Liver Decompensation in Patients With Hepatocellular Carcinoma Treated With Atezolizumab Plus Bevacizumab: A Real-life Study

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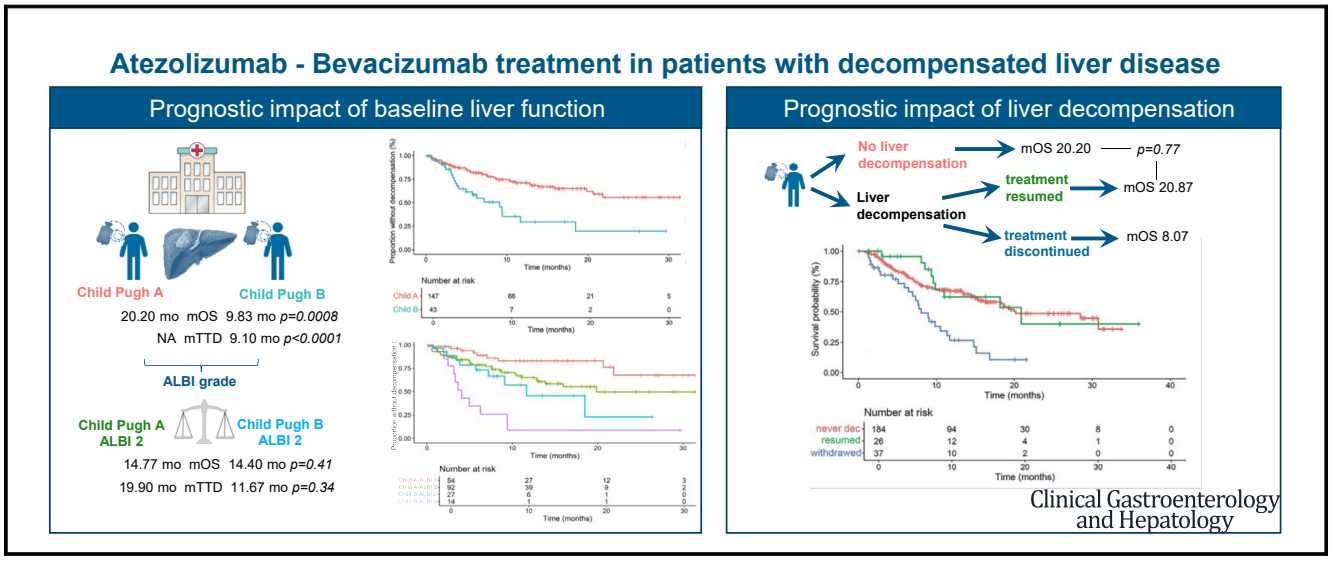

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Abbreviations used in this paper: AE, adverse event; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate (CR + PR + SD); EASL, European Association for the Study of the Liver; ECOG-PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; mRECIST, modified Response Evaluation Criteria In Solid Tumors; MRI, magnetic resonance imaging; ORR, objective response rate (CR + PR); OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; sAE, serious adverse event; SD, stable disease; trAE, treatment-related adverse event; TTD, time to decompensation; TTP, time to progression.

1542-3565
https://doi.org/10.1016/j.cgh.2024.12.028

BACKGROUND & AIMS: **Atezolizumab plus bevacizumab (atezobeva) has changed the treatment landscape of advanced hepatocellular carcinoma, but its efficacy and safety in patients with impaired liver function are still debated. This study aimed to evaluate the prognostic impact of baseline liver function and liver decompensation during treatment on clinical outcomes.**

METHODS: **In this multicenter study, we included 247 patients with advanced or unresectable hepatocellular carcinoma treated with atezobeva. We analyzed data on survival, tumor progression, and liver decompensation and introduced time to decompensation as a new safety endpoint.**

RESULTS: **The reported overall survival (OS) was 18.30 months, time to progression 13.07 months, and progression-free survival (PFS) 9.83 months. Although OS was better in Child Pugh A compared with Child Pugh B patients (20.20 vs 9.83 months; $P = .0008$), no differences were observed in time to progression and treatment safety. Liver decompensation occurred in 63 patients (25.51%), specifically 27.89% Child Pugh A and 51.16% Child Pugh B patients; in 41.26% of patients, atezobeva was resumed after decompensation, achieving an OS comparable to those who never decompensated (20.87 vs 20.2 months; $P = .77$), and better than those who permanently stopped treatment (8.07 months; $P = .02$). Time to decompensation was similar for patients with albumin-bilirubin score 2 regardless of Child Pugh class, and the probability of recovery from decompensation was similar for Child Pugh A and B patients.**

CONCLUSION: **Atezobeva is effective in both Child Pugh A and B patients. The possibility to resume treatment after an episode of decompensation underscores the importance of integrated hepato-oncological management.**

Keywords: ALBI; Child Pugh; Cirrhosis; Immunotherapy; Liver Decompensation.

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide, and it poses a significant therapeutic challenge, as most cases are diagnosed at an advanced stage, requiring systemic therapy. Atezolizumab plus bevacizumab (atezobeva) has been approved as first-line systemic treatment for advanced unresectable HCC, showing improved overall survival (OS) and progression-free survival (PFS) compared with the tyrosine kinase inhibitor sorafenib.[1,2]

However, clinical trials typically adopt strict inclusion criteria that may limit the applicability of their results to real-life scenarios, particularly in patients with mild-to-moderate deterioration of liver function, and/or significant portal hypertension.[3] The management of decompensation during therapy, as well as its impact on the continuation of therapy, remains unclear. In addition, liver decompensation, which is not usually classified as a specific adverse event (AE) in clinical trials, presents a significant challenge, as distinguishing between pure liver decompensation and tumor progression is often problematic, although they are distinct clinical issues. Recently, real-life studies have sought to overcome this knowledge gap, focusing on the efficacy and safety of treatment based on liver function, with contrasting results.[4–9]

This study aimed to analyze the impact of mild-to-moderate liver dysfunction in patients with HCC treated with atezobeva in a real-life setting, focusing on time to decompensation (TTD) as a novel outcome measure, and assessing the safety and efficacy of resuming treatment in patients who experienced an episode of liver decompensation.

Methods

We retrospectively analyzed data from 247 consecutive patients with advanced HCC who were treated with atezobeva. The study period ranged from December 2020 to July 2023 and involved 4 hepatology centers (the Liver Unit of the Beaujon Hospital, Clichy, France; the Liver Unit of the Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; the Liver Unit of the Azienda Ospedaliero-Universitaria Careggi, Florence, Italy; the Liver Unit of the IRCCs Sant'Orsola-Malpighi Hospital, Bologna, Italy). All patients were older than 18 years, with a radiologic or histologic diagnosis of unresectable HCC not amenable to locoregional treatment, and eligible for systemic therapy after multidisciplinary evaluation. Treatment was conducted according to guidelines.

Data Collection

Demographic data, biometric data, and extensive laboratory parameters before and after treatment start were recorded. We also considered the etiology of liver disease, presence of cirrhosis, the severity of liver dysfunction (according to the Child Pugh score, the Model for End-Stage Liver Disease [MELD]) score, and the ALBI score), the Eastern Cooperative Oncology Group performance status (ECOG-PS), signs of portal hypertension (gastric, esophageal, or ectopic varices at endoscopy, porto-systemic collateral vessels at imaging, or history of portal hypertensive bleeding), and active

alcohol consumption >12 g/day in women and >24 g/day in men. Radiologic features of HCC (ie, maximum diameter, number of nodules, vascular invasion, extrahepatic spread), the Barcelona Clinic Liver Cancer (BCLC) stage, previous treatments, duration of systemic therapy, the reasons for discontinuation, any AE occurred during treatment along with their grading according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v 5.01221 were also recorded.

