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Atezolizumab Plus Bevacizumab Treatment for Unresectable Hepatocellular Carcinoma: Real-life Experience from a Single Tertiary Centre in Spain and ALBI Score as a Survival Prognostic Factor

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Abstract. *Background/Aim: Atezolizumab/bevacizumab (atez/bev) has been established as first-line systemic treatment for hepatocellular carcinoma (HCC). However, concerns regarding safety and efficacy have been raised, and no biomarkers to predict response have yet been identified. We aimed to evaluate the real-life experience of atez/bev in a Spanish tertiary hospital and identify factors associated with overall survival (OS). Patients and Methods: A prospective study of consecutive patients with HCC treated with atez/bev was conducted from December 2020 to December 2022. Efficacy was assessed through OS and progression-free survival (PFS), whereas safety was evaluated based on adverse events (AE). Twenty-three patients were included; 91% were males with a mean of 70 years. Thirteen patients were classified as having BCLC-C. Results: The median treatment duration was 126 days (range=567). Median OS was 381 days (95%CI=205-557) with a cumulative probability of death of 13%, 30%, and 49% at 3, 6 and 12-month follow-up, respectively. The only factor associated with OS was the ALBI score (HR=5.03; 95%CI=1.3-19.1), which showed an AUROC of 0.906 (95%CI=0.78-1.00) for the risk of death at 18 months follow up. Median PFS was 141 days (95%CI=110-172). Twenty (86.9%) patients experienced AE, which in nine (39.1%) cases led to the definitive discontinuation of the treatment, four of them (17.4%) due to an AE grade 5. Conclusion: The initial experience with atez/bev at our center demonstrated poorer outcomes compared to the original trial (IMbrave150). A careful assessment of the ALBI score may serve as a crucial factor in the selection of systemic treatment for patients with HCC.*

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Key Words: Hepatocellular carcinoma, atezolizumab, bevacizumab, real-world, adverse events, prognostic factors.

For over a decade, sorafenib has been the first-line treatment for advanced-stage hepatocellular carcinoma (HCC) (1). In late 2019, the first results of the IMbrave150 study were released and subsequently published in May 2020 in the New England Journal of Medicine (2). In that study, the efficacy and safety of a two-drug combination, atezolizumab and bevacizumab (atez/bev), was assessed and compared with sorafenib as first-line treatment, for patients with locally advanced, metastatic or unresectable HCC who had not previously received systemic therapy. The results showed that combination of atez/bev significantly improved overall survival (OS) and objective response rate compared to sorafenib. Since then, atez/bev has become first-line treatment for patients with stage C HCC according to the Barcelona Clinic Liver Cancer (BCLC) classification (3), or for those in earlier stages who do not respond to, or progress on local treatments. There exist few studies analyzing real-world data with atez/bev. A significant proportion of these studies have been conducted in Asia, involving a cohort of patients with primarily viral etiology. In general, the results described an efficacy and safety of atez/bev similar to that published in the pivotal study (4-6). In Europe, two recent German studies

demonstrated that their real-world progression free survival (PFS) and OS with atez/bev were comparable to those of the IMbrave trial (7, 8). To date, most centers in Spain still have limited experience using these drugs and, to the best of our knowledge, there is no real-life data with atez/bev in Spanish hospitals. Therefore, the aim of our study was to evaluate the real-life efficacy and safety of atez/bev over a two-year period in patients with HCC in a Spanish tertiary hospital. A secondary aim was to identify factors associated with OS.

Patients and Methods

Study design and patient selection. This was a prospective longitudinal study of consecutive patients with HCC treated with atez/bev from December 2020 to December 2022 in the University Clinic Hospital of Valencia, Spain. Patients' data including demographics, history of liver disease and comorbidities, previous treatments, laboratory results and radiological exams were collected. The main endpoints to evaluate efficacy were OS and PFS; while rate and severity of adverse events (AE) were considered to evaluate safety. Patients were followed-up until death or study closure in August 2023, whichever came first. The study conforms to the ethical guidelines of the Declaration of Helsinki and was approved by the local ethics committee.

