ORIGINAL RESEARCH ARTICLE

Adverse Events as Potential Predictive Factors of Activity in Patients with Advanced HCC Treated with Atezolizumab Plus Bevacizumab

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Abstract

Background In the context of patients with hepatocellular carcinoma (HCC) treated with systemic therapy, the correlation between the appearance of adverse events (AEs) and reported efficacy outcomes is well-known and widely investigated. From other pathological settings, we are aware of the prognostic and predictive value of the occurrence of immune-related AEs in patients treated with immune-checkpoint inhibitors.

Objective This retrospective multicenter real-world study aims to investigate the potential prognostic value of AEs in patients with HCC treated with atezolizumab plus bevacizumab in the first-line setting.

Patients and methods The study population consisted of 823 patients from five countries (Italy, Germany, Portugal, Japan, and the Republic of Korea).

Results Of the patients, 73.3% presented at least one AE during the study period. The most common AEs were proteinuria (29.6%), arterial hypertension (27.2%), and fatigue (26.0%). In all, 17.3% of the AEs were grade (G) 3. One death due to bleeding was reported. The multivariate analysis confirmed the appearance of decreased appetite G < 2 [versus G ≥ 2; hazard ratio (HR) 0.60; 95% confidence interval (CI) 0.13–0.90; $p < 0.01$] and immunotoxicity G < 2 (versus G ≥ 2; HR: 0.70; 95% CI 0.24–0.99; $p = 0.04$) as independent prognostic factors for overall survival, and the appearance of decreased appetite G < 2 (versus G ≥ 2; HR: 0.73; 95% CI 0.43–0.95; $p = 0.01$), diarrhea (yes versus no; HR: 0.57, 95% CI 0.38–0.85; $p = 0.01$), fatigue (yes versus no; HR: 0.82, 95% CI 0.65–0.95; $p < 0.01$), arterial hypertension G < 2 (versus G ≥ 2; HR: 0.68, 95% CI 0.52–0.87; $p < 0.01$), and proteinuria (yes versus no; HR: 0.79, 95% CI 0.64–0.98; $p = 0.03$) as independent prognostic factors for progression-free survival.

Conclusions As demonstrated for other therapies, there is also a correlation between the occurrence of AEs and outcomes for patients with HCC for the combination of atezolizumab plus bevacizumab.

Key Points

There is a correlation between the occurrence of adverse events and outcomes for patients with hepatocellular carcinoma treated with atezolizumab plus bevacizumab.

This understanding is crucial for further enhancing our daily clinical practice and providing patients with hepatocellular carcinoma with the best possible management of the currently available therapeutic strategies.

Mara Persano and Margherita Rimini are co-first authors.

1 Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and accounts for approximately 90% of cases [1]. Recently, the therapeutic armamentarium available for the systemic treatment of this disease has expanded. Sorafenib was approved in 2007 thanks to the results of two phase III trials [2, 3]. Lenvatinib became the new standard first-line therapy in 2017 due to the results of the REFLECT trial [4]. The combination of the monoclonal antibody, bevacizumab, which inhibits the vascular endothelial growth factor (VEGF), with atezolizumab, a monoclonal antibody inhibiting the programmed cell death ligand-1 (PD-L1), represents the first therapeutic doublet available for HCC treatment. The IMbrave150 trial showed that this combination can achieve a median overall survival (OS) of 19.2 months and a median progression-free survival (PFS) of 6.9 months [5].

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Recently, an immunotherapeutic combination was approved by the Food and Drug Administration (FDA) and the European Medicines Agency in light of the final data from the HIMALAYA trial. This combination comprises a single dose of tremelimumab (anti-cytotoxic T-lymphocyte antigen 4) with another anti-PD-L1, durvalumab, and it achieved a median OS of 16.4 months [6]. Although this combination is indicated in international guidelines as the new standard of care for first-line HCC treatment, it is not yet reimbursed in all countries [7]. Currently, the most widely used systemic therapy, therefore, remains the combination of atezolizumab plus bevacizumab.

In the context of treating patients with HCC with systemic therapy, the correlation between the appearance of adverse events (AEs) and reported efficacy outcomes is well known and widely investigated. For sorafenib and lenvatinib, there is evidence regarding the prognostic and predictive value of the appearance of specific AEs during treatment, which has increased clinicians' ability to better manage the use of these two tyrosine kinase inhibitors (TKIs) in daily clinical practice [8–29]. However, from other pathological settings (such as non-small-cell lung cancer and melanoma), we are aware of the prognostic and predictive value of the occurrence of immune-related AEs in patients treated with immune-checkpoint inhibitors [30–37]. However, studies investigating this aspect in the context of systemic treatment of patients with HCC are still very limited [38, 39].

This retrospective multicenter real-world study aims to investigate the potential prognostic and predictive value of AEs occurring during first-line treatment with the combination of atezolizumab plus bevacizumab in a large cohort of patients with HCC.

