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ORIGINAL ARTICLE

Early bevacizumab dose and time modifications may affect efficacy of atezolizumab plus bevacizumab for advanced hepatocellular carcinoma treatment

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Background: Atezolizumab (1200 mg) plus bevacizumab (15 mg/kg) every 3 weeks (AtezBev) became a standard-of-care first-line treatment for advanced hepatocellular carcinoma (aHCC) following IMbrave150. However, real-world data suggest milder efficacy. Early bevacizumab interruption due to adverse events (AEs) is a frequent occurrence in real-world scenario associated with poor prognosis. Additionally, early bevacizumab dose/time modifications (eBEVmod) may negatively impact outcome.

Materials and methods: Data from AtezBev-treated aHCC patients ($n = 100$) in five Italian institutions were retrospectively analyzed. Cumulative bevacizumab dose (mg/kg) received in the first 3 months of treatment was analyzed by receiver operating characteristic (ROC) to identify a cut-off value to estimate survival and dichotomize the variable. Baseline clinical and laboratory characteristics were analyzed with uni-/multivariate models to explore potential differences on overall survival (OS), objective response rate (ORR) and disease control rate (DCR) based on eBEVmod. Progression-free survival (PFS) was a secondary endpoint.

Results: In the overall population, the median (m) follow-up was 11.4 months, mOS was 20.5 months, mPFS was 10.4 months, ORR was 31% and DCR was 75%. ROC on 3-month cumulative bevacizumab dose revealed an area under the curve of 0.74 ($P = 0.001$) and eBEVmod cut-off of <45 mg/kg/3 months (i.e. 10.5 mg/kg/3 weeks) having 73% sensitivity and specificity in predicting death. Twenty-three percent of patients had eBEVmod (of which 39.1% had treatment delay, 39.1% discontinuation and 21.7% dose reduction), with no differences in baseline characteristics nor second-line treatments compared with non-eBEVmod, except for sex. eBEVmod patients had inferior ORR/DCR (14%/48% versus 36%/82%) and increased risk of death [hazard ratio (HR) 4.2, $P = 0.0049$], with a 12-month survival probability of 53.3% versus 77.4%. eBEVmod was an independent negative prognostic factor of survival at multivariate analysis (HR 3.3, $P = 0.0125$). Patients with eBEVmod also had a trend in worse PFS, although not statistically significant (mPFS 3.8 versus 12.6 months, HR 1.8, $P = 0.0774$).

Conclusions: eBEVmod is an independent unfavorable prognostic factor of response and survival in AtezBev-treated aHCC patients. Optimization of bevacizumab AE management to reduce eBEVmod may substantially improve treatment outcome in real-world practice.

Key words: HCC, atezolizumab, bevacizumab, immunotherapy, dose modification

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most prevalent malignancies globally, with a high mortality rate due to late-stage diagnosis and limited treatment options.[1] The introduction of the atezolizumab (an anti-programmed death-ligand 1 antibody) and bevacizumab (an anti-vascular endothelial growth factor antibody) combination (AtezBev)

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therapy has marked a significant advancement in the first-line treatment for advanced HCC, as demonstrated by the IMbrave150 trial.[2,3] This combination has been shown to improve overall survival (OS) and progression-free survival (PFS) compared with the previous standard, sorafenib.[2,3]

Despite the clinical trial success, real-world data indicate a discrepancy in efficacy, with shorter median OS (mOS 14-18 months) compared with the registration trial (19.2 months).[4-9]

In the IMbrave150 trial, 17% of patients experience interruptions in bevacizumab treatment due to adverse events of special interest (AESI).[10] Common adverse events (AEs), such as hypertension and proteinuria, often necessitate dose reductions besides delays, impacting the cumulative dose received and, consequently, the treatment's effectiveness.[6,11,12]

The significance of maintaining the therapeutic dose of bevacizumab is underscored by real-world findings that early interruptions are associated with reduced survival rates and lower response rates.[11]

In apparent contrast, a *post hoc* analysis of the IMbrave150 trial population provides further insight into the impact of early bevacizumab dose modifications on patient outcomes.[10] This analysis revealed that efficacy was similar between patients who skipped bevacizumab due to AESIs and those who did not, indicating that careful management of AESIs can mitigate the potential negative impact on treatment outcomes.[10] This finding suggests that with appropriate monitoring and management strategies, the negative effects of dose interruptions can be minimized, thus maintaining the overall efficacy of the treatment regimen.

