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Hypertension as an Adverse Event Potentially Impacting the Therapeutic Efficacy of Atezolizumab Plus Bevacizumab in Patients With Unresectable Hepatocellular Carcinoma

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ABSTRACT

Background and Aim: Atezolizumab plus bevacizumab is used as a first-line treatment for unresectable hepatocellular carcinoma (uHCC). However, the relationship between its adverse events (AEs) and treatment efficacy remains unclear. In this study, we aimed to clarify this association.

Abbreviations: AE, adverse event; AFP, α-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; IQR, interquartile range; irAE, immune-related adverse event; mALBI, modified albumin-bilirubin; NLR, neutrophil-to-lymphocyte ratio; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PR, partial response; PT, prothrombin time; RECIST, Response Evaluation Criteria in Solid Tumor; SD, stable disease; uHCC, unresectable hepatocellular carcinoma; VEGF, vascular endothelial growth factor.

Kazuki Maesaka, MD, PhD, and Machiko Kai, MD, are co-first authors.

Methods: This study included 187 patients with uHCC treated with atezolizumab plus bevacizumab as first-line therapy at 19 affiliated hospitals in the Osaka Liver Forum. A landmark analysis was conducted to address biases in AE incidence.
Results: The objective response and disease control rates were 28.2% and 69.6%, respectively. The median progression-free survival (PFS) and overall survival (OS) were 7.4 and 24.6 months, respectively. Among the 187 patients, 178 (95.2%) experienced at least one AE, with proteinuria being the most common (41.7%), followed by hypertension (34.8%) and fatigue (30.5%). All three major AEs had a median onset time of 6 weeks. We set the landmark point at Week 9 after treatment initiation, considering that the onset time for most AEs was within 9 weeks. In the landmark analysis, multivariable analysis identified the absence of bevacizumab interruption within 9 weeks and the occurrence of hypertension within 9 weeks as predictors of prolonged PFS. mALBI Grade 1/2a, the occurrence of hypertension, and the absence of fatigue and rash within 9 weeks were associated with prolonged OS. These results were consistent with those from the 6-week landmark analysis.
Conclusions: Patients with hypertension occurring as an AE within 9 weeks are expected to have better PFS and OS with atezolizumab plus bevacizumab therapy for uHCC.

1 | Introduction

The combination of atezolizumab, a programmed death-ligand 1 (PD-L1) inhibitor, and bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, has emerged as a groundbreaking treatment option for patients with unresectable hepatocellular carcinoma (uHCC). This combination therapy has demonstrated superior efficacy compared with sorafenib, the previous standard of treatment, in the IMbrave150 trial [1, 2], leading to its widespread adoption for first-line systemic chemotherapy [3–7].

Although atezolizumab plus bevacizumab has shown promising therapeutic outcomes, the management of adverse events (AEs) remains a critical challenge [8]. Both agents are associated with specific toxicities. Commonly reported AEs associated with bevacizumab include hypertension, proteinuria, hemorrhage, and thromboembolic events [9, 10]. In addition, commonly reported immune-related adverse events (irAEs) associated with atezolizumab include rash, diarrhea, pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis [11–13]. These toxicities may impact the feasibility of prolonged treatment and the overall therapeutic benefit. Recent studies suggest that the occurrence and severity of AEs may also correlate with treatment efficacy, potentially serving as biomarkers for the therapeutic response or prognosis [14–18].

This study aimed to explore the relationship between the therapeutic efficacy and AEs associated with atezolizumab plus bevacizumab in patients with uHCC. Elucidating this relationship may provide insights into optimizing treatment strategies and improving patient outcomes in the clinical management of advanced HCC.

2 | Materials and Methods

2.1 | Patients

We used a prospective registry, which included 292 patients with uHCC treated with atezolizumab plus bevacizumab between November 2020 and January 2023 at Osaka University Hospital and 18 affiliated hospitals in the Osaka Liver Forum. The observation period ended on December 31, 2023. The patients were eligible for this registry if they had been determined to be ineligible for radiofrequency ablation or transcatheter arterial chemoembolization, had an Eastern Cooperative Oncology Group performance status of 0 or 1, were Child–Pugh Class A or B, and agreed to give written informed consent at each hospital. The Ethics Committee of Osaka University Hospital (UMIN 000034611) and each participating institution approved the study protocol. Among the patients included in the registry, those with an observation period of less than 6 weeks, who did not undergo contrast-enhanced imaging examinations, were enrolled in another clinical trial, and those who had received atezolizumab plus bevacizumab as a second-line or later-line treatment were excluded.