2 Methods

The study population consisted of patients with HCC from five countries (Italy, Germany, Portugal, Japan, and the Republic of Korea) being treated with atezolizumab plus bevacizumab between October 2018 and April 2022. Patients were treated with atezolizumab plus bevacizumab in the first-line setting for intermediate [Barcelona Clinic Liver Cancer (BCLC)-B] or advanced (BCLC-C) HCC, judged ineligible for loco-regional procedures. Patients were included in the study if they had HCC histological or imaging diagnosis following recent international guidelines and if they had not received any prior systemic treatments for this neoplasm. All patients were treated with 15 mg/kg of body weight of bevacizumab and 1200 mg of atezolizumab administered intravenously every 3 weeks as determined by the IMbrave150 trial [5]. Treatment interruptions and/or dose reductions were allowed to manage AEs. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 [40].

2.1 Statistical Analysis

This analysis aimed to examine the association between toxicity, graded using CTCAE 5.0, and clinical outcomes in patients with HCC treated with atezolizumab plus bevacizumab.

Categorical variables were compared with Fisher's exact test. OS was defined as the time interval from the first day of treatment to the day of death. PFS was defined as the time interval from the first day of treatment to the progression of the disease or the day of death for any cause. OS and PFS were estimated by the Kaplan–Meier method, and curves were compared by the log-rank test. Hazard ratios (HRs) adjusted and not adjusted by baseline characteristics were calculated using the Cox proportional hazards model.

MedCalc package (MedCalc® version 16.8.4) was used for statistical analysis.

3 Results

The overall cohort included 852 patients treated with atezolizumab plus bevacizumab. A total of 29 patients were excluded for follow-up (FU), since, at less than 3 months, the first re-evaluation computed tomography scan for the assessment of the response to treatment had not yet been performed; hence, 823 were available for the analysis. Median FU was 10.4 months (95% CI 9.6–11.0). Clinical and laboratory baseline characteristics are summarized in Supplementary Table 1. The most frequent etiology of cirrhosis was viral (53.7%). Most of the patients were asymptomatic [performance status (PS) 0: 74.7%] and in the advanced stage (BCLC-C: 59.3%). A total of 93.4% were Child–Pugh A class.

3.1 Survival Outcomes

Median OS was 15.9 months (95% CI 14.7–23.9), and median PFS was 7.6 months (95% CI 6.7–8.6).

A proportion of 73.3% of patients presented at least one AE during the study period (Table 1). The most common AEs were proteinuria (29.6%), arterial hypertension (27.2%), and fatigue (26.0%). Of the AEs, 17.3% were grade (G) 3. One death due to bleeding was reported.

At univariate analysis, the occurrence of several AEs was related to OS, as shown in Table 2. After adjusting for positive clinical covariates at univariate analysis, the multivariate analysis confirmed the appearance of decreased appetite G < 2 (versus G ≥ 2; HR: 0.60; 95% CI 0.13–0.90; $p < 0.01$) and immunotoxicity G < 2 (versus G ≥ 2; HR: 0.70; 95% CI

Table 1 Adverse events

	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
Arterial hypertension	599 (72.8%)	65 (7.9%)	107 (13.0%)	52 (6.3%)	0 (0.0%)	0 (0.0%)
Fatigue	609 (74.0%)	145 (17.6%)	55 (6.7%)	14 (1.7%)	0 (0.0%)	0 (0.0%)
Decreased appetite	647 (78.6%)	112 (13.6%)	48 (5.8%)	16 (1.9%)	0 (0.0%)	0 (0.0%)
Proteinuria	579 (70.3%)	102 (12.4%)	85 (10.3%)	57 (6.9%)	0 (0.0%)	0 (0.0%)
Diarrhea	756 (91.9%)	48 (5.8%)	15 (1.8%)	4 (0.5%)	0 (0.0%)	0 (0.0%)
Hypothyroidism	779 (94.6%)	14 (1.7%)	27 (3.3%)	3 (0.4%)	0 (0.0%)	0 (0.0%)
Immunotoxicity	717 (87.1%)	54 (6.6%)	27 (3.3%)	21 (2.5%)	4 (0.5%)	0 (0.0%)
Other	659 (80.1%)	49 (5.9%)	57 (6.9%)	48 (5.8%)	9 (1.1%)	1 (0.1%)

0.24–0.99; $p = 0.04$) as independent prognostic factors for OS (Table 2; Fig. 1).

At univariate analysis, the occurrence of several AEs was related to PFS, as shown in Table 3. After adjusting for positive clinical covariates at univariate analysis, the multivariate analysis confirmed the appearance of decreased appetite G < 2 (versus G ≥ 2; HR: 0.73; 95% CI 0.43–0.95; $p = 0.01$), diarrhea (yes versus no; HR: 0.57; 95% CI 0.38–0.85; $p = 0.01$), fatigue (yes versus no; HR: 0.82; 95% CI 0.65–0.95; $p < 0.01$), arterial hypertension G < 2 (versus G ≥ 2; HR: 0.68; 95% CI 0.52–0.87; $p < 0.01$), and proteinuria (yes versus no; HR: 0.79; 95% CI 0.64–0.98; $p = 0.03$) as independent prognostic factors for PFS (Table 3; Fig. 2).