Outcome Measures

Decompensation was defined as the new onset of ascites of any grade according to the European Association for the Study of the Liver (EASL) classification, hepatic encephalopathy of any grade according to the West Haven classification, variceal hemorrhage, or jaundice (total bilirubin >3 mg/dL). If these conditions were present at baseline, decompensation was considered as any worsening in ascites, hepatic encephalopathy, or jaundice (defined as an increase in total bilirubin >3 mg/dL or a worsening of more than 1.0 mg/dL from baseline). At the time of decompensation (±30 days) a computed tomography (CT) scan was performed to exclude worsening of liver function due to tumor progression.

The efficacy and safety of atezobeva were evaluated using both clinical and radiologic outcomes.[10] The primary endpoints included:

- OS, defined as the time from the first treatment dose to patient death;
- TTD, defined as the time from the first treatment dose to the occurrence of any event related to liver function deterioration (hyperbilirubinemia) or clinically significant worsening of portal hypertension (ie, hepatic encephalopathy, ascites, or variceal bleeding)[11];
- Safety outcomes, defined as the incidence of treatment-related AEs (trAEs) graded ≥3 and/or serious AEs (sAEs) defined as any expected or unexpected AE, related or unrelated to treatment resulting in death, life-threatening consequences, persistent or significant disability or incapacity, inpatient admission, or prolongation of existing hospitalization.

The secondary endpoints included:

- Objective response rate (ORR), defined as the sum of complete (CR) and partial (PR) radiologic response (CR + PR);
- Disease control rate (DCR), which included CR, PR, and stable disease (SD), (CR + PR + SD);
- Time to progression (TTP), defined as the time from the first treatment dose to radiologic evidence of tumor progression;
- PFS, defined as the time from the first treatment dose to radiologic evidence of tumor progression or patient death.

Treatment response was assessed by experienced radiologists in each center, using Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 and/or modified RECIST (mRECIST) criteria, through CT scans or magnetic resonance imaging (MRI) performed for periodic disease assessment.

The study was approved by the Ethics Committee 3 of Lazio Region (protocol ID 5890). All procedures were conducted in accordance with the principles outlined in the Declaration of Helsinki. All authors had access to the study data and reviewed and approved the final manuscript.

Statistical Analysis

Data distribution was evaluated using the Shapiro-Wilk test. Continuous variables were reported as the median and interquartile range (IQR), whereas categorical variables were reported as frequency and percentage. To assess differences between groups, the Wilcoxon test or Kruskal-Wallis test was used for continuous variables, and the χ^2 test or Fisher exact test was used for categorical variables, as appropriate. OS, PFS, and TTP were illustrated using Kaplan-Meier curves, with differences between groups compared using the log-rank test. Time-dependent Cox regression was applied to evaluate the impact of covariates on mortality, tumor progression, and liver decompensation, accounting for

What You Need to Know

Background

Atezolizumab/bevacizumab is approved as first-line systemic treatment for advanced unresectable hepatocellular carcinoma. However, its efficacy and safety in patients with impaired liver function is still debated.

Findings

Atezolizumab/bevacizumab is effective and safe for patients with advanced hepatocellular carcinoma and mild-to-moderate liver dysfunction, offering survival benefits for those who resume treatment after liver post-decompensation. The albumin-bilirubin score improves prognostic stratification.

Implications for patient care

Mild-to-moderate liver dysfunction should not exclude patients from atezolizumab/bevacizumab. Integrated hepato-oncological care is crucial. To tailor the limits of therapeutic futility, time to decompensation should be implemented in future studies.

time-varying treatment effects. Variables that were statistically significant (P-value $< .05$) in the univariate analysis were included in the multivariate model.

Table 1. Characteristics of the Study Population

	Atezolizumab plus bevacizumab (N = 247)
Age, *years*	68 (59–76)
BMI, *kg/m²*	25.50 (22.60–28.40)
Male sex	201 (81.37)
Etiology	
Non-viral	102 (41.29)
Viral	70 (28.34)
Mixed	61 (24.70)
Undetermined	14 (5.67)
Cirrhosis	
Yes	190 (76.92)
No	57 (23.08)
Child Pugh score	
A	147 (77.37)
B	43 (22.63)
ALBI grade	
1	87 (35.22)
2	141 (57.09)
3	19 (7.69)
MELD	8 (6–9)
ECOG	
0	161 (65.19)
1	74 (29.95)
2	12 (4.86)
Multinodular	153 (61.94)
Maximum diameter	6.5 (3–12)
Metastases	84 (34.00)
Macrovascular invasion	128 (51.82)
Portal hypertension	121 (48.98)
Ascites at baseline	52 (21.05)
Esophageal varices at baseline	86 (34.81)
HE at baseline	20 (8.09)
Bilirubin, *mg/dL*	0.9 (0.6–1.3)
Albumin, *g/dL*	3.7 (3.3–4.1)
INR	1.1 (1.0–1.20)
Creatinine, *mg/dL*	0.81 (0.7–1.1)
AFP	56.7 (6.7–860.0)
Obesity	80 (32.38)
Surgery	53 (21.45)
RFA	32 (12.95)
PEI	10 (4.04)
TACE	93 (37.65)
TARE	63 (25.50)

Note: Categorical variables are presented as number (%), and continuous variables as median (interquartile range).
AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; HE, hepatic encephalopathy; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; SMD, standardized mean difference; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

Statistical analyses were performed using R version 3.6.2, IBM SPSS Statistics version 25.0, and GraphPad Prism version 9.0.

Results

A total of 247 patients receiving atezobeva were included in the study, with their characteristics summarized in Table 1 and Supplementary Table 1. Most patients had multifocal disease (61.94%), with macrovascular invasion in 51.83% of cases, and a history of prior surgical or locoregional treatments.

The median duration of follow-up was 9.4 months (IQR, 4.2–15.9 months). One hundred three patients (41.70%) died due to tumor progression (63.10%), liver function deterioration (24.28%), or sAEs (12.62%).

Median OS was 18.30 months (95% confidence interval [CI], 14.80–28.50 months) (Figure 1*A*), whereas median TTP and PFS were 13.07 months (95% CI, 10.83–20.10 months) and 9.83 months (95% CI, 7.30–12.87 months), respectively (Figure 1*B and C*). The median duration of treatment was 10.40 months (IQR, 6.10–17.30 months). By the time of analysis, 166 patients (67.21%) had permanently discontinued treatment with atezobeva. The main reason for discontinuation was tumor progression (85; 51.20%), whereas decompensation (35; 21.09%) and sAEs (19; 11.45%) were less common causes. Additionally, 16 patients (9.64%) died from non-hepatic causes, 10 patients (6.02%) achieved down-staging and subsequently underwent resection, and 1 patient (0.60%) voluntarily discontinued treatment.

Disease control was achieved in 54.25% of patients (Supplementary Table 2), with an ORR of 23.07%.

Subsequent subgroup analysis, including age $\geq$75 years and liver disease etiology (viral, non-viral, or mixed), showed no significant impact on outcomes (Supplementary Figure 1).

Impact of Liver Function

Child Pugh A patients treated with atezobeva showed an OS similar to that of non-cirrhotic patients (20.20;

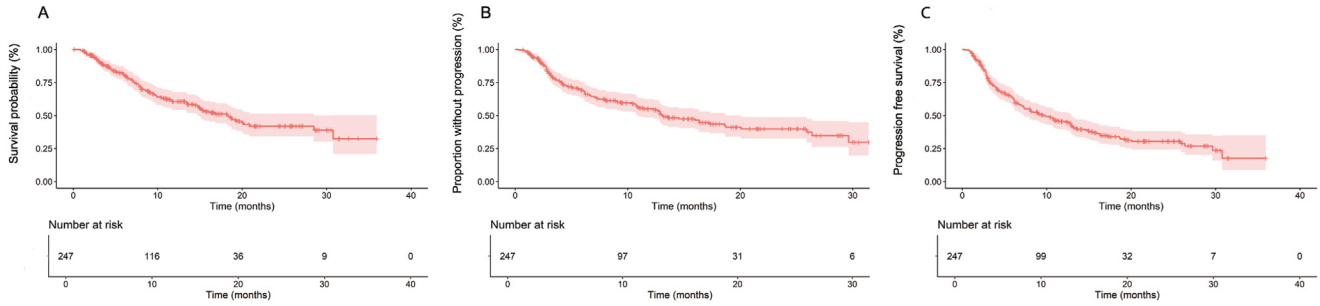

Figure 1. OS (panel *A*), TTP (panel *B*), and PFS (panel *C*) of the study population.