2.2 | Treatment With Atezolizumab Plus Bevacizumab and Assessment of AEs

Based on the IMbrave150 trial, all patients received atezolizumab 1200 mg plus bevacizumab 15 mg/kg once every 3 weeks intravenously as the first-line regimen. If any severe or life-threatening AE related to the treatment occurred, the administration was paused until the symptoms diminished to Grade 1 or 2. Each physician decided to continue atezolizumab plus bevacizumab treatment after severe AEs. Information on any AE was collected during the treatment, and AEs were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. IrAEs were defined as AEs with a potential immunologic basis, leading to inflammation and damage to various organs and tissues, including the skin, gastrointestinal tract, liver, endocrine glands, and lungs [19].

2.3 | Assessment of Therapeutic Efficacy

Imaging studies, including contrast-enhanced computed tomography and magnetic resonance imaging, were performed every 6–8 weeks. The Response Evaluation Criteria in Solid Tumor version 1.1 (RECIST ver 1.1) was used to assess treatment response [20]. The objective response rate (ORR) was defined as the sum of the complete response (CR) rate and partial response (PR) rate. The disease control rate (DCR) was defined as the sum of the CR rate, PR rate, and stable disease (SD) rate. Progress-free survival (PFS) was defined as the period from the start of treatment to the date of disease

progression or death. Overall survival (OS) was defined as the period from the start of treatment to the date of death or the last follow-up.

2.4 | Statistical Analysis

Patient characteristics are expressed as medians and interquartile ranges (IQRs) for continuous variables and as absolute numbers and percentages for categorical variables. Since this study used a prospective observational cohort, most clinical and laboratory data were consistently collected, resulting in minimal missing data. An exception was a few patients on warfarin, whose prothrombin time (PT) could not be reliably assessed. For these cases, a PT score of 1 point was assigned when calculating the Child–Pugh score to avoid overestimating liver dysfunction due to warfarin-induced PT elevation. The OS and PFS were calculated using the Kaplan–Meier method, and their statistical differences were assessed using the log-rank test. Cox proportional hazard models were used to identify independent factors associated with PFS or OS. The selection of baseline clinical covariates for the multivariable analysis was predefined and included age, sex, modified albumin-bilirubin (mALBI) grade, and Barcelona Clinic Liver Cancer (BCLC) stage, based on clinical relevance and prior literature. Cutoff values for continuous factors were based on previous studies [21–23]. Regarding AEs, since their prognostic relevance was exploratory in nature, we did not predefine which AEs to include. Instead, we selected AEs that demonstrated statistical significance in the univariable analysis for inclusion in the multivariable models.

A landmark analysis was conducted to account for immortal time bias, as longer treatment duration with atezolizumab plus bevacizumab was associated with more frequent AEs. The landmark time point was defined as the time when the majority of AEs had surpassed their median onset period. In these landmark analyses, only the occurrence of AEs before the landmark time point was evaluated, and any AE occurring after the landmark time point was not included. The survival analysis was conducted only in patients who were followed for at least the landmark time point, in accordance with the landmark methodology.

Statistical significance was set at a p-value of less than 0.05. All analyses were performed using SPSS statistical software version 24.0 for Windows (IBM, Armonk, NY, USA).

3 | Results

3.1 | Patient Characteristics and Efficacy of Atezolizumab Plus Bevacizumab

A total of 187 patients were included in the primary analysis cohort (Figure S1). The median age of the patients was 75 years, 151 (80.7%) were male (Table 1), 174 (93.0%) were classified as Child–Pugh Class A, 32 (17.1%) had macrovascular invasion, 72 (38.5%) had extrahepatic metastasis, and 95 (50.8%) had BCLC Stage C. The median neutrophil-to-lymphocyte ratio (NLR) was 2.63 (IQR: 1.80–4.10). The median observation period was 13.3 months. The best response rates for CR, PR, SD, and progressive disease (PD) were 2.2%, 26.0%, 41.4%, and 30.4%, respectively, whereas six patients were not evaluated with radiological imaging. These six patients without treatment response evaluation were included in the analysis because they experienced clinically relevant events, such as AEs or death, shortly

TABLE 1 | Patient characteristics.