3.2 Response Evaluation

The objective response rate (ORR) was 27.3%: 35 (4.2%) had a complete response (CR), 190 (23.1%) had a partial response, 428 (52.0%) had stable disease, and 170 (20.7%) had progressive disease. We analyzed the correlation between the appearance of AEs and the response obtained. The appearance of hypothyroidism of any G (odds ratio: 0.52; 95% CI 0.28–0.97; $p = 0.04$) and immunotoxicity of any G (odds ratio: 0.54; 95% CI 0.36–0.82; $p < 0.01$) was correlated with higher ORR, while the absence of fatigue of any G (odds ratio: 3.90; 95% CI 1.18–12.87; $p = 0.02$) and decreased appetite of any G (odds ratio: 9.71; 95% CI 1.31–71.41; $p = 0.02$) were correlated with more CR (Table 4). There were no differences in baseline characteristics between patients presenting and not presenting with immunotoxicity and hypothyroidism during treatment with atezolizumab plus bevacizumab (Supplementary Table 2). Patients presenting with decreased appetite more frequently had non-viral etiology ($p < 0.01$), an advanced stage (BCLC-C; $p = 0.03$), and PS ≥ 1 ($p < 0.01$) compared with patients not presenting with decreased appetite, while patients with presenting fatigue more frequently had macrovascular invasion compared with patients not presenting with fatigue ($p = 0.03$; Supplementary Table 3).

4 Discussion

Ours is the first international real-world investigation to explore the correlation between AEs and outcomes in a large cohort of patients with HCC treated with the combination of atezolizumab plus bevacizumab. In our analysis, at least one AE was observed in 73.3% of patients, with G 3 AEs occurring at a frequency of 17.3%. The most common AEs were proteinuria (29.6%), arterial hypertension (27.2%), and fatigue (26.0%). These data are consistent with those from a retrospective study conducted by Tada and colleagues, who reported a frequency ≥ 20% for proteinuria, decreased appetite, and fatigue in a cohort of 263 patients with HCC treated with atezolizumab plus bevacizumab [39]. These real-world results confirmed findings from prospective studies. Similarly, the same AEs were the most frequent in the pivotal phase III IMbrave 150 trial, in which 86.0% of patients receiving the combination experienced at least one AE, with 43.0% of these being G 3 or 4 [5]. Very similar data were also observed in another prospective study, the phase II–III ORIENT-32 trial, which investigated the efficacy of combining a PD-1 inhibitor, sintilimab, with a biosimilar bevacizumab in the first-line setting for 595 Chinese patients with HCC. This trial reported that 88.7% of patients experienced at least one AE, of which 33.7% were G 3/4 [41].

Fatigue and decreased appetite are well-known symptoms characterizing patients with impaired liver function and advanced disease; both are often present in the neoplastic cachexia scenarios that can arise in these cases [42–45]. In our population, patients who experienced these symptoms more frequently had advanced-stage disease ($p = 0.03$), along with macrovascular invasion ($p = 0.03$), and worse PS ($p < 0.01$). It is not surprising, then, that G ≥ 2 decreased appetite was associated with both worse OS (HR: 0.60 95% CI 0.13–0.90; $p < 0.01$) and worse PFS (HR: 0.73; 95% CI 0.43–0.95; $p = 0.01$). The onset of fatigue of any G was identified as a negative prognostic factor for PFS (HR: 0.82; 95% CI 0.65–0.95; $p < 0.01$), and the absence of these symptoms correlated with higher CR rates (Table 4). Our findings are consistent with the multivariate analyses conducted by

Table 2 Univariate and multivariate analyses for OS

Characteristics	Univariate analysis OS		Multivariate analysis OS	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Sex		0.16		
Female	1			
Male	0.80 (0.59–1.09)			
Age		0.18		
≤ 70 years	0.84 (0.66–1.08)			
> 70 years	1			
Etiology		0.75		
Viral	0.96 (0.75–1.23)			
Non-viral	1			
BCLC		**0.03**		0.79
B	0.76 (0.59–0.98)		0.96 (0.72–1.28)	
C	1		1	
AFP		**< 0.01**		**< 0.01**
< 400 ng/mL	0.47 (0.36–0.62)		0.65 (0.38–0.85)	
≥ 400 ng/mL	1		1	
Child–Pugh		**< 0.01**		
A	0.10 (0.05–0.20)			
B	1			
NLR		**< 0.01**		**< 0.01**
< 3	0.56 (0.43–0.73)		0.67 (0.42–0.87)	
≥ 3	1		1	
EHD		0.77		
Yes	1			
No	0.96 (0.75–1.24)			
ALBI		**< 0.01**		**< 0.01**
1	0.11 (0.06–0.19)		0.13 (0.07–0.22)	
2	1		1	
PS		**0.01**		
≤ 1	0.24 (0.07–0.76)			
> 1	1			
PVT		**< 0.01**		
Yes	1			
No	0.53 (0.39–0.71)			
Decreased appetite		**< 0.01**		
Yes	1			
No	0.59 (0.43–0.80)			
Decreased appetite		**< 0.01**		**< 0.01**
G < 2	0.37 (0.23–0.60)		1	
G ≥ 2	1		0.60 (0.13–0.90)	
Fatigue		**< 0.01**		
Yes	1			
No	0.57 (0.43–0.77)			
Fatigue		**< 0.01**		0.21
G < 2	0.50 (0.31–0.80)		0.84 (0.47–1.07)	
G ≥ 2	1		1	
Proteinuria		0.25		
Yes	0.86 (0.66–1.11)			
No	1			

Table 2 (continued)

