is either response and/or stable disease or better for at least 12 weeks.
* Patients were classified as "Stable Disease" if assessment was at least 6 weeks from randomization
Median duration of follow-up of 18.8 and 17.2 months for Muza + Atezo + Bev and for Atezo + Bev, respectively.

Conclusions

- Encouraging Efficacy: In 1L HCC, Muza + Atezo + Bev demonstrated promising ORR of 66.7% by HCC-specific modified RECIST v1.1 and 50.0% by RECIST v1.1 (n=6), compared with 32.5% and 17.5%, respectively, for Atezo + Bev (n=40). These findings suggest deep responses with the Muza-containing triplet despite the limited sample size. Notably, a similar triplet regimen of Ipi at 1 mg/kg Q3W + Atezo + Bev did not improve outcomes versus Atezo + Bev and showed slightly worse tolerability[1].
- Long-term Safety and Durability: Muza + Atezo + Bev showed a safety profile comparable to Atezo + Bev and demonstrated encouraging durability, with duration of response not reached and responses maintained beyond 84 weeks in some patients. Ongoing Muza + Atezo treatment after Bev discontinuation further suggests potential flexibility to modify individual agents during safety-related interruptions while preserving durable clinical benefit.
- Redefine the Combination Dose Ceiling: Muza successfully uncoupled efficacy from typical anti-CTLA-4 toxicity. It was safely administered continuously at 6 mg/kg Q6W in this triplet setting. Approved HCC CTLA-4 regimens have shown dose-dependent ORR and survival (e.g., CheckMate 040) but are limited by toxicity. Muza exceeded the dosing ceilings of currently approved HCC regimens, operating at 2x the dose of Ipi (capped at 3 mg/kg for only 4 cycles) and contrasting sharply with Treme (restricted to a single 300 mg priming dose).
- Future directions: These encouraging results support further clinical development of the Muza-containing triplet in 1L HCC and beyond. The safe combination of continuous, high-dose CTLA-4 blockade with current SoC of PD-(L)1 + VEGF suggests that Muza may improve efficacy over current SoCs while preserving the flexibility to discontinue Bev in the setting of Bev-related toxicity, an optionality that may not be available with bispecific PD-(L)1/VEGF antibodies.

Reference: 1. Philippe Merle. ESMO 2025 (Oral) 1471MO and references within.

Methods and study design schema

- The MORPHEUS-Liver study is a Phase 1b/2, open-label, multicenter, randomized umbrella study designed to evaluate immunotherapy-based combinations in patients with locally advanced or metastatic HCC. The primary endpoint was ORR. Secondary endpoints include DoR, safety, PFS and OS. We report here on the Muza (6 mg/kg Q6W IV) + Atezo (1200 mg Q3W IV) + Bev (15 mg/kg Q3W IV) as well as the Atezo + Bev control arm. Patients were randomized between arms.

Randomization between relevant arms

- Muza + Atezo + Bev (N = 6)
- Atezo + Bev (N = 40)

Patient characteristics

- As of Jul 11, 2025, 6 Pts have been treated with Muza + Atezo + Bev. 40 Pts have been treated with Atezo + Bev.

Baseline Characteristics

Characteristic	Atezo+Bev (N=40)	Muza 6 mg/kg Q6W Atezo+Bev (N=6)
Median Age (Years), (range)	66.5 (42-86)	65 (54-82)
Female, n(%)	5 (12.5)	1 (16.7)
Race, n(%)		
Other, n(%)	14 (35)	2 (33.3)
Asian, n(%)	16 (40)	2 (33.3)
White, n(%)	10 (25)	2 (33.3)
ECOG 0/1, n(%)	31 (77.5)/9 (22.5)	5 (83.3)/1 (16.7)
Child-Pugh Class A5/A6/B7, n(%)	28 (70)/11 (27.5)/1 (2.5)	5 (83.3)/1 (16.7)/0
Metastatic disease, n(%)	17 (42.5)	1 (16.7)
BCLC Stage at study entry, n (%)		
A1	1 (2.5)	0
A4	1 (2.5)	0
B	9 (22.5)	1 (20)
C	28 (70)	4 (80)
D	1 (2.5)	0