Characteristic		All $n = 187$	Missing
Age, years	Median (IQR)	75 (69–80)	0
Sex, n (%)	Male	151 (80.7)	0
	Female	36 (19.3)	
ECOG PS, n (%)	0	174 (93.0)	0
	1	13 (7.0)	
Etiology, n (%)	Viral	85 (45.5)	0
	Nonviral	102 (54.5)	
History of hypertension, n (%)	With	130 (69.5)	0
	Without	57 (30.5)	
Child–Pugh class, n (%)	A	174 (93.0)	0
	B	13 (7.0)	
ALBI score	Median (IQR)	−2.35 (−2.65 to −2.07)	0
mALBI grade, n (%)	1	52 (27.8)	0
	2a	52 (27.8)	
	2b	80 (42.8)	
	3	3 (1.6)	
Maximum intrahepatic tumor size, mm	Median (IQR)	27.5 (17.0–64.0)	0
Intrahepatic tumor number, n (%)	≤ 4	94 (50.3)	0
	≥ 5	93 (49.7)	
Macrovascular invasion, n (%)	Absent	155 (82.9)	0
	Present	32 (17.1)	
Extrahepatic metastasis, n (%)	Absent	115 (61.5)	0
	Present	72 (38.5)	
BCLC stage, n (%)	A	7 (3.7)	0
	B	85 (45.5)	
	C	95 (50.8)	
AFP, ng/mL	Median (IQR)	20.8 (4.1–757)	0
NLR	Median (IQR)	2.63 (1.80–4.10)	0

Abbreviations: AFP, α-fetoprotein; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; mALBI, modified albumin-bilirubin; NLR, neutrophil-to-lymphocyte ratio.

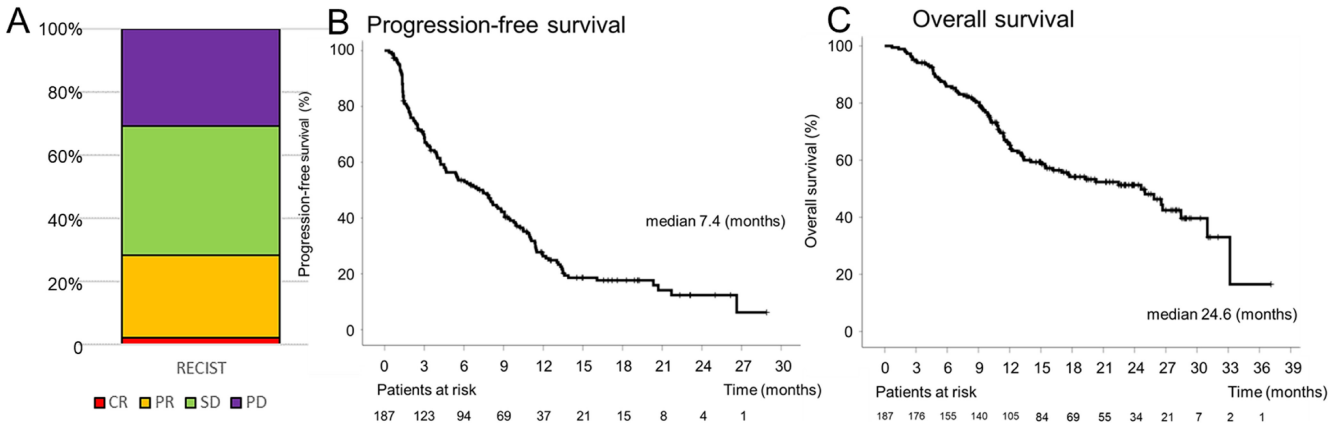

FIGURE 1 | Therapeutic responses according to RECIST v1.1 (A), progression-free survival (B), and overall survival (C) in all patients. CR, complete response; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

TABLE 2 | Adverse events in whole cohort.