Underlying liver disease. For the present study, HCC due to hepatitis C virus (HCV) was defined by the presence of positive anti-HCV was identified. HCC due to alcohol was defined by a clear history of alcohol abuse of 60 g/day or more. Child-Pugh classification (9), model for end-stage liver disease (MELD) (10) and ALBI score and modified ALBI grade (mALBI) (11) were used for the assessment of liver reserve function. These variables were assessed at baseline and during follow-up to evaluate deterioration. Before starting atez/bev therapy, all patients underwent upper endoscopy to assess the presence of esophagogastric varices. Patients with a risk of bleeding due to portal hypertension were treated according to clinical practice guidelines (12).

HCC diagnosis. HCC was diagnosed according to radiological criteria as recommended by the European Association for the Study of the Liver guidelines (13) and therapeutic response was evaluated using the modified Response Evaluation Criteria in Solid Tumours (RECIST) (14). Patients with HCC were stratified according to the BCLC staging system (3).

Atez/bev treatment and adverse events assessment. Intravenous treatment with atez/bev at a dose of 1200 mg of atezolizumab plus 15 mg/kg of body weight of bevacizumab, was given every three weeks (2). The National Cancer Institute Common Terminology Criteria for AE, version 5.0, was used to assess AE (15). Treatment was discontinued if any unacceptable or serious AE appeared, or if there was clinical tumor progression.

Statistical analysis. Continuous demographic, clinical, laboratory and radiological variables were analyzed for normality using the Shapiro-Wilk test. Normally distributed data were reported as mean and (SD) and non-normally distributed data were reported as median and range (R). Categorical data was reported as frequencies and percentage (%). Duration of therapy was defined as the time from the first administration of atez/bev until the last dose, taking into account transient interruptions. OS and PFS were evaluated using Kaplan Meier curves from the first date of treatment until the date of censoring (death or study closure). Univariable and multivariable Cox-regression analyses were used to identify factors independently associated with OS. Time-dependent receiver-operating characteristics (ROC) curves were constructed to evaluate the predictive accuracy of factors associated with OS. Paired *t*-test or Wilcoxon tests were used to evaluate deterioration of liver function during follow-up. All tests were two sided and a p-value <0.05 was considered statistically significant. All analyses were performed with SPSS Statistics (version 29.0.0.0) and R (version 4.0.2).

Ethical considerations. This study conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the local ethics committee. This study protocol was reviewed and approved by Ethics Committee of Investigation With Drugs from Hospital Clínico Universitario de Valencia approval number [2021/196] and has been granted an exemption from requiring written informed consent given that this is an anonymized observational study.

Results

Study population. Twenty-three patients were included in the study. Twenty-one patients were male (91%) and the mean age was 70 (SD=7.8) years old. Baseline characteristics of the study population are summarized in Table I and Table II. Thirteen patients (56.5%) were classified as BCLC-C and ten (43.4%) as BCLC-B. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and all of them had compensated cirrhosis while they were on treatment, with a median Child-Pugh of 5. Mean ALBI score was –2.43 (SD=0.5) at baseline with a mALBI grade of 1 in nine (39.1%) patients, 2a in four (17.4%) and 2b in ten (43.4%). Mean ALBI score at six weeks of treatment with atez/bev was –2.26 (SD=0.5) with significant differences compared with baseline (mean difference=0.17; 95%CI=0.07-0.28; p=0.003). Nine patients (39%) were naive before starting atez/bev and fourteen patients (61%) had received previous treatments, including transarterial chemoembolization (TACE), radiofrequency ablation, transarterial radioembolization (TARE), surgery, sorafenib or cabozantinib. In this latter group, atez/bev was initiated following progression or lack of response to prior therapies. Four patients received a second-line treatment (sorafenib/lenvatinib) after tumor progression on atez/bev or upon discontinuation. Patients were followed-up during a median of ten (0-28) months. Time on treatment was 126 days (567) with a median of 6 (27) cycles of atez/bev per patient.