Previous trials of bevacizumab indicated that doses of 5 or 10 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks were well tolerated in HCC patients, and pharmacokinetic analyses showed comparable serum concentrations for 10 mg/kg every 2 weeks and 15 mg/kg every 3 weeks.[13,14] In phase II studies, response rates for 5 and 10 mg/kg doses were 8.3% and 14.7%, respectively, while disease control rates (DCRs) at 16 weeks ranged from 39% to 45%, respectively, suggesting a possible dose-dependent efficacy.[15,16] While the IMbrave150 trial itself did not specifically highlight a prior dedicated dose-finding study for HCC, the choice of the 15 mg/kg dose aligns with previous findings in other cancer types, e.g. non-small-cell lung cancer (NSCLC) where this dosage was associated with optimal therapeutic outcomes.[17] Interestingly, while dose escalation studies of bevacizumab have not been carried out in HCC, a meta-analysis on unresectable NSCLC revealed that high-dose bevacizumab (15 mg/kg) increased 2-year OS, PFS and tumor response rate compared with the low dose (7.5 mg/kg), but with a higher risk of treatment-related death.[18]

Overall, these data highlight the relevance of the topic and the need of further evidence to clarify the relationship between not only early interruption/skipping, but also of early dose/time bevacizumab modifications (eBEVmod) and clinical outcomes.

In this paper, we retrospectively analyzed data from HCC patients treated with AtezBev regimen in five Italian institutions describing hard outcomes based on the received cumulative bevacizumab dose over the first 3 months, with the aim of possibly providing real-world evidence of eBEVmod impact on OS, DCR and objective response rate (ORR).

This knowledge could be instrumental to develop strategies to enhance the real-world efficacy of the AtezBev regimen in advanced HCC, ultimately aiming to improve patient prognosis and quality of life.

MATERIALS AND METHODS

Study population

Patients with advanced-stage HCC [Barcelona Clinic Liver Cancer stage C (BCLC-C)] or intermediate HCC (BCLC-B) who were ineligible for surgical or locoregional therapies and received AtezBev as first-line systemic therapy between May 2020 and June 2023 were included in the study population. The overall cohort included patients ($n = 100$) from five Italian institutions, with data for analysis collected retrospectively.

Patients who were eligible had their HCC diagnoses confirmed histologically or by imaging criteria according to international guidelines, and none had previously received systemic therapy.

The current study was approved by the ethics committees at each center, and it followed the Good Clinical Practice guidelines, the Declaration of Helsinki and local laws, as well as the European Parliament and Council Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data, which was enacted on 27 April 2016.

Written informed consent for treatment was obtained for all patients.

Treatments and definitions

AtezBev was administered as described in the IMbrave150 trial (1200 mg of atezolizumab plus 15 mg/kg of body weight of bevacizumab intravenously every 3 weeks).[2]

Treatment interruptions and dose reductions were allowed to manage AEs or intercurrent procedures as per local practice. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

Patients were followed every 2-4 months with multiphasic scanning technique, based on clinical practice of the center. Tumor assessment was carried out regardless of dose interruption until radiological disease progression. When progression was diagnosed according to mRECIST criteria, the adoption of any subsequent anticancer medication depended on the local physician decision.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) etiologies were assigned to those patients with demonstrated prior or ongoing respective infection. Patients not included in the prior definition were classified as having

nonviral etiology. For patients with multiple etiologies, we used a trumping algorithm and prioritized etiology as HBV > HCV > nonviral.

Statistical analysis

Categorical variables were reported as the number of cases and percentage, and continuous variables were expressed as median and 95% confidence interval (CI). OS was computed as the interval between the date of therapy start until the date of death from any cause.

PFS, defined as the time from treatment start until disease progression or death from any cause whichever comes first, was a secondary endpoint due to inter-center variability in assessment timing and modalities.

OS and PFS were reported as median value expressed in months, with 95% CI. Survival curves were estimated using the product-limit method of Kaplan–Meier. The role of stratification factors was analyzed using the log-rank and Cox proportional hazards regression tests.

Hazard ratios (HRs) in multivariate analyses of baseline characteristics were calculated using the Cox proportional hazards regression model.

To account for potential immortal time bias, 3-month landmark univariate and multivariate analyses have been carried out with the above-described methods.