Adverse events	Any grade	Grade ≥ 3	Missing
Any adverse event, *n* (%)	178 (95.2)	62 (33.2)	0
Proteinuria, *n* (%)	78 (41.7)	16 (8.6)	0
Hypertension, *n* (%)	65 (34.8)	12 (6.4)	0
Fatigue, *n* (%)	57 (30.5)	6 (3.2)	0
Decreased appetite, *n* (%)	48 (25.7%)	8 (4.3)	0
Rash, *n* (%)	30 (16.0)	5 (2.7)	0
Liver injury, *n* (%)	26 (13.9)	5 (2.7)	0
Thyroid dysfunction, *n* (%)	23 (12.0)	0 (0.0)	0
Diarrhea, *n* (%)	18 (9.6)	1 (0.5)	0
Adrenal insufficiency, *n* (%)	11 (5.9)	0 (0.0)	0
Interstitial pneumonia, *n* (%)	8 (4.3)	4 (2.1)	0
Varices rupture, *n* (%)	3 (1.6)	3 (1.6)	0
Any irAE	86 (46.0)	17 (9.1)	0

Abbreviation: irAE, immune-related adverse event.

after treatment initiation. The ORR was 28.2%, and the DCR was 69.6% (Figure 1A). The median PFS was 7.4 months, and the median OS was 24.6 months, calculated using the Kaplan–Meier method (Figure 1B,C).

3.2 | AEs Related to Atezolizumab Plus Bevacizumab Treatment

Among the 187 patients, 178 (95.2%) experienced at least one AE (Table 2). The most frequent AE was proteinuria (41.7%), followed by hypertension (34.8%) and fatigue (30.5%). Eighty-six patients (46.0%) experienced irAE, and 20 (10.7%) required high-dose steroid administration. Sixty-two patients (33.2%) developed any Grade 3 or higher AE, and 33 (17.6%) discontinued atezolizumab plus bevacizumab treatment due to any severe AE. Among the AEs, fatigue, diarrhea, hypertension, proteinuria, liver injury, and interstitial pneumonia had a median onset period of 6 weeks or less after treatment initiation (Figure S2).

3.3 | Landmark Analysis for PFS and OS

We performed landmark analysis to address immortal time bias related to the treatment duration of atezolizumab plus bevacizumab. Most AEs were determined to have occurred within 9 weeks of treatment initiation (Figure S2); hence, the landmark point was set at Week 9. A total of 138 patients whose disease was controlled and who continued treatment with atezolizumab plus bevacizumab 9 weeks after treatment initiation were included in the landmark analysis (Figure S1 and Table S1). The number of events was 98 for PFS and 55 for OS. Moreover, 43 patients experienced temporary interruption or permanent discontinuation of bevacizumab within the first 9 weeks of treatment. Of these, 12 patients discontinued treatment due to irAEs. However, none of the patients discontinued treatment due to hypertension. To further validate the association between early-onset AEs and clinical outcomes, we conducted a multivariable analysis incorporating "bevacizumab interruption within 9 weeks" as a covariate in the 9-week landmark cohort.

Regarding PFS, the multivariable analysis identified that the absence of bevacizumab interruption within 9 weeks and hypertension as an AE occurring within 9 weeks were associated with prolonged PFS (Table 3). The median PFS was significantly longer in patients without bevacizumab interruption within 9 weeks than in those with bevacizumab interruption within 9 weeks (11.0 vs. 7.4 months, respectively; $p = 0.006$; Figure 2A). The median PFS was significantly longer in patients with the AE of hypertension than in those without it (11.4 vs. 9.1 months, respectively; $p = 0.026$; Figure 2B).

TABLE 3 | Factors associated with PFS in the 9-week landmark analysis.