Efficacy. A total of fifteen (65%) patients died during the study period with twelve (80%) liver-related deaths. Median OS was 381 days (95%CI=205-557) with a cumulative probability of death of 13%, 30%, and 49% at 3, 6 and 12-month follow-up, respectively (Figure 1). Factors associated with OS in the univariable Cox-regression analyses were ALBI score at baseline and tumor size (Table III); while in the multivariable analysis, only ALBI score (HR=5.03; 95%CI=1.3-19.1; p=0.018) but not

Table I. *Baseline demographic and clinical characteristics of the study population.*

Parameter	Total (n=23)
Age, years (mean, SD)	70 (7.8)
Sex, male:female (n, %)	21 (91):2 (9)
Diabetes mellitus (n, %)	11 (47.8)
Obesity (n, %)	2 (8.7)
Arterial hypertension (n, %)	11 (47.8)
Chronic kidney disease (n, %)	4 (17.4)
Hyperlipidemia (n, %)	9 (39.1)
Heart disease (n, %)	3 (13)
Pulmonary disease (n, %)	2 (8.7)
Etiology of HCC (n, %)	
HCV	10 (39)
Alcohol	8 (35)
HCV and alcohol	2 (9)
MASLD	2 (9)
Unknown	1 (4)
Naive HCC (n, %)	9 (39)
Previous treatments (n, %)	14 (61)
TACE	6
TARE	3
RFA	1
Surgery	4
Sorafenib	2
Cabozantinib	1
ECOG (n, %)	
0	10 (43)
1	13 (57)
BCLC stage (B/C) (n, %)	10 (39)/13 (56)
Esophageal varices (n, %)	
Small	8 (35)
Big	1 (4)
Child-Pugh (median, range) (n, %)	5 (5-8)
A	19 (83)
B	4 (17)
C	0 (0)
MELD (median, range)	9 (6-16)
ALBI score (mean, SD)	–2.43 (0.5)
mALBI grade 1:2a:2b:3 (n)	9:4:10:0
ALBI at 6 weeks (mean, SD)	–2.26 (0.5)
mALBI at 6 weeks 1:2a:2b:3 (n)	3:7:9:2
Tumor size (median, range; cm)	3.4 (1-17)
Single intrahepatic tumor (n, %)	5 (22)
Macro-vascular invasion (n, %)	7 (30)
Bilobar (n, %)	14 (61)
Extrahepatic metastasis (n, %)	10 (44)

SD: Standard deviation; BCLC: Barcelona Clinic Liver Cancer; ECOG: Eastern Cooperative Oncology Group; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; MASLD: metabolic associated steatotic liver disease; MELD: model for end-stage liver disease; RFA: radiofrequency ablation; TACE: transarterial chemoembolization; TARE: transarterial radioembolization; mALBI: modified ALBI.

Table II. *Baseline laboratory data of the study population.*

Parameter (median, range)	Total (n=23)
AFP (ng/ml)	12.5 (1-121,000)
Glucose (mg/dl)	115 (70-378)
Creatinine (mg/dl)	0.88 (0.54-1.85)
Cholesterol (mg/dl)	175 (84-380)
Triglycerides (mg/dl)	141 (62-285)
Albumin (g/dl)	3.9 (3-5)
Total bilirubin (mg/dl)	1.02 (0-4)
INR	1.11 (1-2)
Platelets ($\times 10^9$/l)	173 (600-602)
Hemoglobin (g/dl)	13.7 (9-21)
AST (U/l)	44.5 (17-165)
ALT (U/l)	34 (15-292)

AFP: Alpha-fetoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; INR: international normalized ratio.