Continuous variables were dichotomized using receiver operating characteristic (ROC) curves applying the survival either above or below the mean OS as classification variable to identify a possibly prognostic cut-off value based on Youden's index in case of area under the curve (AUC) > 0.5 and $P < 0.05$, unless a cut-off value with a prognostic role has already been described. With regard to the latter case, the cut-off for albumin was set at 3.5 g/dl and α-fetoprotein (AFP) at 400 mg/ml according to Carr et al., Kariyama et al. and Fu et al.,[19-21] and Kelley et al., Zhu et al. and Brandes et al.,[22-24] respectively.

For cumulative bevacizumab dose analysis, we empirically define an 'early' time window of modification as occurring in the first 3 months of treatment. The cumulative bevacizumab dose (mg/kg) received in the first 3 months of treatment was analyzed by ROC as above described. Patients having received a cumulative dose below the cut-off were classified as 'eBEVmod' and those above as 'non-eBEVmod'. Differences in baseline characteristics between the eBEVmod and non-eBEVmod groups were estimated using the Mann–Whitney test or Fisher's exact test, as specified in the Results section.

A MedCalc package (MedCalc® version 16.8.4) was used for the above statistical analyses.

To adjust for potential differences in baseline characteristics in patients either experiencing or not eBEVmod, we carried out an inverse probability of treatment weighting (IPTW) analysis using propensity scores. The propensity score for receiving eBEVmod was estimated for each patient using a logistic regression model that included nine baseline categorical covariates: sex, age group (<70 versus ≥70 years), HCC etiology (viral versus nonviral), Child–Pugh score, BCLC stage, ECOG PS, macrovascular invasion/portal vein thrombosis (PVT), AFP group (<400 versus ≥400 ng/ml) and albumin–bilirubin (ALBI) grade. Stabilized inverse probability weights were calculated to reduce variance and improve balance. Covariate balance between treatment groups was assessed before and after weighting using standardized mean differences (SMDs). Survival outcomes (OS and PFS) were analyzed in the weighted pseudo-population. Weighted Kaplan–Meier curves were generated with the stabilized weights, and differences between groups were assessed using weighted log-rank tests. Weighted Cox proportional hazards models were used to estimate HRs and 95% CIs for the association between eBEVmod and OS or PFS. R software was used to implement IPTW and fit the survival models.

RESULTS

Patients' characteristics

The baseline clinical and laboratory characteristics of the study population ($n = 100$) are presented in Table 1. Patients had a median age at treatment start of 69.5 years (95% CI 65.7-73.0 years), 81% were male and 19% female, 96% had Child–Pugh score A and 4% B, 63% had ECOG PS of 0 and 37% ≥1, 57% had ALBI grade of 1 and 43% 2, 26% had BCLC stage B and 74% C, 62% had viral and 38% nonviral etiologies, 37% had macrovascular invasion (including PVT) and 35% AFP > 400 ng/ml. Among patients progressed to first-line AtezBev, 50.9% received second-line treatments and beyond.

Median follow-up was 11.4 months (95% CI 9.1-26.9 months), mOS was 20.5 months (95% CI 16.2-26.0 months), mPFS was 10.4 months (95 CI 7.5-16.1 months) (Figure 1A), ORR was 30.9% and DCR was 74.5%, specifically with 6.4% achieving a complete response (CR), 24.5% a partial response (PR), 43.6% stable disease (SD) and 25.5% progressive disease (PD) as best response (Figure 1B).

Early bevacizumab modifications

ROC on 3-month cumulative bevacizumab dose revealed an AUC of 0.74 ($P = 0.001$) and eBEVmod cut-off of <45 mg/kg/3 months (i.e. 10.5 mg/kg/3 weeks) having 73.3% sensitivity and 72.5% specificity in predicting worse survival (Figure 2A); 23% of patients had eBEVmod (of which 39.1% had dose delay/interruption, 39.1% had treatment discontinuation, 21.7% had dose reduction), with no differences in baseline characteristics nor second-line treatments received compared with non-eBEVmod, except for sex (96% versus 77% males, $P = 0.0423$; Table 1).

Reasons for eBEVmod are depicted in Supplementary Table S1, available at https://doi.org/10.1016/j.esmogo.2025.100186.