95% CI, 14.80–NA vs 18.7; 95% CI, 15–NA months; $P = .36$), but better than Child Pugh B patients (9.83; 95% CI, 7–16.80 months; $P = .0008$) (Figure 2*A*). Similar results were obtained when comparing PFS between the groups (PFS: 10.8; 95% CI, 8.0–16.30 months vs 8.30; 95% CI, 5.40–14.50 months, respectively; $P = .02$) (Figure 2*B*–*C*). In contrast, TTP was comparable between Child Pugh A and B patients (TTP: 15.97; 95% CI, 11.43–NA months vs 12.67; 95% CI, 11.03–NA months, respectively; $P = .32$). Non-cirrhotic patients showed a non-statistically

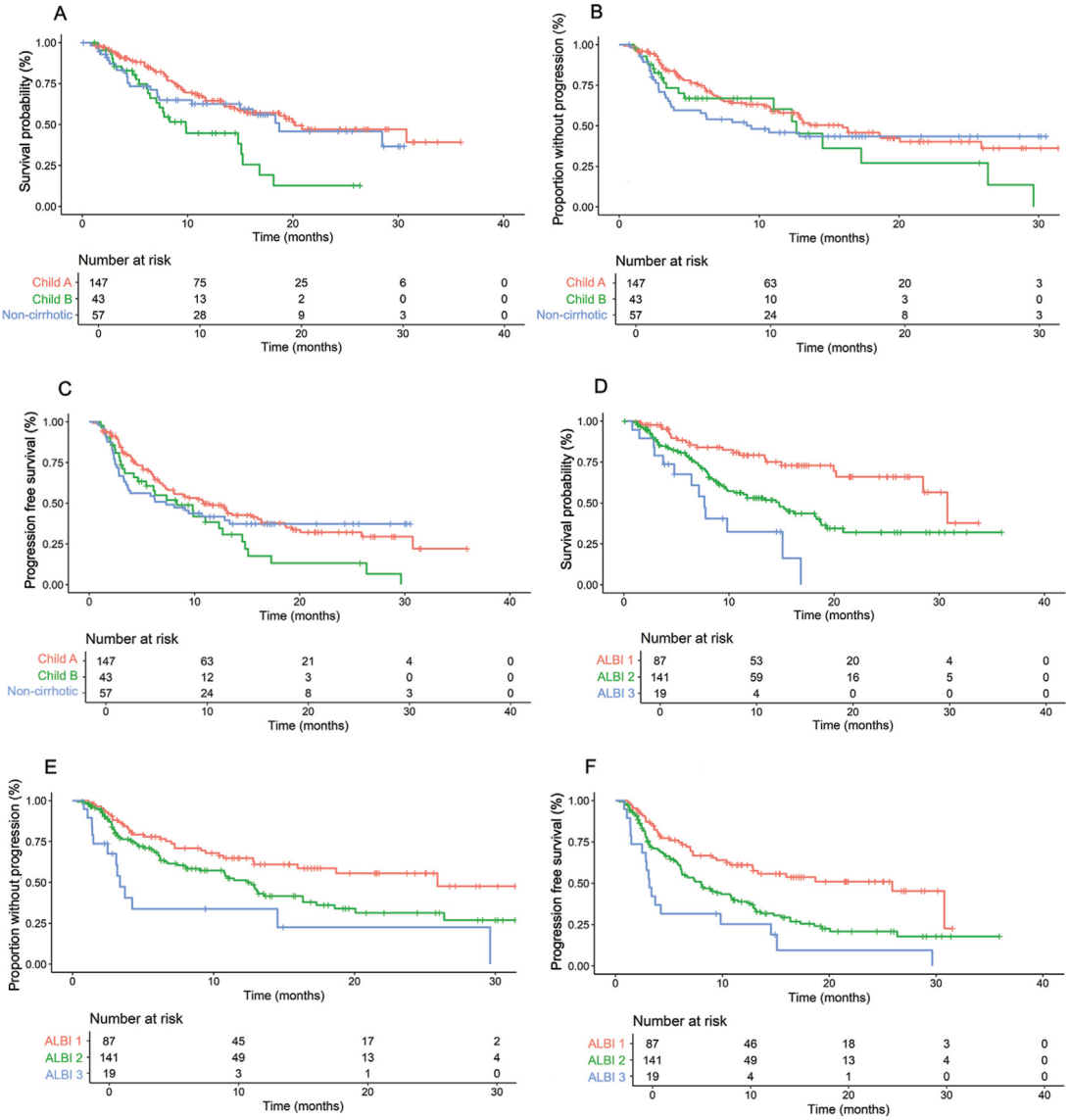

Figure 2. OS (panels *A, D*), TTP (panels *B, E*), and PFS (panels *C, F*) of patients treated with atezolizumab plus bevacizumab stratified by liver function.

Table 2. Characteristics of Patients Who Experienced Liver Decompensation During Treatment With Atezolizumab Plus Bevacizumab

Variable	Decompensated during treatment (n = 63)	Never decompensated during treatment (n = 184)	*P*-value
Age, *years*	68 (60–76)	68 (59–76)	.83
Male sex	54 (85.71)	147 (79.89)	.34
BMI, *kg/m²*	25.82 (23.08429.50)	25.28 (22.37–28.40)	.22
ECOG 1–2	**30 (47.61)**	**56 (30.34)**	**.01**
Etiology			
Non-viral	27 (42.85)	75 (40.76)	.7705
Viral	17 (27)	53 (28.81)	.7820
Other	19 (30.15)	42 (22.82)	.2440
Undetermined	–	14 (7.61)	–
Child Pugh score			
A	**41 (65.79)**	**106 (57.61)**	**.30**
B	**22 (34.21)**	**21 (11.41)**	**< .0001**
Non cirrhotic	**–**	**57 (30.98)**	–
ALBI			
1	**10 (15.87)**	**77 (41.85)**	**.0002**
2	41 (65.08)	100 (54.35)	.14
3	**12 (19.05)**	**7 (3.80)**	**< .0001**
Portal hypertension	**49 (77.77)**	**72 (39.13)**	**< .0001**
Ascites at baseline	**37 (58.73)**	**15 (8.15)**	**< .0001**
Esophageal varices at baseline	**36 (57.14)**	**50 (27.17)**	**< .0001**
HE at baseline	**13 (20.63)**	**7 (3.80)**	**< .0001**
MELD	9 (6-12)	8 (6-9)	.23
Bilirubin, *mg/dL*	**1.3 (0.8-1.7)**	**0.8 (0.5-1.37)**	**.01**
INR	**1.31 (1.07-1.55)**	**1.1 (1-1.2)**	**.007**
Albumin, *g/dL*	**3.6 (3.1-3.8)**	**3.8 (3.5-4.3)**	**.006**
Creatinine, *mg/dL*	0.8 (0.7-1.1)	0.9 (0.7-1.1)	.69
Multinodular	43 (68.25)	110 (59.78)	.23
Metastases	20 (31.74)	64 (34.78)	.66
Macrovascular invasion	38 (60.31)	90 (48.91)	.12

Note: Categorical variables are presented as number (%), and continuous variables as median (interquartile range).
Note: Significant comparisons are highlighted in bold.
BMI, body mass index; ECOG: Eastern Cooperative Oncology Group; HE, hepatic encephalopathy; INR, international normalized ratio; MELD, Model for End-stage Liver Disease.

significant trend toward a worse TTP (9.43; 95% CI, 3.72–NA months vs Child A $P = .24$; vs Child B $P = .95$), despite similar tumor characteristics across all subgroups (Supplementary Table 3).