tumor size (HR=1.1; 95%CI=0.9-1.2; p=0.204) was kept as an independent predictor of OS. Risk of death was lower in patients with mALBI grade 1 (HR=0.234; 95%CI=0.07-0.76; p=0.016) or 2a (HR=0.196; 95%CI=0.04-0.93; p=0.04) compared with 2b (Figure 2). Baseline ALBI score showed an area under the ROC curve of 0.906 (95%CI=0.78-1.00; p=0.004) for 18-months' death. An improvement in the ALBI score from baseline to week 6 of treatment was associated with higher OS (HR=0.027; 95%CI=0.002-0.36; p=0.006). Neither the presence of metastasis, vascular invasion, bilobar disease, Child-Pugh, MELD, cirrhosis etiology, nor comorbidities were associated with OS.

Overall, nineteen patients (83%) had at least one follow-up imaging for the assessment of tumor response. A total of two patients (9%) presented a complete response, four patients (17%) a partial response and one patient (4%) stable disease. The remaining twelve patients (52%) did not show radiological response to the treatment. Median PFS was 141 days (95%CI=110-172) with a cumulative probability of progression of 14%, 56% and 78% at 3, 6 and 12 months of follow-up, respectively.

At the end of the study period, a total of twenty (86.9%) patients who initiated treatment with atez/bev, discontinued it permanently. Eleven of them due to tumor progression or illness complications, subsequently starting sorafenib, lenvatinib or best supportive therapy, while the other nine due to severe AE.

Safety. Of the twenty-three patients included in our study, twenty (86.9%) experienced AE of any grade (Table IV). Sixteen patients (69.5%) discontinued treatment for AE, although seven were able to resume it once the situation that led to the discontinuation was resolved. As mentioned before, the other nine patients (39.1%) experienced AE that led to the definitive discontinuation of the treatment, four of them (17.4%) due to an AE grade 5. One patient experienced hepatic function deterioration and the development of a large right iliac intramuscular hematoma. Four patients developed hepatic decompensation with ascites and/or encephalopathy and three