Impact of early bevacizumab modifications (eBEVmod) on treatment outcomes

Patients with eBEVmod had inferior ORR (14% versus 36%, Fisher's test $P = 0.1056$) and DCR (48% versus 82%, Fisher's test $P = 0.0033$) compared with patients without eBEVmod. Specifically, best responses in eBEVmod patients were

Table 1. Baseline clinical and laboratory characteristics of study population

Variable	Total (n = 100)	eBEVmod (n = 23)	Non-eBEVmod (n = 77)	P value	Test
Clinical					
Sex					
Male	81 (81%)	22 (95.7%)	59 (76.6%)	**0.0423**	Fisher
Female	19 (19%)	1 (4.3%)	18 (23.4%)		
Age	69.5 (65.7-73.0)	63.0 (57.3-77.8)	71.0 (62.0-77-0)	0.2830	Mann–Whitney
Age (cut-off)					
<70	50 (50%)	14 (60.9%)	36 (46.7%)	0.2371	Fisher
≥70	50 (50%)	9 (39.1%)	41 (53.3%)		
Child–Pugh					
A	96 (96%)	21 (91.3%)	75 (97.4%)	0.1926	Fisher
B	4 (4%)	2 (8.7%)	2 (2.6%)		
BCLC					
B	26 (26%)	4 (17.4%)	22 (28.6%)	0.4174	Fisher
C	74 (74%)	19 (82.6%)	55 (71.4%)		
ECOG PS:					
0	63 (63%)	13 (56.5%)	50 (64.9%)	0.4716	Fisher
≥1	37 (37%)	10 (43.5%)	27 (35.1%)		
Etiology					
Viral (HBV and/or HCV)	62 (62%)	16 (69.6%)	46 (59.7%)	0.3967	Fisher
Nonviral	38 (38%)	7 (30.4%)	31 (40.3%)		
Neutrophils (/μl)	3575 (2773-4808)	4000 (2978-5352)	3570 (2720-4762)	0.5233	Mann–Whitney
Lymphocytes (/μl)	1430 (893-1745)	1460 (1038-1892)	1410 (863-1708)	0.3123	Mann–Whitney
Lymphocytes (cut-off)	n = 86	n = 21	n = 65	0.2019	Fisher
<950/μl	26 (30.2%)	4 (19.0%)	22 (33.8%)		
≥950/μl	60 (69.8%)	17 (81.0%)	43 (66.2%)		
NLR	n = 86	n = 21	n = 65	0.4541	Fisher
<3	43 (50.0%)	9 (42.9%)	34 (52.3%)		
>3	43 (50.0%)	12 (57.1%)	31 (47.7%)		
Albumin (g/dl)	4.00 (3.90-4.20)	3.90 (3.50-4.10)	4.00 (3.90-4.30)	0.1993	Mann–Whitney
Albumin (cut-off)				0.2324	Fisher
≥3.5 g/dl	80 (80.0%)	16 (69.6%)	64 (83.1%)		
<3.5 g/dl	20 (20.0%)	7 (30.4%)	13 (16.9%)		
Bilirubin (mg/dl)	0.80 (0.70-0.92)	0.91 (0.63-1.39)	0.80 (0.70-0.92)	0.1817	Mann–Whitney
Bilirubin (cut-off)				0.6138	Fisher
>1 mg/dl	33 (33.0%)	9 (39.1%)	24 (31.2%)		
≤1 mg/dl	67 (67.0%)	14 (60.9%)	53 (68.8%)		
ALBI grade				0.3445	Fisher
Grade 1	57 (57.0%)	11 (47.8%)	46 (59.7%)		
Grade 2	43 (43.0%)	12 (52.2%)	31 (40.3%)		
Tumor					
Macrovascular invasion/PVT	37 (37%)	10 (43.5%)	27 (35.1%)	0.4656	Fisher
AFP	n = 94	n = 21	n =73	0.0612	Fisher
≥400 ng/ml	33 (35%)	11 (52.4%)	22 (30.1%)		
<400 ng/ml	61 (65%)	10 (47.6%)	51 (69.9%)		
Second-line therapy					
Second-line therapy/progressed patients	28/55 (50.9%)	5/15 (33.3%)	23/40 (57.5%)	0.4227	Fisher

Continuous variables are reported as median and 95% confidence interval, categorical variables as absolute numbers and percentage of total. If a variable had missing data, the real sample size for that variable is reported in the respective row. P values <0.05 are reported in bold.