A remarkably longer OS was observed in the ALBI 1 group (30.77; 95% CI, 28.47–NA months) compared with the ALBI 2 group (14.77; 95% CI, 9.73–18.80 months; $P = .0002$) and the ALBI 3 group (7.67; 95% CI, 4.8–NA months; $P < .0001$) (Figure 2*D*). Similarly, the ALBI 1 group showed better TTP (25.90; 95% CI, 15.97–NA months) and PFS (25.90; 95% CI, 12.87–NA months) compared with the ALBI 2 group (TTP 12.33; 95% CI, 8.07–16.3 months; $P = .015$; PFS 8.00; 95% CI, 6.17–11.00 months; $P = .0004$) or the ALBI 3 group (TTP 3.36; 95% CI, 2.49–NA months; $P = .0002$; PFS 3.17; 95% CI, 2.83–NA months; $P < .0001$) (Figure 2*E–F*). Notably, Child Pugh A and B patients with ALBI score 2 showed similar survival rates (Supplementary Figure 2)

Liver Decompensation During Treatment

Liver decompensation occurred in 63 patients (25.51%), including 41 Child Pugh A (27.89%), 22 Child Pugh B (51.16%) ($P = .004$), 10 ALBI 1 (11.49%), 41 ALBI 2 (29.08%), and 12 ALBI 3 (63.16%) (Table 2). The most frequent signs of decompensation were ascites

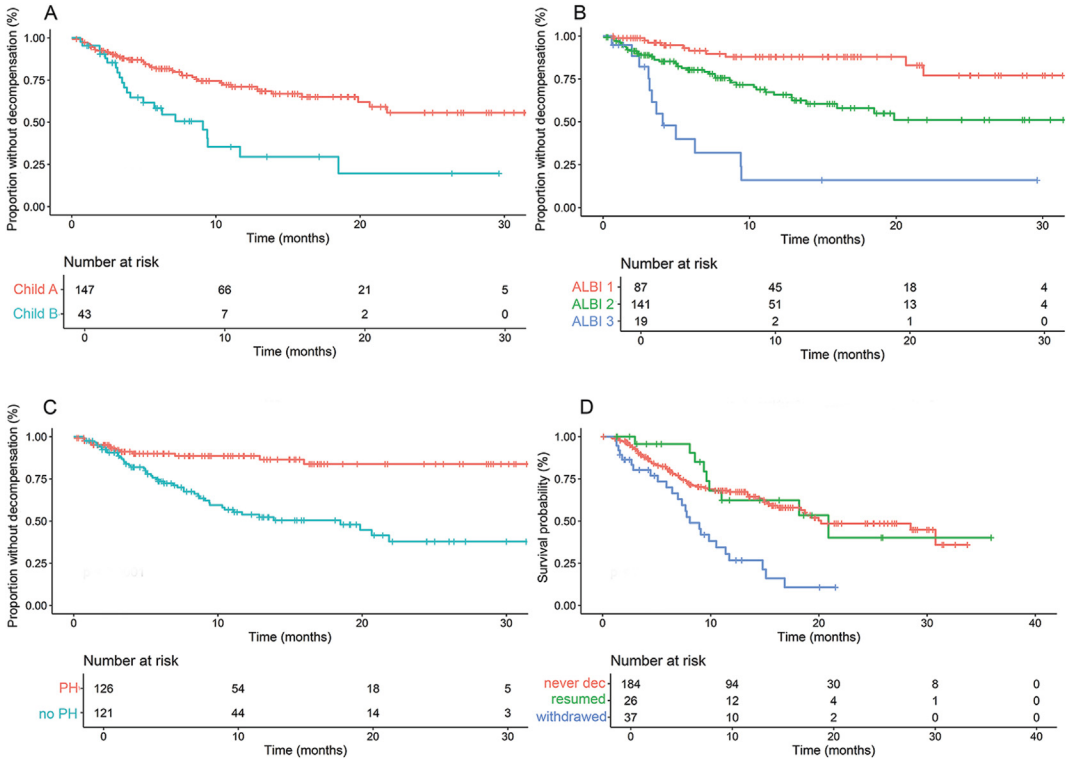

Figure 3. TTD in cirrhotic patients treated with atezolizumab plus bevacizumab stratified by Child Pugh score (panel *A*), ALBI score (panel *B*), and the presence of portal hypertension (PH; panel *C*). Panel *D* shows OS for patients who never decompensated, those who resumed treatment after liver decompensation, and those who did not.

(84.12%), jaundice (46.03%), and hepatic encephalopathy (38.09%). Child Pugh B patients showed a remarkably higher rate of ascites (65.11% vs 29.93%; $P < .0001$), jaundice (25.58% vs 12.24%; $P = .03$) and hepatic encephalopathy (32.55% vs 14.28%; $P = .004$) compared with Child Pugh A patients. There was no difference in the rate of variceal bleeding between the two groups (8.84% vs 13.95%; $P = .32$). A significantly higher occurrence of bleeding was reported in cirrhotic patients with pre-existing esophageal varices detected on endoscopy (14/83; 16.86%) compared with those without (6/107; 5.60%; $P = .01$), but not in patients with macrovascular invasion (14/101; 13.86% vs 6/89; 6.74%; $P = .11$). No episodes of decompensation occurred in the 57 non-cirrhotic patients; jaundice, ascites, hepatic encephalopathy, and variceal bleeding were reported in 8.8%, 15.8%, 8.8%, and 5.26% of these patients, respectively, all of which were associated with tumor progression.

Patients who experienced liver decompensation had significantly shorter OS than those who never decompensated during treatment (10.50; 95% CI, 8.93–16.80 months vs 20.20; 95% CI, 18.33–NA months; $P = .006$).

Median TTD was significantly longer for Child Pugh A patients, not reached within the study timeframe, compared with 9.10 (95% CI, 5–NA) months for Child Pugh B patients ($P < .0001$) (Figure 3*A*). TTD was not reached for the ALBI 1 group, compared with 19.87 months (95% CI, 12.90–NA months) for the ALBI 2 group ($P = .01$) and 3.63 months (95% CI, 3.17–NA months) for the ALBI 3 group ($P < .0001$) (Figure 3*B*). There was no significant difference in TTD between Child Pugh A and B patients with an ALBI score of 2 (19.90; 95% CI, 13.90–NA months and 11.67; 95% CI, 7.20–NA months, respectively; $P = .34$) (Supplementary Figure 3). Patients with portal hypertension also showed worse TTD compared with those without (18.50; 95% CI, 10.30–NA months vs not reached; $P < .0001$) (Figure 3*C*).

Thirty-seven patients (58.73%) could not resume treatment due to persistent decompensation (25; 67.57%), sAEs (11; 29.73%), or personal decision (1; 2.70%); of these patients, 27 (72.97%) died for tumor progression, 3 (8.11%) for end-stage liver disease, 2 (5.40%) for sepsis, 1 (2.70%) for bleeding, and 1 (2.70%) for sudden death. Interestingly, in the 26 patients (41.27%) who restarted atezobeva after decompensation, OS was similar to that of patients who never decompensated (20.87; 95% CI, 9.87–NA months vs 20.20; 95% CI, 18.33–NA months, respectively; $P = .77$) (Figure 3*D*), and better than those who permanently discontinued treatment (8.07; 95% CI, 6.97–11.70 months; $P = .02$). Although liver decompensation was more frequent for Child Pugh B than Child Pugh A patients, as previously discussed, the rate of decompensation resolution was similar between the 2 groups (Child A, 27/41; 65.90% vs Child B, 11/22; 50%; $P = .34$).