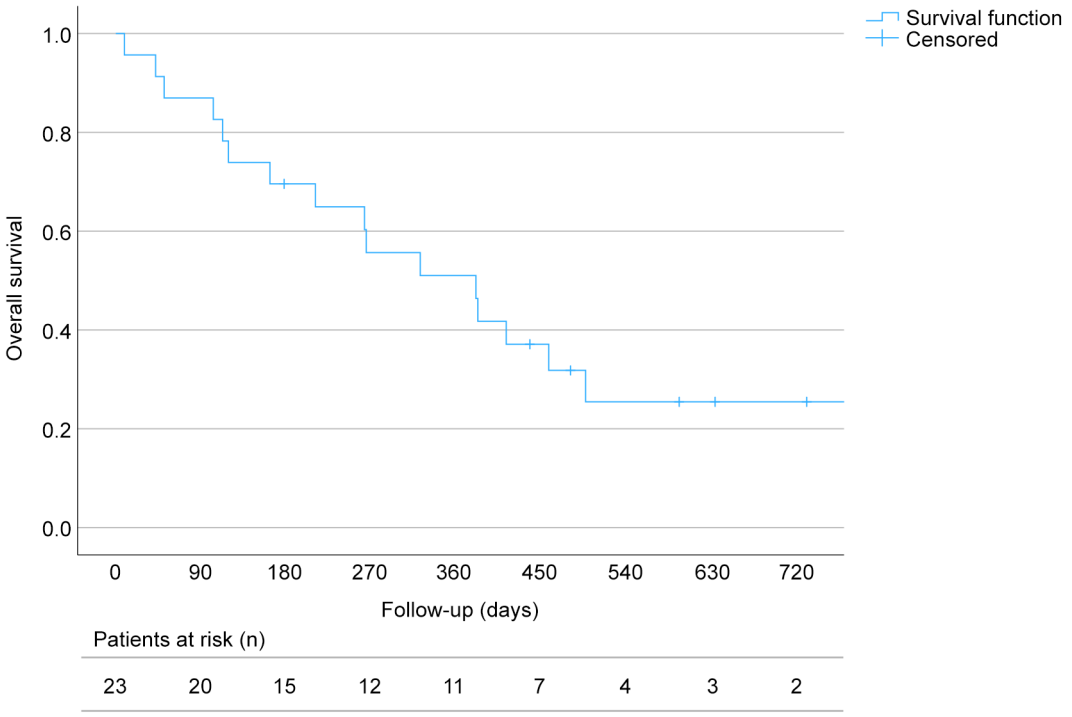


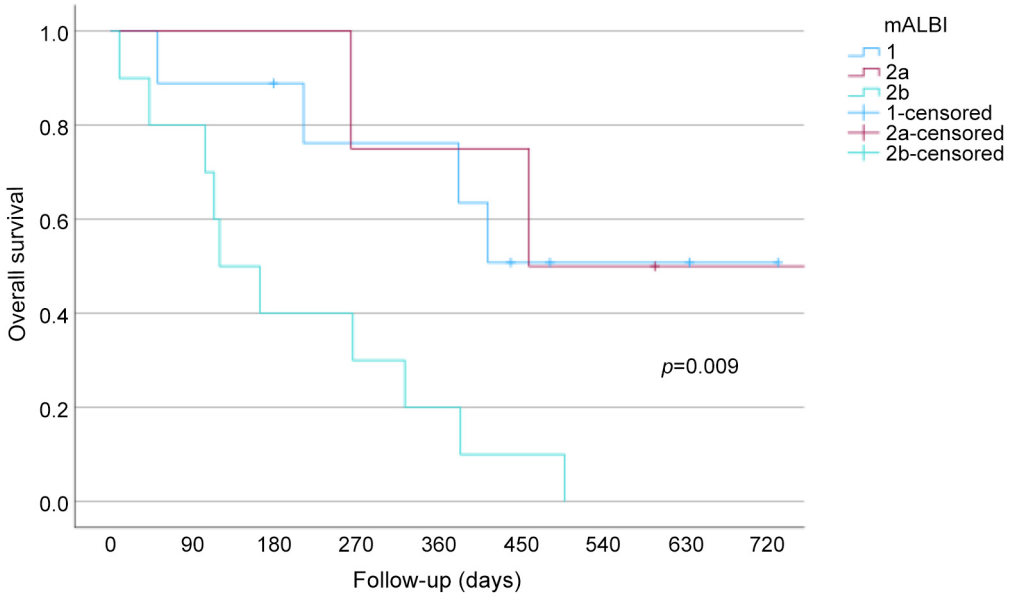
Figure 1. *Kaplan Meier plot of overall survival in the study population (n=23 patients that received atez/bev treatment).*

patients died after receiving only 1 to 3 sessions of atez/bev due to: 1- myositis, myocarditis and Guillain-Barre syndrome, 2- pulmonary embolism, and hemorrhagic shock originating from maxillary metastasis and 3- abdominal sepsis. All of them were initially admitted to the intensive care unit without achieving control of any of the referred clinical conditions. Both patients, the one with myositis, myocarditis and Guillain-Barre syndrome and the one with pulmonary embolism and hemorrhagic shock, had HCC BCLC stage C. The patient with abdominal sepsis was BCLC B but with extensive bilobar involvement. The patient with pulmonary embolism was treatment-naive, whereas the patient with myositis and Guillain-Barre had previously undergone surgery and experienced subsequent recurrence following TACE. The patient with abdominal sepsis had been previously treated through TACE and TARE. All three had a Child-Pugh score of 5-6, a MELD score of 9-10 and a mALBI grade 1, 2b y 2b, respectively. One patient died after 1 cycle, but the cause of this death is unknown.