Variable	Category	Univariable analysis		Multivariable analysis	
		Hazard ratio (95% CI)	*p*	Hazard ratio (95% CI)	*p*
Age, years	< 75	1		1	
	≥ 75	1.035 (0.692–1.550)	0.866	1.011 (0.658–1.554)	0.960
Sex	Male	1		1	
	Female	1.152 (0.715–1.855)	0.562	0.954 (0.572–1.593)	0.858
mALBI grade	1 or 2a	1		1	
	2b or 3	1.736 (1.166–2.586)	0.007	1.511 (0.963–2.370)	0.072
BCLC stage	A or B	1		1	
	C	1.301 (0.872–1.941)	0.198	1.340 (0.886–2.026)	0.165
Bevacizumab interruption within 9 weeks	Absent	1		1	
	Present	1.870 (1.186–2.951)	0.007	1.733 (1.062–2.826)	0.028
Fatigue	Absent	1		1	
	Present	1.656 (1.034–2.652)	0.036	1.326 (0.810–2.170)	0.262
Decreased appetite	Absent	1			
	Present	0.903 (0.520–1.567)	0.716		
Diarrhea	Absent	1			
	Present	0.813 (0.351–1.884)	0.630		
Hypertension	Absent	1		1	
	Present	0.619 (0.404–0.949)	0.028	0.631 (0.408–0.977)	0.039
Rash	Absent	1			
	Present	1.383 (0.736–2.597)	0.313		
Thyroid dysfunction	Absent	1			
	Present	0.927 (0.466–1.846)	0.830		
Proteinuria	Absent	1			
	Present	0.710 (0.469–1.075)	0.105		
Liver injury	Absent	1			
	Present	1.084 (0.561–2.095)	0.810		
Any irAE	Absent	1			
	Present	1.301 (0.855–1.979)	0.219		

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; irAE, immune-related adverse event; mALBI, modified albumin-bilirubin.

Regarding OS, the multivariable analysis identified that mALBI Grade 1 or 2a, hypertension as an AE occurring within 9 weeks, and the absence of fatigue or rash as AEs within 9 weeks were associated with prolonged OS (Table 4). The median OS was significantly longer in patients with mALBI Grade 1 or 2a than in those with mALBI Grade 2b or 3 (33.2 vs. 13.1 months, respectively; $p < 0.001$; Figure 3A). The median OS was significantly longer in patients with the AE of hypertension than in those without it (not reached vs. 24.6 months, respectively; $p = 0.007$; Figure 3B). Conversely, the median OS was significantly longer in patients without the AEs of fatigue or rash than in those with these AEs (Fatigue: 33.2 vs. 11.4 months, respectively; $p < 0.001$; Rash: 33.2 vs. 11.7 months, respectively; $p = 0.003$; Figure 3C,D).

Regarding the occurrence of any irAE within 9 weeks, no difference in PFS was observed between the patients with and without any irAE; however, the median OS was significantly longer in the patients without any irAE than in those with any irAE (not reached vs. 13.3 months, respectively; $p < 0.001$; Figure S3).

3.4 | Additional Analysis on the Association Between the AE of Hypertension and Clinical Outcomes

Patients who experienced hypertension as AE within 9 weeks ($n = 50$) tended to have viral hepatitis as the underlying liver