Characteristics	Univariate analysis OS		Multivariate analysis OS	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Proteinuria		0.23		
G < 2	1			
G ≥ 2	0.83 (0.61–1.13)			
Hypertension		**< 0.01**		0.10
Yes	0.69 (0.53–0.89)		0.77 (0.57–1.05)	
No	1		1	
Hypertension		**0.03**		
G < 2	1			
G ≥ 2	0.72 (0.54–0.97)			
Immunotoxicity		**0.02**		
Yes	1			
No	0.66 (0.46–0.94)			
Immunotoxicity		**< 0.01**		**0.04**
G < 2	0.45 (0.27–0.77)		0.70 (0.24–0.99)	
G ≥ 2	1		1	
Diarrhea		0.46		
Yes	0.85 (0.56–1.30)			
No	1			
Diarrhea		0.12		
G < 2	0.50 (0.21–1.18)			
G ≥ 2	1			
Hypothyroidism		0.47		
Yes	0.83 (0.51–1.37)			
No	1			
Hypothyroidism		0.91		
G < 2	1			
G ≥ 2	0.97 (0.52–1.80)			
Other toxicity		0.56		
Yes	1			
No	0.92 (0.68–1.23)			
Other toxicity		0.10		
G < 2	0.75 (0.53–1.06)			
G ≥ 2	1			

p < 0.05 are reported in bold

AFP alpha-feto-protein, *ALBI* albumin-bilirubin, *BCLC* Barcelona Clinic Liver Cancer, *EHD* extrahepatic disease, *G* grade, *NLR* neutrophil-lymphocyte ratio, *OS* overall survival, *PS* performance status, *PVT* portal vein thrombosis

Japanese colleagues, who highlighted how the appearance of fatigue of any G is independently associated with worse OS (HR: 2.35; 95% CI 1.30–4.51; *p* = 0.01) [39]. Despite having completely different mechanisms of action, decreased appetite and fatigue have been linked to worse outcomes even in patients treated with lenvatinib as a first-line therapy [9–11]. Therefore, these negative prognostic factors need to be carefully considered in daily clinical practice for the proper management of patients with HCC.

A crucial point of our discussion is certainly the correlation between immune-related AEs and the efficacy of immunological therapies, a topic that has been widely discussed for several years in various disease contexts. Indeed, we are aware that, in patients with non-small-cell lung cancer, melanoma, urothelial carcinoma, and other conditions, the occurrence of immunotoxicity correlates with improved efficacy outcomes [30–37]. This aspect remains a field to be explored in HCC treatment. The most significant data available to us stem from an FDA pooled analysis conducted by Pinato and colleagues on a cohort of 406 patients with HCC treated with immunotherapy within international clinical trials. This analysis highlighted how the development
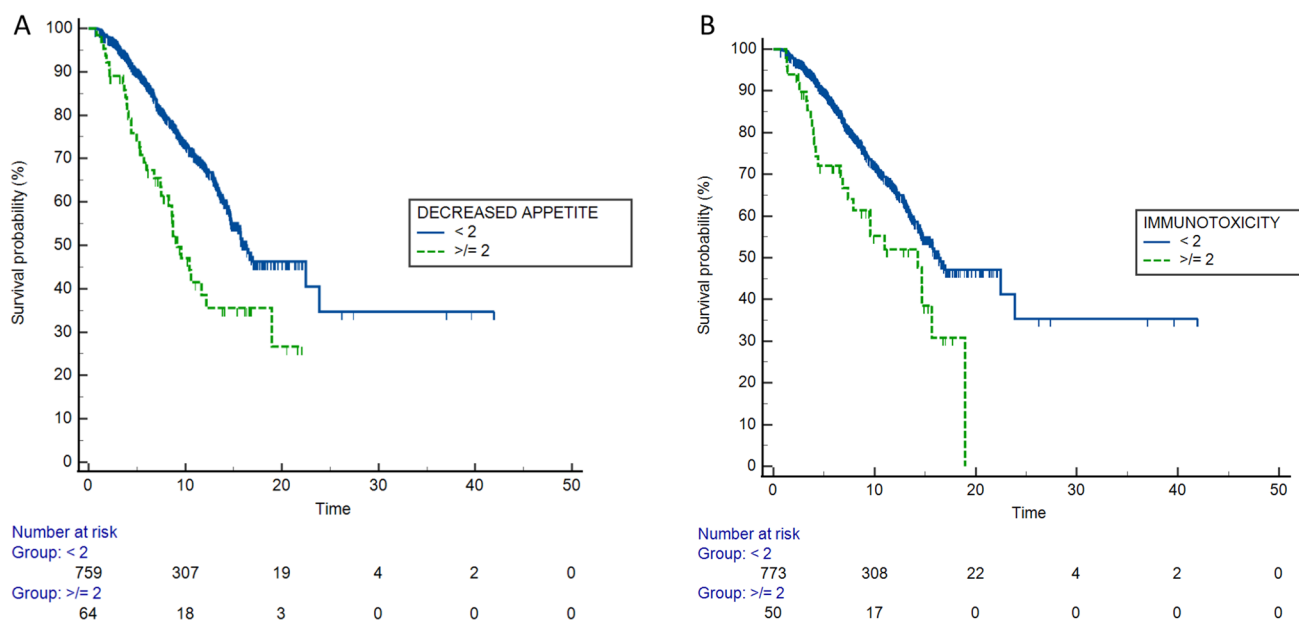
Fig. 1. Kaplan–Meier curves for OS according to the occurrence of decreased appetite (**A**) and immunotoxicity (**B**)