Discussion

The approval of atez/bev as first-line treatment for unresectable HCC, marked a significant shift in the therapeutic landscape, challenging the longstanding use of sorafenib. In this study, we report a real-life experience with atez/bev in a tertiary center in Spain during the first two years following the publication of the IMbrave150 study.

The baseline characteristics of the study cohort align with the inclusion criteria used in the Imbrave150 study, except for three main aspects. First, the age of the patients in our study was slightly higher with a mean of 70 years compared with 64 years old in IMbrave150. In relation to this, a recent multicenter analysis evaluated the safety and efficacy of atez/bev in elderly patients with HCC (6). Although age is a factor that has generally been associated with a worse prognosis of HCC, the referenced study concluded that atez/bev can be used safely and efficiently in elderly patients. Similarly, our study did not show an association between age and death. Secondly, we included two patients who had received previous treatment with sorafenib and cabozantinib, showing that these patients did not exhibit lower survival benefit. Likewise, Sho *et al*. investigated 64 patients treated with atez/bev of whom 44 received previous systemic treatment, showing good safety and efficacy after atez/bev regimen (5). Finally, the main etiology of cirrhosis in our study was HCV and alcohol, with alcohol being the sole etiology or cofactor of HCV in almost 50% of the cases, whereas in the Imbrave150 study, 70% of patients presented viral etiology (50% of them being hepatitis B virus) and 30% non-viral, specifically referring to: alcohol, other, and unknown non-hepatitis B and C causes (2). Thus, the presence of active or previous alcohol abuse is clearly lower in Imbrave150 than in our cohort. In our setting, with a higher prevalence of HCV and alcohol-related liver disease, comparable real-world data on atez/bev are still scarce.



Patients at risk (n)

1	9	8	7	6	6	3	2	2	1
2a	4	4	4	3	3	3	2	1	1
2b	10	8	4	3	1	1	0	0	0

Figure 2. *Kaplan Meier plot of overall survival of the study population according to mALBI group. Differences in median overall survival were assessed by log-rank test.*

The median OS of 12.7 months observed in our study is inferior to that described in the IMbrave150 study (median 19.2 months) (2). An exploratory subgroup analysis of the Imbrave150 trial favored immunotherapy for patients with viral hepatitis (16). Other publications have also demonstrated poorer survival in patients with non-viral HCC (8). Recently, Pfister *et al*. presented widely debated findings indicating reduced efficacy of immunotherapy in non-alcoholic steatohepatitis (NASH)-HCC patients compared to patients with virus-induced HCC, attributed to the presence of specialized resident-like activated CD8+ cells in patients with NASH (17). Two studies conducted in Germany also showed controversial results regarding the efficacy of atez/bev in non-viral HCC. Himmelsbach *et al*. analyzed the experience of four hospital centers, describing that patients with viral hepatitis tended to have a more favorable prognosis than patients without viral-related HCC (8); while the second study (7), including 100 patients treated with atez/bev, reported that patients with non-viral liver cirrhosis benefit from immunotherapy to the same extent than patients with viral HCC although patients with NASH and diabetes mellitus showed a shorter OS. We did not find significant differences in OS according to the etiology of liver disease. Nonetheless, the small number of patients in our study could preclude the evaluation of cirrhosis etiology as a prognostic factor of response to immunotherapy. In addition, the high proportion of patients with non-viral related HCC could account for the lower survival benefit in our cohort.

The incidence and severity of observed AE are also noteworthy. It is true that our study took place during the COVID-19 pandemic, and several patients discontinued atez/bev treatment after acquiring the infection, but none of these patients experienced severe COVID-19 and all of them were able to resume immunotherapy treatment once the resolution of the infection was confirmed. The IMbrave150 study reported a median treatment duration of approximately 7 months (2), while our study showed a median of 4.2 months. The percentage of patients who discontinued any treatment component in Imbrave150 because of AE was 15.5% in the atez/bev group (7% discontinued both components) (2) while nine patients in our group (39.1%) permanently discontinued medication due to severe AE, of which a non-negligible 17% were grade 5 (4.6% in the IMbrave150 study). Similarly, the type of observed AE is notable. Our study shows asthenia, loss of appetite, infections, hepatic decompensation and hypertension as the