AFP, α-fetoprotein; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; eBEVmod, early bevacizumab modifications; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus, HCV, hepatitis C virus; NLR, neutrophils-to-lymphocytes ratio; PVT, portal vein thrombosis.

14.3% CR, 0% PR, 33.3% SD and 52.4% PD, while those in non-eBEVmod ones were 4.1% CR, 31.5% PR, 46.6% SD and 17.8% PD (chi-square test, P = 0.0005; Figure 2B).

Consistently, the risk of death at any time was significantly increased in patients undergoing eBEVmod compared with non-eBEVmod (HR 4.2, 95% CI 1.5-11.6, P = 0.0049), with a mOS of 19.7 months (95% CI 4.3-22.8 months) versus 20.8 months (95% CI 16.2-26.0 months) and displaying a 12-month survival probability of 53.3% (95% CI 27.4% to 79.2%) versus 77.4% (65.8% to 89.0%), respectively (Figure 2C).

At multivariate analysis of OS (n = 86 patients; Supplementary Table S2, available at https://doi.org/10.1016/j.esmogo.2025.100186), ALBI grade 2 and eBEVmod were identified as independent negative prognostic factors of survival. In particular, eBEVmod conferred an HR for death of 3.3 (95% CI 1.3-8.3, P = 0.0125; Figure 2D).

Given the retrospective nature of the study, we carried out 3-month landmark analyses for OS to address potential immortal time bias. Univariate Cox's regression resulted in a detrimental effect of eBEVmod with borderline significance (HR 2.92, 95% CI 0.96-8.84, P = 0.0587), while significance was maintained in the more relevant multivariate analysis, demonstrating eBEVmod as the sole negative independent prognostic factor of survival in our study population (HR 2.82, 95% CI 1.05-7.53, P = 0.0389; Supplementary Table S3, available at https://doi.org/10.1016/j.esmogo.2025.100186).

Regarding disease progression to first-line AtezBev, we observed a trend in shorter PFS for patients with eBEVmod compared with those without it (Figure 2E), although not

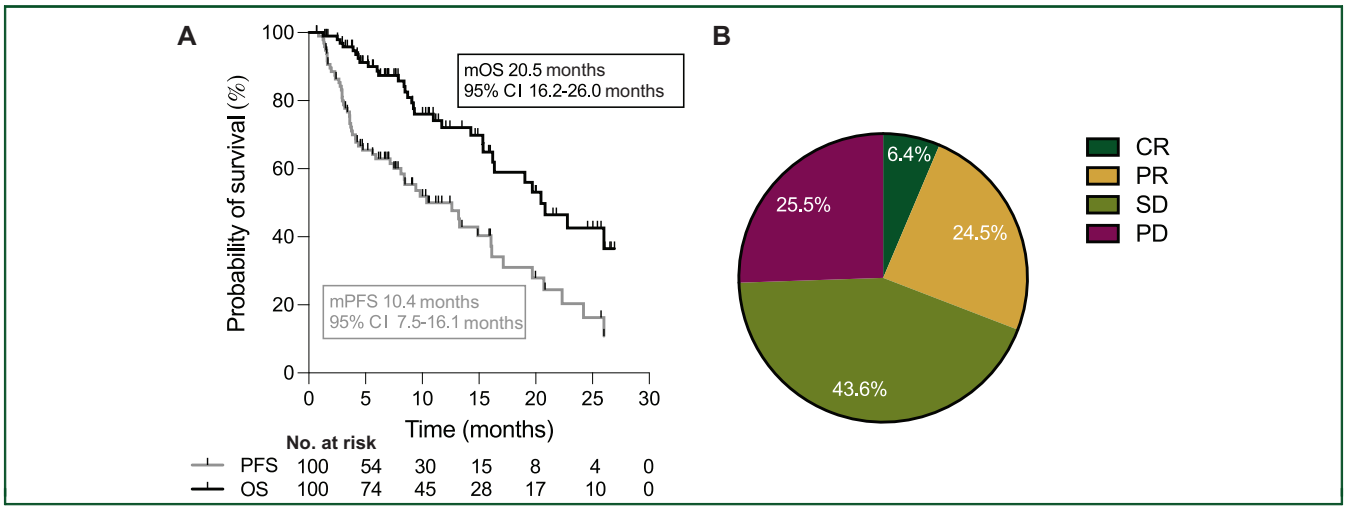

Figure 1. Atezolizumab plus bevacizumab outcomes on the overall population. (A) Kaplan–Meier survival curves of overall and progression-free survival (OS and PFS). (B) Percentage of best responses.
CI, confidence interval; CR, complete response; mOS, median overall survival; mPFS, median progression-free survival; PD, progressive disease; PR, partial response; SD, stable disease.