of immune-related G $\geq$ 2 AEs was linked to longer OS (HR: 0.49; 95% CI 0.34–0.70) and PFS (HR: 0.43; 95% CI 0.32–0.59). The authors further confirmed these correlations in a cohort of 357 patients from an international consortium comprising 10 centers [38]. The other significant data we have available are from the Japanese study mentioned above. However, this study did not identify any significant correlation between immune-related AEs and the efficacy outcomes of the combination of atezolizumab plus bevacizumab [39]. These data appear to be inconsistent, but it is important to consider that the results of the Japanese study might have been influenced by the small sample size. Additionally, in the FDA pooled analysis, the population cohorts were very heterogeneous from a standpoint, including patients treated with both immunological combinations and monotherapies, as well as different molecules [38]. Amidst this complex landscape, our data demonstrate that the emergence of G $\geq$ 2 immunotoxicity is associated with worse OS (HR: 0.70; 95% CI 0.24–0.99; $p = 0.04$). Moreover, the appearance of immunotoxicity of any G is linked to a higher response rate ($p < 0.01$). Furthermore, our analysis suggests that the onset of diarrhea of any G is associated with a longer PFS (HR: 0.57; 95% CI 0.38–0.85; $p = 0.01$), while the development of hypothyroidism of any G relates to a higher ORR ($p = 0.04$). These data may appear contradictory, as the onset of a response is a well-known positive prognostic factor for patients with HCC [46, 47]. Some careful reflections are therefore necessary. The first point to consider is that we did not observe any differences in baseline characteristics between patients

who experienced immunotoxicity and those who did not, or between patients who experienced hypothyroidism and those who did not. This could lead us to the conclusion that no other factors related to patients' baseline characteristics might have influenced response rates or median OS and PFS. The fact that the increase in response rates in those with immunotoxicity does not necessarily translate into an increase in survival could be explained by considering that, in clinical practice, higher G AEs often result in long-term or permanent therapy interruption and in the use of steroid-based therapeutic regimens, with potentially negative repercussions on efficacy and the overall trend of median survival. There are still incompletely clarified aspects underlying the biological mechanisms that cause immune-related AEs and the use of high-dose steroids for their treatment. We are, in fact, aware of the immunosuppressive effect of steroid therapy, but numerous studies have shown how its use not only does not involve a reduction in the effectiveness of immunotherapy but also, if used to treat immune-related AEs, translates into better outcomes given by the possibility for patients to continue antineoplastic treatment [48, 49]. The second reflection pertains to the results regarding diarrhea and hypothyroidism, two AEs typically linked to atezolizumab-induced activation of the immune system. HCC clinicians have been familiar with managing these AEs for years, as they are quite common even in patients treated in first-line with sorafenib or lenvatinib, even though they are caused by entirely different mechanisms of action [2–4, 8–29]. Given their early and timely management in daily clinical practice, these AEs

Table 3 Univariate and multivariate analyses for PFS

Characteristics	Univariate analysis PFS		Multivariate analysis PFS	
	HR (95% CI)	p value	HR (95% CI)	p value
Sex		0.65		
Female	0.95 (0.75–1.19)			
Male	1			
Age		0.80		
≤ 70 years	1			
> 70 years	0.98 (0.81–1.17)			
Etiology		0.39		
Viral	0.92 (0.77–1.11)			
Non–viral	1			
BCLC		**0.03**		0.86
B	0.82 (0.68–0.98)		0.98 (0.80–1.21)	
C	1		1	
AFP		**< 0.01**		**< 0.01**
< 400 ng/mL	0.60 (0.49–0.74)		0.74 (0.57–0.89)	
≥ 400 ng/mL	1		1	
Child–Pugh		**< 0.01**		
A	0.48 (0.31–0.75)			
B	1			
NLR		**< 0.01**		**< 0.01**
< 3	0.69 (0.57–0.84)		0.81 (0.66–0.94)	
≥ 3	1		1	
EHD		0.85		
Yes	1			
No	0.98 (0.81–1.19)			
ALBI		**< 0.01**		**0.01**
1	0.53 (0.36–0.78)		0.74 (0.45–0.95)	
2	1		1	
PS		**< 0.01**		
≤ 1	0.28 (0.12–0.65)			
> 1	1			
PVT		**< 0.01**		
Yes	1			
No	0.71 (0.56–0.89)			
Decreased appetite		**< 0.01**		
Yes	1			
No	0.67 (0.53–0.84)			
Decreased appetite		**< 0.01**		**0.01**
G < 2	0.55 (0.38–0.80)		0.73 (0.43–0.95)	
G ≥ 2	1		1	
Fatigue		**< 0.01**		**< 0.01**
Yes	1		1	
No	0.74 (0.60–0.91)		0.82 (0.65–0.95)	
Fatigue		0.11		
G < 2	0.75 (0.53–1.07)			
G ≥ 2	1			
Proteinuria		**0.03**		**0.03**
Yes	0.80 (0.66–0.98)		0.79 (0.64–0.98)	
No	1		1	

Table 3 (continued)