Characteristic n(%)	Atezo+Bev (N=40)	Muza 6 mg/kg Q6W Atezo+Bev (N=6)
Prior cancer surgery	7 (17.5)	2 (33.3)
Prior cancer radiotherapy	6 (15)	0
MVI and/or EHS at study entry	20 (50)	2 (33.3)
Varices at enrollment	10 (25)	2 (33.3)
Varices treated	4 (23.5)	1 (100)
Disease caused by Hepatitis B	9 (22.5)	5 (83.3)
Disease caused by Hepatitis C	12 (30)	1 (16.7)
Disease caused by Alcohol	8 (20)	2 (33.3)
Disease caused by Non-viral Etiology	19 (47.5)	0
Baseline Alpha Fetoprotein <400μg/L	20 (50)	6 (100)

This study MORPHEUS-Liver (NCT04524871) is sponsored by Roche and is in collaboration with Adagene Inc.

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

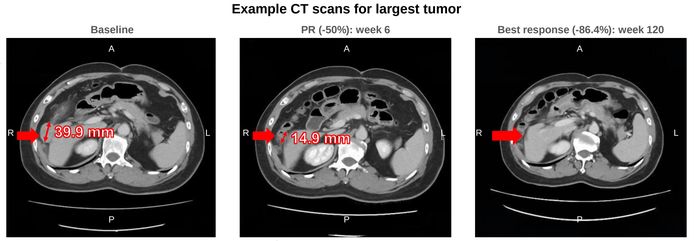
Case Study for Muza + Atezo + Bev

Asian Male, Taiwan, 63 years old, ECOG PS 0

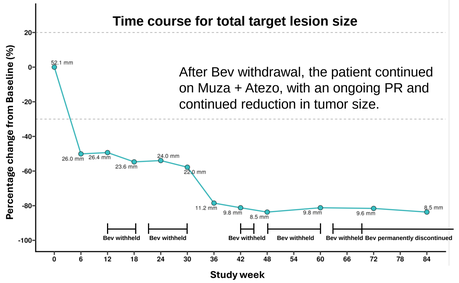
Tumor Type:
HCC, BCLC-C, Child-Pugh Class A5, EHS, 2 Metastatic sites, HBV

Baseline Total Target Lesion Size: 52.1 mm

Example CT scans for largest tumor



Time course for total target lesion size



After Bev withdrawal, the patient continued on Muza + Atezo, with an ongoing PR and continued reduction in tumor size.

- Case illustrates benefit of continuous Muza + Atezo treatment after Bev discontinuation
- Patient presented significant tumor burden (2 target lesions; 52.1 mm total target lesion) at baseline and was PR after first scan with continued reduction to -86% (as of Feb 4th, 2026)
- AEs related to Bev including Gr3 hypertension and Gr3 proteinuria led to permanent discontinuation of Bev
- Muza + Atezo continue to be administered safely after 84 weeks

Additional baseline characteristics: alpha fetoprotein: <400 ug/L; Albumin: >= 35 g/L; no macro-vascular invasion; metastatic disease; no prior radiotherapy; prior cancer surgery; BCLC stage C; no varices at enrollment; primary site of tumor: liver

Safety parameters

- The safety profile for Muza + Atezo + Bev (n=6) is comparable to Atezo + Bev doublet control (n=40)
- In the triplet cohort, Bev was discontinued for 2 patients without impacting Muza + Atezo treatment, illustrating treatment flexibility for the triple combo
- Muza safety allows for continuous dosing without impacting Atezo + Bev

Safety Summary

Safety parameter n (%)	Atezo + Bev (N=40)	Muza + Atezo + Bev (N=6)
TEAEs (all grades)	40 (100)	6 (100)
Grade≥3	28 (70)	4 (67)
Serious AEs	22 (55)	2 (33)
TRAEs (all grades)	31 (78)	6 (100)
TR Grade≥3	18 (45)	3 (50)
TR Serious AEs	9 (23)	2 (33)
TEAE leading to Bev discontinuation	3 (8)	2 (33)
TEAE leading to Atezo +Bev discontinuation	4 (10)	0
TEAE leading to Muza discontinuation	/	0
Drug discontinuations	7 (18)	2 (33)

Most common TRAEs related to Atezo+Bev and Muza+Atezo+Bev (≥5% or TRAE ≥ G3)