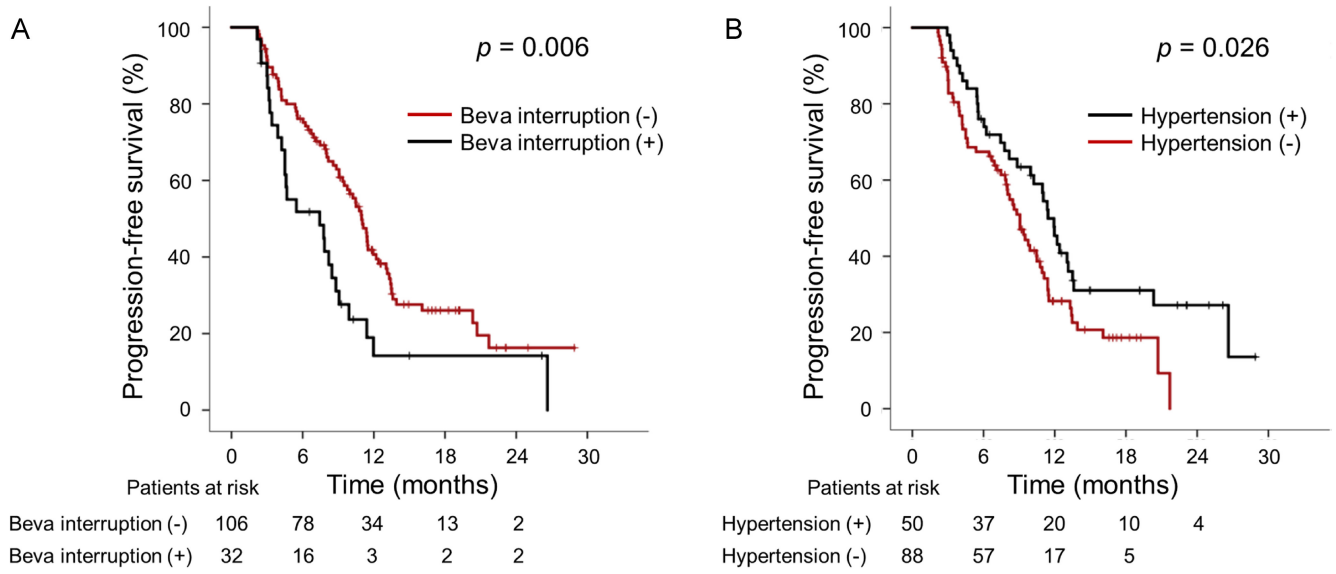

FIGURE 2 | Comparisons of PFS in the landmark analysis according to bevacizumab interruption within 9 weeks (A) or the presence of hypertension as an AE occurring within 9 weeks (B). The total number of PFS events was 98. The median PFS (95% confidence interval) was 11.0 (9.9–12.0) months in patients without bevacizumab interruption and 7.4 (2.0–12.8) months in those with. For hypertension, the median PFS was 11.4 (10.1–12.7) months in patients with hypertension as an AE and 9.1 (7.7–10.4) months in those without. AE, adverse event; PFS, progression-free survival.

disease, no prior history of hypertension, smaller intrahepatic tumor size, and lower NLR compared with those who did not develop hypertension within 9 weeks ($n = 88$; Table S2).

We compared clinical outcomes among three groups within the 9-week landmark cohort: patients without the AE of hypertension, patients with the AE of hypertension and a history of hypertension (pre-existing hypertension), and patients with the AE of hypertension but no history of hypertension (new-onset hypertension). Patients who developed new-onset hypertension showed significantly better OS compared with those with pre-existing hypertension (Figure S4). In the multivariable analysis for OS, the presence of new-onset hypertension remained a significant independent prognostic factor (Table S3). Moreover, we compared survival outcomes across these severity groups; no significant differences in PFS or OS according to hypertension grade were observed (Figure S5).

3.5 | Supplementary Landmark Analysis at Week 6 to Validate Predictive Factors

We conducted a supplementary landmark analysis at Week 6, using the same set of variables included in the 9-week analysis. A total of 156 patients whose disease was controlled and who continued treatment with atezolizumab plus bevacizumab 6 weeks after treatment initiation were included in the supplementary landmark analysis. In the multivariable analysis, both mALBI Grade 1 or 2a and the occurrence of hypertension by Week 6 were significantly associated with prolonged PFS (Table S4). In the multivariable analysis for OS, mALBI Grade 1 or 2a, BCLC Stage A or B, and the occurrence of fatigue, hypertension, and rash by Week 6 were significantly associated with OS (Table S5). These results are consistent with those from the 9-week analysis.

3.6 | Sequential Treatment After Atezolizumab Plus Bevacizumab

Among the 108 patients who discontinued atezolizumab plus bevacizumab, 55 received second-line systemic therapy, six underwent transcatheter arterial chemoembolization, four continued atezolizumab plus bevacizumab beyond radiological progression, and three received radiotherapy. The remaining 40 patients received best supportive care. Among the 13 patients who developed rash as an AE within 9 weeks, 11 (84.6%) also developed liver injury, and only six (46%) proceeded to receive second-line systemic therapy.