Characteristics	Univariate analysis PFS		Multivariate analysis PFS	
	HR (95% CI)	p value	HR (95% CI)	p value
Proteinuria		0.07		
G < 2	1			
G ≥ 2	0.81 (0.64–1.02)			
Hypertension		**< 0.01**		
Yes	0.72 (0.59–0.87)			
No	1			
Hypertension		**< 0.01**		**< 0.01**
G < 2	1		1	
G ≥ 2	0.67 (0.54–0.83)		0.68 (0.52–0.87)	
Immunotoxicity		0.14		
Yes	1			
No	0.81 (0.61–1.07)			
Immunotoxicity		**0.01**		0.07
G < 2	0.55 (0.36–0.86)		0.77 (0.42–1.06)	
G ≥ 2	1		1	
Diarrhea		**0.01**		**0.01**
Yes	0.67 (0.49–0.91)		0.57 (0.38–0.85)	
No	1		1	
Diarrhea		0.81		
G < 2	1			
G ≥ 2	0.93 (0.51–1.70)			
Hypothyroidism		0.07		
Yes	0.71 (0.49–1.03)			
No	1			
Hypothyroidism		0.17		
G < 2	1			
G ≥ 2	0.72 (0.45–1.15)			
Other toxicity		0.21		
Yes	0.87 (0.70–1.08)			
No	1			
Other toxicity		0.98		
< 2	1			
≥ 2	1.00 (0.77–1.29)			

p < 0.05 are reported in bold

AFP alpha-feto-protein, *ALBI* albumin-bilirubin, *BCLC* Barcelona Clinic Liver Cancer, *EHD* extrahepatic disease, *G* grade, *NLR* neutrophil-lymphocyte ratio, *PFS* progression-free survival, *PS* performance status, *PVT* portal vein thrombosis

rarely escalate into higher-G immune-related toxicities, which our analysis identifies as factors independently correlated with worse survival. Certainly, further studies are required to definitively clarify these aspects and solidify our understanding of the biological phenomena underpinning the efficacy and toxicity induced by immunotherapy in the treatment of patients with HCC, just as has been done for other pathologies [50–54].

Another important aspect of our discussion concerns two AEs typically related to bevacizumab administration: arterial hypertension and proteinuria. Our data demonstrate that the occurrence of G ≥ 2 hypertension or any G proteinuria is associated with longer PFS. These findings are consistent with the multivariate analysis from the Japanese study, which also indicates a positive correlation between PFS and patients with any G of arterial hypertension [39]. Proteinuria and arterial hypertension are the result of the nephrotoxic action and damage to the vascular endothelium induced by VEGF inhibitory drugs, such as bevacizumab, lenvatinib, and sorafenib [55, 56]. Even in patients treated in the first-line setting with these TKIs, there is ample evidence of a positive correlation between survival outcomes and the
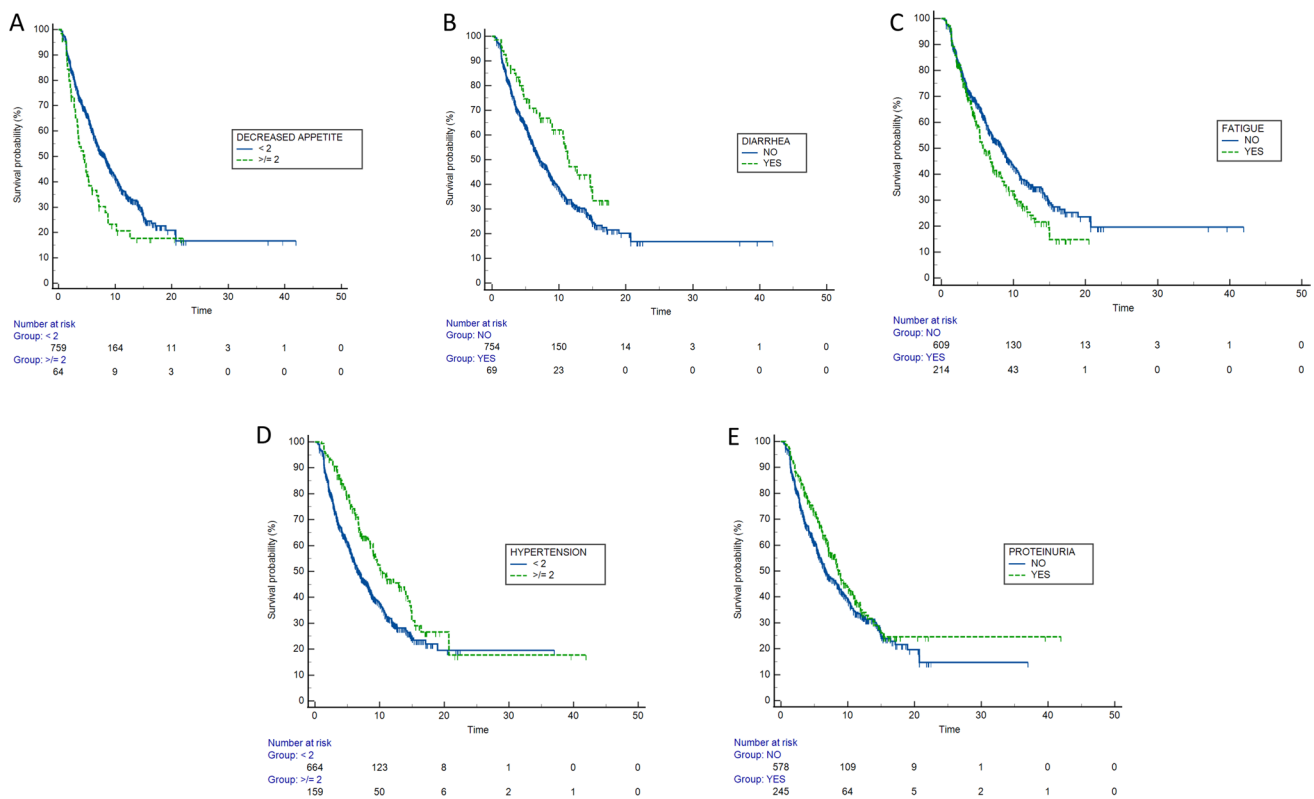
Fig. 2. Kaplan–Meier curves for PFS according to the occurrence of decreased appetite (**A**), diarrhea (**B**), fatigue (**C**), arterial hypertension (**D**), and proteinuria (**E**)