Table III. *Univariable analysis of factors associated with overall survival.*

Parameter	HR	95%CI	*p*-Value
Age	1.03	0.96-1.11	0.416
Sex, male:female	0.7	0.1-5.3	0.718
Diabetes mellitus	1	0.4-2.7	0.99
Obesity	0.8	0.4-1.8	0.63
Arterial hypertension	0.9	0.3-2.3	0.774
Chronic kidney disease	1	0.5-1.9	0.973
Dyslipidemia	0.9	0.6-1.5	0.777
Heart disease	1.3	0.6-2.7	0.486
Pulmonary disease	0.7	0.3-1.6	0.423
Etiology of HCC			
HCV	ref	ref	ref
Alcohol	1.1	0.4-3.6	0.825
HCV and alcohol	0.7	0.1-5.3	0.66
MASLD	3.7	0.6-21	0.142
Naive HCC	0.8	1.1-0.6	0.83
BCLC stage (C *vs*. B)	1.4	0.5-3.7	0.574
Child-Pugh	1.4	0.8-2.4	0.256
MELD	1.2	0.99-1.5	0.057
ALBI score	3.9	1.3-11.8	0.015
Tumor size	1.1	1.01-1.3	0.034
Macro-vascular invasion	0.7	0.4-1.1	0.124
Bilobar	0.8	0.5-1.4	0.4
Extrahepatic metastasis	1.01	0.6-1.7	0.975
Number of sessions	0.9	0.7-1.1	0.072

BCLC: Barcelona Clinic Liver Cancer; HCV: hepatitis C virus; HCC: hepatocellular carcinoma; MASLD: metabolic associated steatotic liver disease; MELD: model for end-stage liver disease.

Table IV. *Documented adverse events.*

Adverse events (n)	Any Grade	>Grade 3
General fatigue	14	0
Appetite loss	12	0
Infections	6	2
Hepatic decompensation (ascites/HE)	5 (4/2)	5
Hypertension	4	0
Neurological toxicity	3	3
Proteinuria	2	0
Thyroid function abnormality	2	0
Abdominal sepsis	2	2
Bleeding events related to bevacizumab	2	2
Infusion reaction	1	0
Wound healing	1	0
Pulmonary embolism	1	1
Elevation of transaminase	0	0
Diarrhea/colitis	0	0
Death of unknown cause	0	1

most frequent AE, while in the IMbrave150 study, the most common AE included proteinuria, diarrhea, and elevated transaminases (2). Importantly, there were no cases of immune-mediated hepatitis in our cohort. Liver-related deaths accounted for a significant proportion (80%) of deaths, underlining the importance of addressing hepatic complications in the management of atez/bev treatment.