At the last follow-up (t1), 103 cirrhotic patients (54.21%) were reclassified as Child Pugh A, 57 patients (30%) as Child Pugh B, and 30 patients (15.79%) as Child Pugh C (Supplementary Figure 4). Notably, 38 (25.85%) of the 147 patients classified as Child Pugh A at

Table 3. Univariate and Multivariate Time-dependent Analyses of Factors Predictive of Mortality, Tumor Progression, and Liver Decompensation

	Univariate				Multivariate			
Risk factor	HR	95% CI (lower)	95% CI (upper)	*P*-value	HR	95% CI (lower)	95% CI (upper)	*P*-value
Mortality								
Child Pugh B class vs A[a]	2.19	**1.36**	**3.55**	**.001**				
ALBI 2–3 vs 1	2.61	**1.63**	**4.19**	**.00007**	**1.62**	**1.11**	**2.37**	**.01**
Tumor progression (yes vs no)	3.20	**2.10**	**4.87**	**< .0001**	**2.18**	**1.56**	**3.06**	**< .0001**
Portal hypertension (yes vs no)	1.03	0.69	1.51	.89				
Viral vs non-viral	0.81	0.54	1.20	.29				
Multinodular vs single nodule	1.26	0.85	1.86	.24				
Macrovascular invasion (yes vs no)	1.64	**1.11**	**2.44**	**.013**	1.30	0.95	1.79	.09
Decompensation (yes vs no)	1.78	**1.18**	**2.68**	**.006**	0.99	0.70	1.40	.94
ECOG 1–2 vs 0	2.12	**1.44**	**3.14**	**.0002**	**1.71**	**1.25**	**2.33**	**.0007**
Metastases (yes vs no)	0.95	0.63	1.43	.81				
AFP >400 ng/mL	1.35	0.63	2.89	.43				
Grade ≥3 trAEs (yes vs no)	1.85	**1.25**	**2.72**	**.002**	1.22	0.89	1.67	.21
Treatment interruption after decompensation (yes vs no)	2.80	**1.77**	**4.43**	**< .0001**	**2.86**	**2.02**	**4.49**	**.004**
Obesity (yes vs no)	0.63	0.40	1.01	.06				
Progression								
Child Pugh B class vs A[a]	1.39	0.83	2.33	.20				
ALBI 2–3 vs 1	**1.80**	**1.19**	**2.71**	**.005**	1.00	0.67	1.49	.99
Portal hypertension (yes vs no)	0.86	0.59	1.25	.44				
Viral vs non-viral	0.86	0.59	1.28	0.48				
Multinodular vs single nodule	1.11	0.76	1.62	.58				
Macrovascular invasion (yes vs no)	**1.37**	**0.94**	**1.98**	**.01**	0.93	0.64	1.35	.70
Decompensation (yes vs no)	1.35	0.89	2.05	.16				
ECOG 1–2 vs 0	1.35	0.92	1.99	.13				
Metastases (yes vs no)	0.83	0.56	1.23	.35				
AFP >400 ng/mL	**2.26**	**1.45**	**3.49**	**.0002**	**1.98**	**1.37**	**2.86**	**.0002**
Grade ≥3 trAEs (yes vs no)	**1.84**	**1.27**	**2.67**	**.001**	**1.46**	**1.01**	**2.86**	**.04**
Treatment interruption after decompensation (yes vs no)	**13.27**	**7.92**	**22.26**	**< .0001**	**3.21**	**2.15**	**4.80**	**< .0001**
Decompensation								
Child Pugh B class vs A[a]	**2.74**	**1.62**	**4.64**	**.0002**				
ALBI 2–3 vs 1	**3.72**	**1.89**	**7.32**	**.0001**	**2.55**	**1.26**	**5.15**	**.009**
Tumor progression (yes vs no)	1.53	0.92	2.52	.10				
Portal hypertension (yes vs no)	**3.73**	**2.06**	**6.75**	**< .0001**	**2.73**	**1.48**	**5.03**	**.001**
Viral vs non-viral	1.05	0.64	1.73	.85				
Multinodular vs single nodule	0.77	0.45	1.31	.34				
Macrovascular invasion (yes vs no)	**1.78**	**1.07**	**2.95**	**.03**	1.61	0.96	2.69	.07
ECOG 1–2 vs 0	**2.12**	**1.29**	**3.48**	**.003**	1.48	0.90	2.45	.12
Metastases (yes vs no)	0.79	0.47	1.36	.41				
AFP >400 ng/mL	1.19	0.61	2.32	.61				
Grade ≥3 trAEs (yes vs no)	**2.01**	**1.22**	**3.30**	**.006**	**1.79**	**1.08**	**2.95**	**.04**

Note: Significant comparisons are highlighted in bold.
AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; trAEs, treatment-related adverse events.
[a]Not included in the multivariate model due to collinearity.

baseline (t0) progressed to Child Pugh B and 16 (10.88%) to Child Pugh C, whereas 14 (32.55%) of the 43 Child Pugh B patients at t0 progressed to Child Pugh C. Of interest, 10 (23.25%) Child Pugh B patients improved their liver function during treatment and reverted to Child Pugh class A.

A comprehensive description of other AEs that occurred during treatment is provided in the Supplementary Appendix.

Prognostic Factors for Survival, Tumor Progression, and Liver Decompensation

Variables significantly associated with mortality, tumor progression, and liver decompensation during atezobeva treatment are shown in Table 3.

Time-dependent multivariate analysis identified the following independent predictors of mortality: ALBI score 2 to 3 (hazard ratio [HR], 1.62; 95% CI, 1.10–2.37; $P = .01$),

tumor progression (HR, 2.18; 95% CI, 1.56–3.06; $P < .0001$), ECOG-PS 1 to 2 (HR, 1.71; 95% CI, 1.25–2.33; $P = .0007$), and treatment interruption after decompensation (HR, 2.86; 95% CI, 2.02–4.49; $P < .0001$).

For tumor progression, significant predictors included alpha-fetoprotein (AFP) >400 (HR, 1.98; 95% CI, 1.37–2.86; $P = .0002$), grade ≥3 trAE (HR, 1.46; 95% CI, 1.01–2.86; $P = .04$), and treatment interruption after decompensation (HR, 3.21; 95% CI, 2.15–4.80; $P < .0001$). Regarding PFS, the time-dependent multivariate analysis found that significant prognostic predictors included treatment interruption after decompensation (HR, 2.85; 95% CI, 2.00–4.06; $P < .0001$), ECOG-PS 1 to 2 (HR, 1.70; 95% CI, 1.23–2.36; $P = .001$), grade ≥3 trAE (HR, 1.59; 95% CI, 1.15–2.19; $P = .01$), and AFP >400 ng/mL (HR, 1.49; 95% CI, 1.07–2.07; $P = .02$).

Finally, ALBI 2 to 3 (HR, 2.55; 95% CI, 1.26–5.15; $P = .009$), portal hypertension (HR, 2.73; 95% CI, 1.48–5.03; $P = .001$), and grade ≥3 trAE (HR, 1.79; 95% CI, 1.08–2.95; $P = .02$) were confirmed as significant predictors of decompensation in the multivariate time-dependent Cox model.

Discussion

In this study, we reinforce the paradigm shift in HCC treatment introduced by atezobeva in a real-life cohort, also extending the feasibility of this combination to patients with mild-to-moderate liver impairment.