occurrence of these AEs [10, 11, 20–22]. In the case of the combination of atezolizumab plus bevacizumab, it was highlighted that proteinuria was the AE that most frequently (29.7%) caused early bevacizumab interruption, resulting in a negative prognostic factor for both OS and PFS, as demonstrated in an interesting Japanese study involving 239 patients with HCC [57]. All this further reinforces the awareness we already had about the key role of the VEGF pathway in HCC pathogenesis and how its inhibition is central to the mechanisms underlying the demonstrated efficacy of the combination of atezolizumab plus bevacizumab [58].

Our study has some limitations. The primary limitation is its retrospective nature, which means we cannot rule out biases and gaps in the collected data, especially those related to minor AEs that may not have been reported correctly. Moreover, the available data did not allow the analysis of all types of immune-related AEs, except for diarrhea and hypothyroidism, and the potential correlation between steroid treatment of immune-related AEs and patients' outcomes. Another important limitation is the lack of a centralized

review of reevaluation exams, which would have ensured more robust data regarding response rates and median survival. Nonetheless, our study provides valuable insight into our real-world daily clinical practice, encompassing a large population of both Eastern and Western patients from five different countries. However, further research is needed to confirm our findings and to address the limitations of our study.

In conclusion, similar to what has been demonstrated for other therapies used in HCC treatment, there is a correlation between the occurrence of AEs and patient outcomes for the combination of atezolizumab plus bevacizumab as well. The presence of G < 2 decreased appetite or G < 2 immunotoxicity was found to be a positive prognostic factor for OS, while the occurrence of any grade proteinuria or diarrhea or G ≥ 2 hypertension was associated with improved PFS. This understanding is crucial for further enhancing our daily clinical practice and providing patients with HCC with the best possible management of the currently available therapeutic strategies.

Table 4 ORR and CR in patients treated with atezolizumab plus bevacizumab

	N (%)	p value	Odds ratio		N (%)	p value	Odds ratio
Decreased appetite **ORR** No ORR	49 (27.8%) 127 (72.1%)	0.87	0.97	*Decreased appetite* **CR** No CR	1 (0.6%) 175 (99.4%)	**0.02**	9.71
No decreased appetite ORR No ORR	176 (27.2%) 471 (72.8%)		(0.67–1.40)	*No decreased appetite* CR No CR	34 (5.2%) 613 (94.7%)		(1.31–71.41)
Decreased appetite G < 2 **ORR** No ORR	210 (27.7%) 549 (72.3%)	0.47	0.80	*Decreased appetite* G < 2 **CR** No CR	35 (4.6%) 724 (95.4%)	0.20	0.16
Decreased appetite G ≥ 2 ORR No ORR	15 (23.4%) 49 (76.6%)		(0.44–1.46)	*Decreased appetite* G ≥ 2 CR No CR	0 (0.0%) 64 (100.0%)		(0.01–2.61)
Fatigue **ORR** No ORR	49 (22.9%) 165 (77.1%)	0.09	1.37	*Fatigue* **CR** No CR	3 (1.4%) 211 (98.6%)	**0.02**	3.90
No fatigue ORR No ORR	176 (28.9%) 433 (71.1%)		(0.95–1.97)	*No fatigue* CR No CR	32 (5.2%) 577 (94.7%)		(1.18–12.87)
Fatigue G < 2 **ORR** No ORR	212 (28.1%) 542 (71.9%)	0.10	0.59	*Fatigue G < 2* **CR** No CR	35 (4.6%) 719 (95.3%)	0.18	0.14
Fatigue G ≥ 2 ORR No ORR	13 (18.8%) 56 (81.1%)		(0.32–1.11)	*Fatigue G ≥ 2* CR No CR	0 (0.0%) 69 (100.0%)		(0.01–2.40)
Proteinuria **ORR** No ORR	78 (32.0%) 166 (68.0%)	0.05	0.72	*Proteinuria* **CR** No CR	13 (5.3%) 231 (94.7%)	0.32	0.70
No proteinuria ORR No ORR	147 (25.4%) 432 (74.6%)		(0.52–1.00)	*No proteinuria* CR No CR	22 (3.8%) 557 (96.2%)		(0.35–1.42)
Proteinuria G < 2 **ORR** No ORR	183 (26.9%) 498 (73.1%)	0.51	1.14	*Proteinuria G < 2* **CR** No CR	31 (4.5%) 650 (95.4%)	0.36	0.61
Proteinuria G ≥ 2 ORR No ORR	42 (29.6%) 100 (70.4%)		(0.77–1.70)	*Proteinuria G ≥ 2* CR No CR	4 (2.8%) 138 (97.2%)		(0.21–1.75)
Hypertension **ORR** No ORR	71 (31.7%) 153 (68.3%)	0.09	0.74	*Hypertension* **CR** No CR	12 (5.3%) 212 (94.6%)	0.34	0.70
No hypertension ORR No ORR	154 (25.7%) 445 (74.3%)		(0.53–1.04)	*No hypertension* CR No CR	23 (3.8%) 576 (96.2%)		(0.34–1.44)
Hypertension G < 2 **ORR** No ORR	179 (26.9%) 485 (73.0%)	0.61	1.10	*Hypertension G < 2* **CR** No CR	27 (4.1%) 637 (95.9%)	0.59	1.25
Hypertension G ≥ 2 ORR No ORR	46 (28.9%) 113 (71.1%)		(0.75–1.62)	*Hypertension G ≥ 2* CR No CR	8 (5.0%) 151 (95.0%)		(0.56–2.81)
Immunotoxicity **ORR** No ORR	43 (38.7%) 68 (61.3%)	**< 0.01**	0.54	*Immunotoxicity* **CR** No CR	6 (5.7%) 105 (94.6%)	0.52	0.74
No immunotoxicity ORR No ORR	182 (25.6%) 530 (74.4%)		(0.36–0.82)	*No immunotoxicity* CR No CR	29 (26.1%) 683 (95.9%)		(0.30–1.83)
Immunotoxicity G < 2 **ORR** No ORR	210 (27.2%) 563 (72.8%)	0.66	1.15	*Immunotoxicity G < 2* **CR** No CR	34 (4.4%) 739 (95.6%)	0.43	0.44