4 | Discussion

This study investigated the relationship between AEs and the therapeutic efficacy of atezolizumab plus bevacizumab in patients with uHCC. The occurrence of hypertension within 9 weeks of initiating treatment was associated with prolonged PFS and OS, highlighting its potential as a biomarker of treatment efficacy. Conversely, fatigue and rash were associated with poorer OS, indicating that these AEs may negatively impact long-term outcomes. Patients with mALBI Grade 1 or 2a demonstrated better OS, underscoring the importance of baseline liver function in determining prognosis. A key strength of this study is the use of landmark analysis to account for immortal time bias in evaluating the impact of AEs. This study focused on AEs occurring early in the treatment course while excluding events in patients with rapid disease progression by setting the landmark at 9 weeks. This approach revealed that hypertension occurring within the landmark period was significantly associated with better PFS and OS, providing robust evidence of its prognostic value. Moreover, hypertension as an AE in patients without a prior history of hypertension remained a significant independent prognostic factor in this study. This finding suggests that

TABLE 4 | Factors associated with OS in the 9-week landmark analysis.

		Univariable analysis		Multivariable analysis	
Variable	**Category**	**Hazard ratio (95% CI)**	***p***	**Hazard ratio (95% CI)**	***p***
Age, years	< 75	1		1	
	≥ 75	1.957 (1.100–3.481)	0.022	1.722 (0.926–3.202)	0.086
Sex	Male	1		1	
	Female	1.671 (0.890–3.136)	0.110	1.180 (0.581–2.396)	0.648
mALBI grade	1 or 2a	1		1	
	2b or 3	2.702 (1.755–4.161)	< 0.001	2.256 (1.245–4.090)	0.007
BCLC stage	A or B	1		1	
	C	1.477 (0.869–2.509)	0.149	1.650 (0.936–2.911)	0.084
Bevacizumab interruption within 9 weeks	Absent	1		1	
	Present	2.738 (1.560–4.805)	< 0.001	1.804 (0.958–3.396)	0.068
Treatment response	CR or PR	1		1	
	SD or PD	1.467 (0.825–2.606)	0.192	1.499 (0.799–2.814)	0.207
Fatigue	Absent	1		1	
	Present	2.805 (1.588–4.954)	< 0.001	2.112 (1.142–3.905)	0.017
Decreased appetite	Absent	1			
	Present	1.549 (0.798–3.007)	0.196		
Diarrhea	Absent	1			
	Present	2.142 (0.947–4.848)	0.068		
Hypertension	Absent	1		1	
	Present	0.442 (0.240–0.815)	0.009	0.429 (0.228–0.808)	0.009
Rash	Absent	1		1	
	Present	2.733 (1.370–5.455)	0.004	2.822 (1.300–6.126)	0.009
Thyroid dysfunction	Absent	1			
	Present	1.328 (0.600–2.942)	0.484		
Proteinuria	Absent	1			
	Present	0.882 (0.514–1.515)	0.650		
Liver injury	Absent	1			
	Present	2.017 (0.949–4.286)	0.068		
Any irAE	Absent	1			
	Present	2.782 (1.635–4.736)	< 0.001		

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CR, complete response; irAE, immune-related adverse event; mALBI, modified albumin-bilirubin; PD, progressive disease; PR, partial response; SD, stable disease.

new-onset hypertension during treatment may be a stronger predictor of favorable outcomes than either the absence of hypertension or the worsening of pre-existing hypertension.

Our findings align with those of Tada et al. [24] who reported that treatment-related hypertension was independently associated with improved PFS in patients with uHCC treated with atezolizumab plus bevacizumab. The association between hypertension and prolonged survival also aligns with prior studies suggesting that anti-angiogenic therapy-related hypertension reflects effective VEGF pathway inhibition [25, 26]. However, Tada et al. did not perform a landmark analysis, which limits direct comparability. Our study adds to the literature by confirming the association using a methodologically rigorous approach that minimizes bias from varying treatment durations. Similarly, Takaki et al. [27] identified proteinuria as a positive factor for OS, consistent with the notion that AEs reflecting VEGF inhibition may correlate with treatment