The critical role of liver function in determining treatment efficacy is evident, with our findings illustrating the detrimental impact of interruptions/withdrawal due to liver decompensation on outcome. This is particularly relevant for Child Pugh B patients, who are typically excluded from clinical trials, limiting evidence-based recommendations for this subgroup.[3] A few data demonstrated the feasibility of atezobeva in Child Pugh B patients with promising results. Our findings align with these findings, showing a worse OS in Child Pugh B compared with Child Pugh A patients (9.8 vs 20.2 months), despite similar TTP and safety profile. It should be noted that, even in these patients, liver failure was the main reason for treatment discontinuation, but tumor progression remained the leading cause of death. Furthermore, we did not observe a higher rate of variceal bleeding in Child Pugh B patients compared with Child Pugh A patients. We also highlighted that approximately 70% of patients in the Child Pugh B group either remained stable or improved their liver function, reverting to Child Pugh A, likely due to the benefits of reduced tumor burden. Overall, our data, along with those of D'Alessio et al,[4] indicate that atezobeva is well-tolerated also in patients with mild-to-moderate liver dysfunction and can confer a benefit on tumor-related prognosis, even in this patient population. This is particularly significant, given that the natural history of advanced HCC in this setting, if left untreated, typically results in survival of only 3 to 6.9 months.[12,13]

To the best of our knowledge, this is the first study to report liver decompensation as a specific outcome of systemic treatment for HCC and to introduce TTD, challenging the perception of decompensation as merely an AE or a marker of therapeutic failure, inexorably linked to disease progression.

Our analysis identifies pre-treatment liver dysfunction classified as Child Pugh B, among other factors, as a predictor of decompensation, as about one-half of these patients, compared with less than one-third of those classified as Child Pugh A, experienced liver decompensation during treatment. Despite the evident vulnerability of the more compromised patients, it is important to note that the resolution of decompensation occurred at a similar rate in Child Pugh A and B patients. More importantly, those who were able to resume atezobeva after decompensation achieved a better OS than those who had to permanently discontinue treatment. This observation underscores the importance of managing these patients within a multidisciplinary hepato-oncological setting, where therapeutic efforts targeting both the tumor and patient safety can be better balanced.[14–16] Although the small number of Child Pugh B patients in this study prevented a detailed subgroup analysis of the factors for decompensation, the ALBI score may help refine patient stratification. Indeed, the ALBI score independently predicted decompensation alongside the Child Pugh score and identified a group of patients at high risk of decompensation (ALBI 3) that should be carefully considered for treatment. In contrast, patients with an ALBI score of 2 had an intermediate risk and required a strict hepatologic follow-up. This finding is particularly relevant, as TTD was similar for ALBI 2 patients regardless of whether they were classified as Child Pugh A or B. Taken together, these data emphasize the potential relevance of the ALBI score in refining patient stratification for systemic therapy with atezobeva.

The prognostic role of portal hypertension in the context of systemic therapy for HCC is another debated issue.[17,18] In our study, portal hypertension was an independent predictor of decompensation, suggesting that appropriate baseline evaluation and monitoring during treatment, along with the use of preventive and therapeutic strategies (eg, non-selective beta blockers, transjugular intrahepatic portosystemic shunt), are essential. These measures not only ensure patient safety by preventing bleeding but also help avoid treatment discontinuation due to decompensation.

Finally, when assessing prognostic factors, mortality was mainly driven by higher ALBI scores, confirming its strong prognostic significance,[8,19,20] along with tumor progression, poor performance status, and permanent treatment discontinuation following decompensation. AFP, which continues to serve as a surrogate marker of tumor biological aggressiveness even in patients with advanced HCC undergoing immunotherapy, remains the only prognostic factor for progression, besides grade ≥3 trAEs, which often lead to suboptimal treatment and forced discontinuation, negatively impacting treatment efficacy. Although meta-analyses and

retrospective studies show contradictory results,[21,22] we did not observe significant differences in outcomes based on age or liver disease etiology in our cohort.

Despite the strengths of our study, including its real-world applicability and large patient population, some limitations must be acknowledged. The lack of a central review of patient imaging and the absence of a fixed imaging follow-up schedule may have influenced the assessment of treatment response, potentially contributing to the longer than expected TTP and PFS. Additionally, we only included patients classified as Child Pugh B7 to 8, so our findings cannot be generalized to those with Child Pugh scores $\geq$B9.

In conclusion, this real-world study confirms that the combination of atezobeva is safe and effective in patients with unresectable HCC and mild-to-moderate liver dysfunction. Given that HCC remains one of the most lethal cancers, with extremely poor 5-year survival rates, extending eligibility for immunotherapy to patients who are typically excluded from randomized clinical trials represents a major advancement in personalized medicine. Furthermore, the possibility to resume treatment after an episode of liver decompensation and still achieve good survival outcomes underscores the importance of proper management of underlying liver disease, with hepatologists playing a key role. Therefore, close multidisciplinary collaboration between oncologists and hepatologists should be strongly promoted for the current and future management of patients with HCC undergoing systemic treatments.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2024.12.028.

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Acknowledgments
The authors thank Fondazione Roma for the invaluable support for scientific research (FR-CEMAD 21-25).

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Conflicts of interest
These authors disclose the following: Francesco Tovoli received consultation fees from Roche, Ipsen, and Eisai. Giuseppe Cabibbo received advisory board and speaker fees for Bayer, Eisai, Ipsen, AstraZeneca, MSD, Roche, and Gilead. Fabio Marra received consultation fees from Roche, MSD/EISAI, AstraZeneca, and Ipsen. Fabio Piscaglia received consultation fees from Astrazeneca, Bayer, Bracco, ESAOTE, EISAI, Exact Sciences, GE, IPSEN, MSD, Nerviano, Roche, Samsung, and Siemens Healthineers. Mohamed Bouattour received speaker fees from Bayer, MSD, Sirtex Medical and Roche; and advisory board fees from Bayer, MSD, Sirtex Medical, Eisai, AstraZeneca, Ipsen, Servier, Taiho and BMS. Francesca Romana Ponziani received speaker fees, advisory board fees and travel grants from Bayer, MSD, Roche, Eisai, Ipsen, Astra-Zeneca, Gilead, and Abbvie. The remaining authors disclose no conflicts.

Data Availability
The data that support the findings of this study are not publicly available because their containing information could compromise the privacy of research participants, but are available from the corresponding author (Francesca Romana Ponziani) upon reasonable request.