Table 4 (continued)

	N (%)	p value	Odds ratio		N (%)	p value	Odds ratio
Immunotoxicity G ≥ 2 ORR No ORR	15 (30.0%) 35 (70.0%)		(0.62–2.15)	*Immunotoxicity G ≥ 2* CR No CR	1 (2.0%) 49 (98.0%)		(0.06–3.31)
Diarrhea **ORR** No ORR	15 (22.4%) 52 (77.6%)	0.34	1.33	*Diarrhea* **CR** No CR	2 (3.0%) 65 (97.0%)	0.59	1.48
No diarrhea ORR No ORR	210 (27.8%) 546 (72.2%)		(0.73–2.42)	*No diarrhea* CR No CR	33 (4.4%) 723 (95.6%)		(0.35–6.32)
Diarrhea G < 2 **ORR** No ORR	222 (27.6%) 582 (72.4%)	0.26	0.49	*Diarrhea G < 2* **CR** No CR	35 (4.3%) 769 (95.6%)	0.68	0.55
Diarrhea G ≥ 2 ORR No ORR	3 (15.8%) 16 (84.2%)		(0.14–1.70)	*Diarrhea G ≥ 2* CR No CR	0 (0.0%) 19 (100.0%)		(0.03–9.39)
Hypothyroidism **ORR** No ORR	18 (40.9%) 26 (59.1%)	**0.04**	0.52	*Hypothyroidism* **CR** No CR	2 (4.5%) 42 (95.4%)	0.92	0.93
No hypothyroidism ORR No ORR	207 (26.6%) 572 (73.4%)		(0.28–0.97)	*No hypothyroidism* CR No CR	33 (4.2%) 746 (95.8%)		(0.21–4.00)
Hypothyroidism G < 2 **ORR** No ORR	212 (26.7%) 581 (73.3%)	0.05	2.09	*Hypothyroidism G < 2* **CR** No CR	33 (4.2%) 760 (95.8%)	0.51	1.64
Hypothyroidism G ≥ 2 ORR No ORR	13 (43.3%) 17 (56.7%)		(1.00–4.39)	*Hypothyroidism G ≥ 2* CR No CR	2 (6.7%) 28 (93.3%)		(0.37–7.20)
Other toxicity **ORR** No ORR	50 (30.5%) 114 (69.5%)	0.31	0.82	*Other toxicity* **CR** No CR	8 (4.9%) 156 (95.1%)	0.66	0.83
No other toxicity ORR No ORR	175 (26.5%) 484 (73.4%)		(0.57–1.19)	*No other toxicity* CR No CR	27 (4.1%) 632 (95.9%)		(0.37–1.87)
Other toxicity G < 2 **ORR** No ORR	191 (27.0%) 517 (73.0%)	0.56	1.14	*Other toxicity G < 2* **CR** No CR	30 (4.2%) 678 (95.8%)	0.96	1.03
Other toxicity G ≥ 2 ORR No ORR	34 (29.6%) 81 (70.4%)		(0.74–1.75)	*Other toxicity G ≥ 2* CR No CR	5 (4.3%) 110 (95.6%)		(0.39–2.70)

The reference groups are indicated in bold

CR complete response, *G* grade, *ORR* objective response rate

Declarations

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