statistically significant [mPFS 3.8 months (95% CI 2.0-22.3 months) versus 12.6 months (95% CI 7.8-16.1 months), HR 1.8, 95% CI 0.9-3.7, $P = 0.0774$]. Similarly, the trend was observed in multivariate analysis (HR 1.5, 95% CI 0.8-3.0, $P = 0.2076$; Figure 2F), but no independent prognostic factor of response was identified as statistically significant in the present analysis on PFS (Supplementary Table S4, available at https://doi.org/10.1016/j.esmogo.2025.100186), possibly also due to inter-center variability in assessment timing and modalities.

In order to adjust for potential confounding baseline clinical characteristics between patients with and without eBEVmod, we carried out an IPTW propensity score analysis to match for nine covariates between the two groups of patients (see the Methods section). After weighting, the SMD of all covariates was reduced compared with the unweighted population, without significant differences between eBEVmod and non-eBEVmod patients (all $P > 0.42$, Supplementary Table S5, available at https://doi.org/10.1016/j.esmogo.2025.100186). OS was confirmed as significantly different between eBEVmod and non-eBEVmod patients after weighting ($P = 0.0049$), with a strong tendency in increased risk of death in patients experiencing eBEVmod (HR 1.98, 95% CI 0.95-4.12, $P = 0.067$; Supplementary Figure S1A, available at https://doi.org/10.1016/j.esmogo.2025.100186). As in the unweighted population, PFS was only slightly and not significantly different in patients with or without eBEVmod ($P = 0.077$), lacking major differences in the risk of progression (HR 1.18, 95% CI 0.62-2.23, $P = 0.61$; Supplementary Figure S1B, available at https://doi.org/10.1016/j.esmogo.2025.100186).

DISCUSSION

In the present work, we carried out a retrospective analysis of patients ($n = 100$) with advanced HCC treated with first-line atezolizumab and bevacizumab combination regimen across five Italian institutions, providing real-world insights into the impact of early bevacizumab modifications in timing/dose (eBEVmod) on clinical outcomes.

Our findings reveal that patients who experienced eBEVmod within the first 3 months of treatment (below 45 mg/kg cumulative dose) had significantly worse outcomes compared with those who maintained the standard dosing schedule or had only minor modifications (equal to 45 mg/kg cumulative dose or above). Specifically, despite having almost overlapping baseline clinical and laboratory characteristics, the eBEVmod group exhibited lower ORR and DCR, as well as a significantly higher (more than fourfold higher) risk of death. These results underscore the critical importance of maintaining the intended cumulative dose of bevacizumab to achieve optimal therapeutic outcomes in real-world settings, and that no baseline laboratory and clinical characteristics are associated with eBEVmod (except for sex in the present study).

The mOS and 12-month survival were shorter for the eBEVmod group, aligning with the observed trends in other real-world studies.[5,6,11] As a major difference from Hatanaka and colleagues' work,[11] which described poorer prognosis with early bevacizumab interruptions, we also considered dose reductions and treatment discontinuation besides interruption of bevacizumab. Importantly, the real-world scenario highlights also AE-independent modifications in bevacizumab treatment, e.g. due to surgery or invasive procedures for other medical conditions.

However, careful management and mitigation strategies for AEs can potentially ameliorate the negative impacts of bevacizumab modifications,[25,26] as suggested by the recent *post hoc* analysis of the IMbrave150 population.[10]

Explanations for this apparent discordance lie in the differences between clinical trial settings and real-world practice.[27] Clinical trials typically involve rigorous monitoring and management of AEs, which can mitigate the impact of dose modifications.[28] Conversely, in real-world settings, variations in patient management and less