Supplementary Appendix

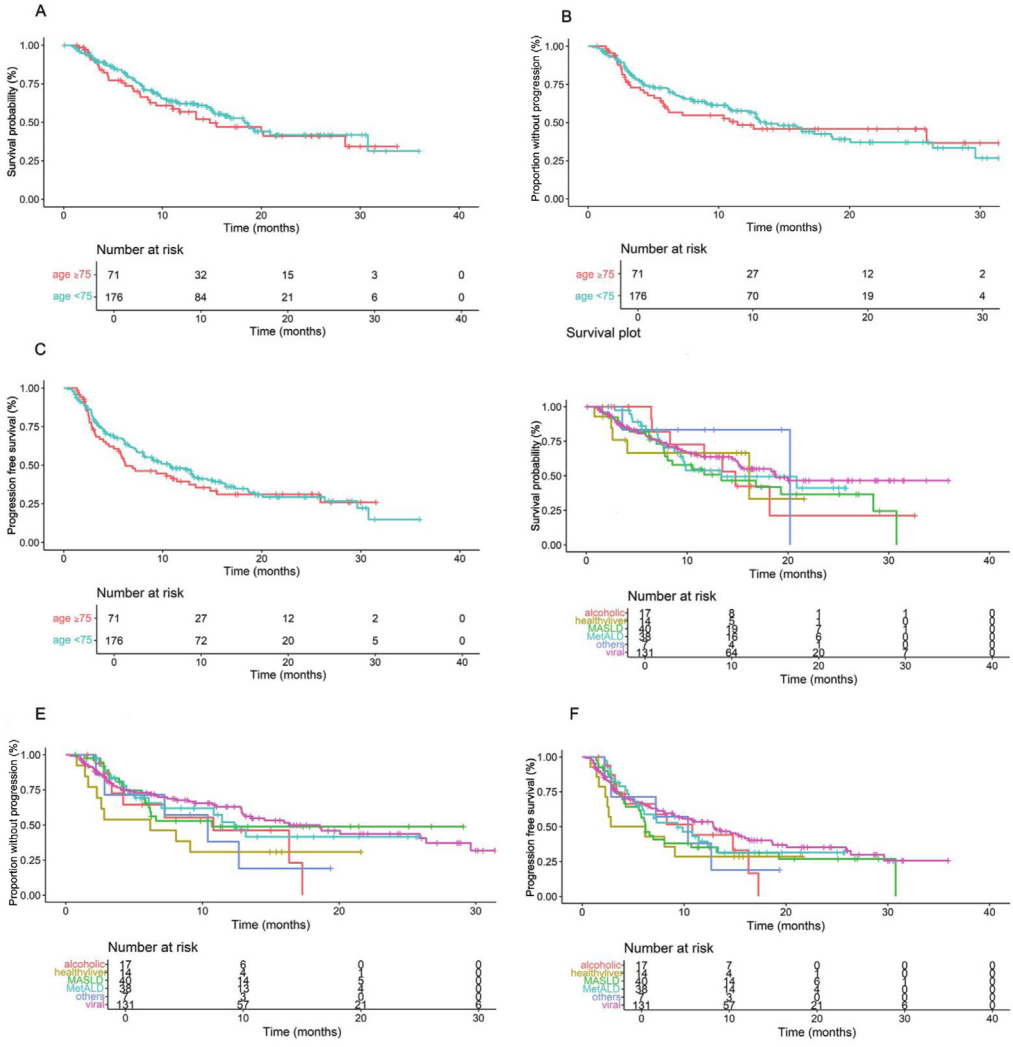
Adverse Events

A total of 221 patients (89.47%) experienced at least one adverse event (AE), of which 41.29% were classified as grade ≥3 treatment-related adverse events (trAEs) and 10.52% as serious adverse events (SAEs) (Supplementary Table 4). The most common immune-related adverse events (irAEs) in this group were thyroid dysfunction (29.14%), pruritus (22.26%), and cutaneous reactions (20.64%). The most common bevacizumab trAEs were proteinuria (23.88%), hypertension (22.26%), and oral mucositis (18.62%). Major bleeding unrelated to portal hypertension occurred in 11.33% patients (10.12% gastrointestinal bleeding and 1.21% other non-gastrointestinal bleeding). Common trAEs related to both drugs were fatigue and anorexia (69.63% and 59.51%, respectively).

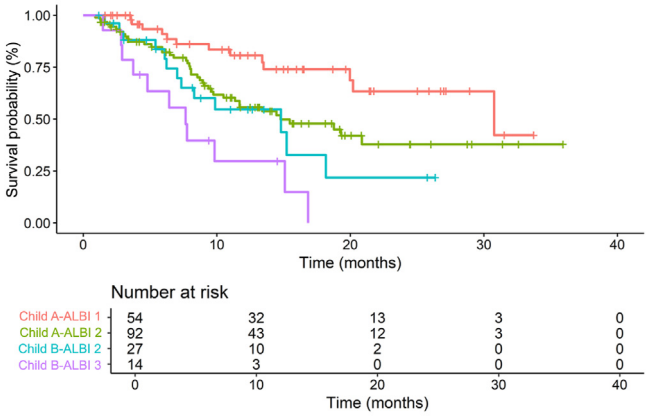
A similar safety profile was observed for Child Pugh A and B patients, with a higher prevalence of anorexia and fatigue in the latter group and a slightly higher occurrence of bleeding unrelated to portal hypertension (Supplementary Table 5).

Age	Etiology
Median OS Age <75: 18.30 (95% CI, 15.10–NA) months Age ≥75: 14.80 (95% CI, 9.37–NA) months OS comparisons Age ≥75 vs <75: $P = .52$	Median OS Healthy: 16.2 (95% CI, 4.07–NA) months MASLD: 13.4 (95% CI, 7.8–NA) months MetALD: 13.4 (95% CI, 9.37–NA) months Alcoholic: 14.8 (95% CI, 11.7–NA) months Viral: 18.80 (95% CI, 15.10–NA) months Others: 20.2 (95% CI, NA–NA) months Comparisons: MASLD vs viral: $P = .15$ Alcoholic vs viral: $P = .62$ MASLD vs alcoholic: $P = .55$
Median TTP Age <75: 13.6 (95% CI, 12.3–20.10) months Age ≥75: 11.40 (95% CI, 5.8–NA) months TTP comparisons Age ≥75 vs <75: $P = .72$	Median TTP Healthy: 6.18 (95% CI, 2.27–NA) months MASLD: 10.7 (95% CI, 6.07–NA) months MetALD: 12.33 (95% CI, 7.00–NA) months Alcoholic: 10.8 (95% CI, 4.20–NA) months Viral: 16.33 (95% CI, 12.87–NA) months Others: 10.39 (95% CI, 2.83–NA) months Comparisons: MASLD vs viral: $P = .75$ Alcoholic vs viral: $P = .21$ MASLD vs alcoholic: $P = .37$
Median PFS Age <75: 10.73 (95% CI, 8.00–14.50) months Age ≥75: 6.23 (95% CI, 5.07–13.3) months PFS comparisons Age ≥75 vs <75: $P = .48$	PFS Healthy: 4.49 (95% CI, 2.47–NA) months MASLD: 6.23 (95% CI 5.57–19.3) months MetALD: 9.37 (95% CI 7.00–NA) months Alcoholic: 10.8 (95% CI 4.20–NA) months Viral: 12.93 (95% CI 9.00–18.6) months Others: 10.39 (95% CI 2.83–NA) months Comparisons: MASLD vs viral: $P = .19$ Alcoholic vs viral: $P = .34$ MASLD vs alcoholic: $P = .99$

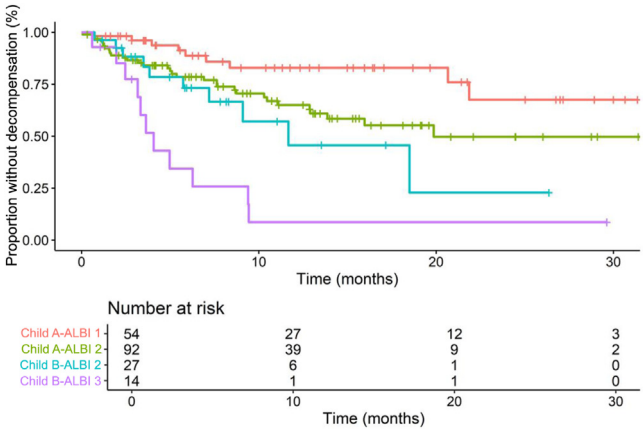
CI, confidence interval; MASLD, metabolic-associated steatotic liver disease; MetALD, metabolic dysfunction-associated liver disease + alcohol; OS, overall survival; PFS, progression-free survival; TTP, time to progression.



Supplementary Figure 1. OS (panel *A, D*), TTP (panel *B, E*), and PFS (panel *C, F*) of patients according to age ($<$ or $\geq$75 years) and etiology of liver disease. Data in months.