Furthermore, in addition to analyzing the real-life clinical evolution of our patient cohort, we have investigated potential predictive factors for the response to atez/bev treatment. One important finding is the association between baseline mALBI grade and survival, with lower risk of death in patients with mALBI grade 1 or 2a compared to 2b. This emphasizes the relevance of hepatic reserve function in predicting outcomes. The ALBI score demonstrated a strong discriminatory ability for predicting 18-month mortality. In contrast, MELD and Child-Pugh showed no significant relationship with survival, showing that in advanced HCC both lose their predictive capacity. The prognostic value of liver function for the survival of patients with cirrhosis and HCC is widely acknowledged (18). There are previous studies investigating the role of ALBI grade in systemic agents for unresectable HCC. Coskun O *et al*. conducted a recent review that included the evaluation of both, multikinase inhibitors and immune checkpoint inhibitors, concluding that ALBI grade could serve as a reliable predictive biomarker for response and liver toxicity (19). A recent study has also evaluated the therapeutic efficacy of atez/bev in patients with Child-Pugh class A or B in the real-world (20). They evaluated mALBI grade, observing that it was important not only for assessing hepatic function, but also as an indicator of nutritional status, considering that a better nutritional condition contributes to maintaining a longer therapeutic response. M. Persano and The HCC Collaborative Group have ascertained a novel prognostic index through recursive partitioning analysis in nearly 800 patients with hepatocellular carcinoma (HCC) who were candidates for the atezolizumab/bevacizumab regimen. In their analysis, they considered several parameters, including the Child-Pugh as well as the ALBI score, enabling stratification of patients into low, moderate, and high risk categories (21). A current clinical trend is the introduction of systemic therapy as soon as possible in patients with a good hepatic reserve function. Moreover, some authors suggest that mALBI 2a should be the minimum grade required to consider treatment with atez/bev, even in Child-Pugh A patients, as well as in those receiving multikinase inhibitor treatments to broaden the clinical possibilities for implementing sequential post-progression treatment (20). Our study included a significant proportion of mALBI grade 2b patients, which may have also contributed to explaining the lower survival compared to the Imbrave150 trial.

Radiological response to atez/bev was observed in a substantial proportion of patients, with complete and partial responses in 9% and 17%, respectively. However, a notable portion (52%) exhibited disease progression, reflecting the heterogeneity in treatment response with a median PFS of 4.7 months. Again, our results are inferior to those shown in the pivotal study, which demonstrated a PFS of 6.9 months

(2). Recently, Atsushi H. *et al*., have evaluated early clinical experience with atez/bev in a multicenter study conducted in Japan. As expected, the authors described that when progressive disease was confirmed at the first imaging evaluation performed at six weeks, OS was much worse than that of patients who exhibited complete response/partial response and stable disease (8.0 months *vs*. 16.1 months) (4).

The results of the study should be interpreted considering its strengths and limitations. This is a single center study with a small group of patients, which is a potential limitation. However, it included a prospective patient registry based on a well-characterized patient cohort with prospectively evaluated outcomes. Although the results of this study evaluate the initial experience with atez/bev, which could have had an impact on the outcomes, these patients were treated by physicians with extensive prior experience in HCC management. Nevertheless, accustomed as we are to the experience gained from using sorafenib over more than a decade—during which the use of this treatment was generalized in patients with poorer liver function than those in the initial trial (1)—it is possible that we included patients with a with less favorable liver function than would have been ideal for receiving the atez/bev regimen. This may account for the moderate initial outcomes and the adverse events reported.

In addition, to the best of our knowledge, this is the first study that reports a real-life experience with atez/bev in a Spanish cohort, with demographic and clinical characteristics that are typical of our environment. Therefore, this study is of utmost importance to improve the management of patients with advanced or unresectable HCC.

In summary, our center's initial experience with the atez/bev regimen has proven less favorable than anticipated, particularly when compared to the IMbrave150 study's outcomes regarding both efficacy and safety. It is essential to rigorously evaluate liver function when selecting systemic treatments for patients with advanced or unresectable hepatocellular carcinoma (HCC). The ALBI score has demonstrated utility in identifying patients who are likely to experience the most favorable risk-benefit ratio prior to starting atez/bev treatment. Additionally, the correlation between baseline mALBI grade and patient survival, along with the incidence of severe adverse events—primarily those linked to hepatic decompensation—underscores the need for a prudent approach in patient selection and monitoring. Further research should assess the impact of atez/bev treatment on hepatic function deterioration relative to other immunotherapies or multikinase inhibitors, especially in HCC patients with mALBI grade 2b or 3, as this could significantly influence the regimen's efficacy and safety.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Statistical analyses were performed using MPB and GS. The manuscript was prepared and written by MPB and PL. VM, CA, CM and JT contributed to data collection and patient selection. MA and NC provided treatment to the patients. All Authors have reviewed and approved the final manuscript.

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