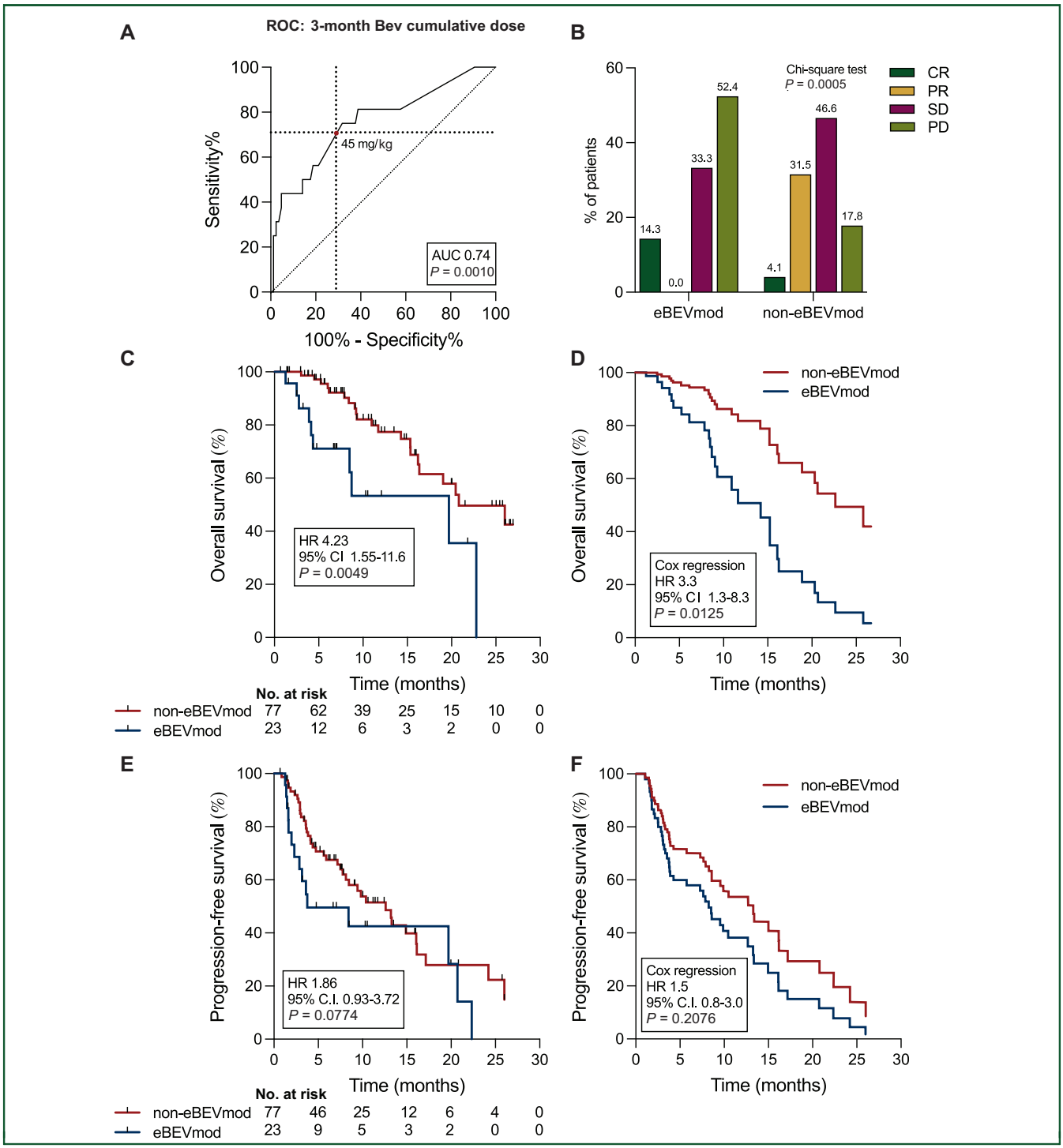

Figure 2. Early bevacizumab modifications (eBEVmod) reduce efficacy of first-line atezolizumab plus bevacizumab. (A) ROC curve analysis on 3-month cumulative bevacizumab dose to classify long and short survival; red dot indicates Youden's cut-off. (B) Percentage of best responses as per mRECIST in patients with and without eBEVmod. (C) Kaplan–Meier overall survival (OS) curves of patients with and without eBEVmod (univariate Mantel–Cox test). (D) Estimated OS curves based on eBEVmod from multivariate Cox proportional hazards regression (Supplementary Table S2, available at https://doi.org/10.1016/j.esmogo.2025.100186). (E) Kaplan–Meier progression-free survival (PFS) curves of patients with and without eBEVmod (univariate Mantel–Cox test). (F) Estimated PFS curves based on eBEVmod from multivariate Cox proportional hazards regression (Supplementary Table S4, available at https://doi.org/10.1016/j.esmogo.2025.100186).
AUC, area under the curve; CI, confidence interval; CR, complete response; HR, hazard ratio; PD, progressive disease; PR, partial response; ROC, receiver operating characteristic; SD, stable disease.