Supplementary Figure 2. OS (months) of cirrhotic patients stratified according to the ALBI score. Median OS: Child A-ALBI 1: 30.77 (95% CI, 20.20–NA); Child A-ALBI 2: 14.77 (95% CI, 11.37–NA); Child B-ALBI 2: 14.40 (95% CI, 7.33–NA); Child B-ALBI 3: 7.67 (95% CI, 4.80–NA). Comparisons: Child A-ALBI 1 vs Child A-ALBI 2: $P = .012$; Child A-ALBI 2 vs Child B-ALBI 2: $P = .41$; Child B-ALBI 2 vs Child B-ALBI 3: $P = .073$; Child A-ALBI 1 vs Child B-ALBI 3: $P < .0001$.



Supplementary Figure 3. TTD (months) of cirrhotic patients stratified according to the ALBI score. Median TTD: Child A-ALBI 1: not reached (95% CI, 21.90–NA); Child A-ALBI 2: 19.90 (95% CI, 13.90–NA); Child B-ALBI 2: 11.67 (95% CI, 7.20–NA); Child B-ALBI 3: 4.07 (95% CI, 3.17–NA). Comparisons: Child A-ALBI 1 vs Child A-ALBI 2: $P = .02$; Child A-ALBI 2 vs Child B-ALBI 2: $P = .34$; Child B-ALBI 2 vs Child B-ALBI 3: $P = .02$; Child A-ALBI 1 vs Child B-ALBI 3: $P < .0001$.

Supplementary Figure 4. Child Pugh score transition from baseline (t0) to last follow-up (t1) of cirrhotic patients after atezolizumab plus bevacizumab treatment.

Supplementary Table 1. Stratification of Patients According to the Child Pugh Score and the ALBI Score

	ALBI 1	ALBI 2	ALBI 3
Child Pugh A	54 (36.73)	92 (62.59)	1 (0.68)
Child Pugh B	2 (4.65)	27 (62.79)	14 (32.56)
No cirrhosis	31 (54.39)	22 (38.59)	4 (7.02)

Note: Data are presented as number (%).
ALBI, Albumin-bilirubin score.

Supplementary Table 2. Radiologic Tumor Response

	Atezolizumab plus bevacizumab (n = 247)
CR	13 (5.26)
PR	44 (17.81)
SD	77 (31.17)
PD	113 (45.76)
ORR	57 (23.07)
DCR	134 (54.25)

CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Supplementary Table 3. Tumor Characteristics and Previous Treatments of Patients Treated With Atezolizumab Plus Bevacizumab According to Liver Function

	Child Pugh A (n = 147)	Child Pugh B (n = 43)	Non-cirrhotic (n = 57)	*P*-value	*P*-value (Child Pugh A vs B)	*P*-value (Child Pugh A vs non-cirrhotic)	*P*-value (Child Pugh B vs non-cirrhotic)
Multinodular	93 (63.26)	27 (62.79)	33 (60)	.77	.95	.48	.62
Number of nodules	5 (3.0-6.0)	3 (2.0-7.0)	3 (1.0-11.0)	.20	.16	.19	.05
Vascular Invasion	70 (47.71)	31 (72.09)	27 (47.36)	**.01**	**.005**	.97	**.01**
Metastases	48 (32.65)	11 (25.58)	25 (43.85)	.14	.38	.13	.06
Resection	28 (19.04)	6 (13.95)	19 (33.33)	**.03**	.44	**.03**	**.03**
PEI	8 (5.44)	2 (4.66)	-	.49	.84	.24	.39
RFA	27 (18.36)	4 (9.30)	1 (1.75)	**.005**	.16	**.002**	.09
TACE	63 (42.85)	16 (37.20)	14 (24.56)	.05	.14	**.01**	.25
TARE	40 (27.21)	9 (20.93)	14 (24.56)	.69	.12	.70	.67

Note: Significant comparisons are highlighted in bold.
PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

Supplementary Table 4. Prevalence of AEs That Occurred During Treatment With Atezolizumab Plus Bevacizumab

AE type	AE frequency (%)
trAEs	221 (89.47)
Grade ≥3 trAEs	102 (41.29)
SAEs	26 (10.52)
Atezolizumab-related	
Thyroid dysfunction	72 (29.14)
Cutaneous reaction	51 (20.64)
Pruritus	49 (19.83)
ALT or AST elevation	35 (14.17)
Arthritis	23 (9.31)
Inflammatory colitis	10 (4.04)
Nephritis	7 (3.64)
Bevacizumab-related	
Proteinuria	59 (23.88)
Hypertension	55 (22.26)
Oral mucositis	46 (18.62)
Thrombosis	34 (13.77)
Major GI bleeding[a]	25 (10.12)
Major non-GI bleeding	3 (1.21)
Related to both drugs	
Fatigue	172 (69.63)
Anorexia	117 (59.51)
Diarrhea[b]	36 (14.57)
Neuropathy	24 (9.71)

ALT, alanine transaminase; AST, aspartate aminotransferase; GI, gastrointestinal; SAEs, serious adverse events; trAEs, treatment-related adverse events.
[a]Not related to portal hypertension.
[b]Not immune-mediated.

Supplementary Table 5. AEs Occurring During Atezolizumab Plus Bevacizumab Treatment According to Liver Function

	Child Pugh A (n = 147)	Child Pugh B (n = 43)	Non cirrhotic (n = 57)	*P*-value	*P*-value (Child Pugh A vs B)	*P*-value (Child Pugh A vs non-cirrhotic)	*P*-value (Child Pugh B vs non-cirrhotic)
trAEs	132 (89.79)	41 (95.34)	48 (84.21)	.18	.26	.27	**.08**
trAEs ≥grade 3	57 (38.77)	22 (51.16)	23 (40.35)	.34	.15	.84	.28
SAEs	16 (10.88)	7 (16.27)	3 (5.26)	.20	.34	.22	.07
Hypertension	33 (22.44)	7 (16.27)	15 (26.31)	.49	.38	.56	.23
Proteinuria	33 (22.44)	11 (25.58)	15 (26.31)	.81	.67	.56	.93
Oral mucositis	27 (18.36)	9 (20.93)	10 (17.54)	.90	.71	.89	.67
Major non-GI bleeding	–	2 (4.65)	1 (1.75)	–	–	–	.71
Major GI bleeding[a]	13 (8.84)	8 (18.6)	4 (7.01)	.12	**.07**	.67	.77
Thrombosis	20 (13.60)	7 (16.27)	7 (12.28)	.84	.66	.80	.57
Pruritus	30 (20.40)	8 (18.60)	11 (19.29)	.96	.79	.86	.93
ALT or AST elevation	25 (17)	5 (11.62)	5 (8.77)	.28	.40	.14	.64
Cutaneous reaction	34 (23.12)	7 (16.27)	10 (17.54)	.49	.34	.38	.87
Inflammatory colitis	5 (3.40)	2 (4.65)	3 (5.26)	.81	.70	.54	.89
Nephritis	4 (2.27)	1 (2.32)	2 (3.50)	.93	.89	.76	.73
Diarrhea[b]	20 (13.60)	7 (16.27)	9 (15.78)	.87	.66	.69	.95
Arthritis	15 (10.20)	3 (6.97)	5 (8.77)	.80	.52	.76	.74
Hypothyroidism	37 (25.17)	11 (25.58)	13 (22.80)	.93	.96	.72	.75
Hyperthyroidism	6 (4.08)	1 (2.32)	4 (7.01)	.51	.60	.38	.29
Neuropathy	15 (10.20)	2 (4.65)	7 (12.28)	.42	.26	.67	.19
Anorexia	63 (42.85)	26 (60.46)	28 (49.12)	.12	**.04**	.41	.26
Fatigue	102 (69.38)	32 (74.41)	38 (66.66)	.70	**.03**	.71	.40

Note: Data are presented as number (%).
Note: Significant comparisons are highlighted in bold.
ALT, alanine transaminase; AST, aspartate aminotransferase; GI, gastrointestinal; SAEs, treatment-related serious adverse events; trAEs, treatment-related adverse events.
[a]Not related to portal hypertension.
[b]Not immune-mediated.