stringent monitoring may lead to more significant negative effects from treatment modifications. Secondly, Kudo and colleagues[10] did not classify appetite loss as AESI, while early treatment interruption by Hatanaka et al.[11] accounted also for it. Thirdly, no temporal parameter for skipping bevacizumab was applied in the former analysis, while a 9-week window was considered to define early interruption in the latter. Consistently with the present work, the early

time window for treatment modification may play a major role in efficacy compared with later ones, possibly masking the impact of treatment modifications when considered overall. Lastly, randomization was applied in the clinical trial setting to minimize differences among baseline characteristics, while some baseline clinical differences were present in the real-world study, e.g. in ALBI grade and prior lines of therapy received.[27]

Similar considerations come from previous experiences with tyrosine kinase inhibitors (TKIs), such as sorafenib, lenvatinib and regorafenib, which act at least partially by blocking angiogenesis through different pathways.[29-31] Some studies suggest that maintaining a certain dose density of TKIs may be crucial for maximizing therapeutic benefit in HCC while managing toxicities.[32-35] Specifically, Oura and colleagues demonstrated both PFS and OS advantages by maintaining an high relative dose intensity (RDI) of sorafenib and lenvatinib in elderly patients.[32] Consistently, Ohki et al. identified RDI $>$ 70% of lenvatinib to be an independent prognostic factor of PFS in a retrospective Japanese population,[34] while Kirino et al. identified that RDI $>$ 70% of lenvatinib is associated with favorable radiological response and longer OS.[35] Moreover, another study with the TKI regorafenib showed that patients with a 1-month RDI $\geq$ 50% had significantly longer OS and PFS than patients with 1-month RDI $<$ 50%.[33]

These studies suggest that optimizing TKI dosing to maintain a certain dose intensity plays a major role for maximizing the therapeutic benefit in HCC while managing toxicity, and this may apply also to bevacizumab as supported by the current and other studies.

The present work accounts for a number of limitations. First of all, the retrospective nature of the analysis could not exclude potential selection and immortal time bias. With regard to the latter, 3-month landmark analyses confirmed our findings, thus mitigating the bias risk. Nevertheless, our data need to be validated on larger samples of patients and prospective evidence is mandatory. Secondly, the evaluation of PFS has to take into account the multicentric and multinational nature of the work, since no centralized imaging review was included in the study protocol and the tumor assessment was made according to the clinical protocol of each institute. However, the small sample size and presence of missing data for some variables in the present study represent limitations that may have led to missing possible associations of baseline characteristics to eBEVmod, since some negative prognostic factors, although not statistically different in the two patient sub-groups, seem to be more frequent in the eBEVmod group, e.g. Child—Pugh score B, BCLC stage C, ECOG PS1 ALBI grade 2 and AFP $>$ 400. Nonetheless, OS findings were confirmed also after IPTW propensity score analysis, thus accounting also for the latter potential bias.

As a further possible limitation, 3 of the 23 patients received also a delayed administration of atezolizumab in one instance, but none of them was discontinued or the dose reduced.

In conclusion, real-world application of the AtezBev regimen suggests the need for stringent AE management and to postpone invasive procedures that require bevacizumab interruption whenever possible to prevent eBEVmod and improve patient outcomes. Unpostponable procedures requiring bevacizumab interruption, such as endoscopic variceal ligation, may suggest the use of other validated first-line treatments lacking antiangiogenic drugs, such as the STRIDE regimen,[36,37] to avoid eBEVmod in the AtezBev strategy.

These findings advocate for the development of standardized protocols and monitoring frameworks to maintain therapeutic dosing, thereby optimizing the efficacy of AtezBev therapy in patients with advanced HCC. Further prospective studies are warranted to validate these results and refine clinical practice guidelines, ultimately aiming to improve the prognosis for HCC patients.

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DATA SHARING

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

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