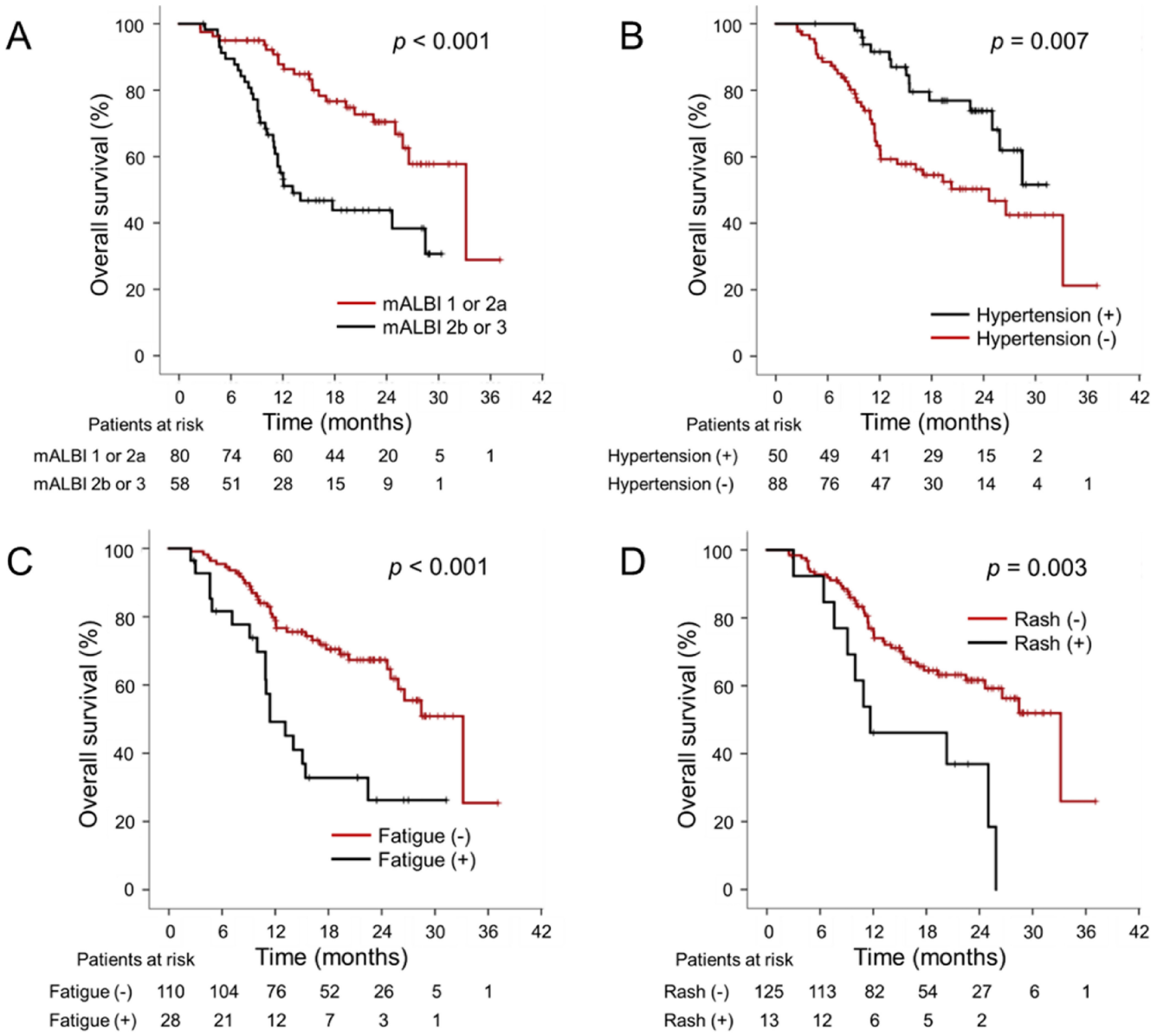

FIGURE 3 | Comparisons of OS in the landmark analysis according to mALBI grade (A), the presence of hypertension (B), fatigue (C), or rash (D) as AEs occurring within 9 weeks. The total number of OS events was 55. The median OS (95% confidence interval) was 33.2 (23.8–42.5) months in patients with mALBI Grade 1 or 2a and 13.1 (5.9–20.3) months in those with mALBI Grade 2b or 3. For hypertension, the median OS was not reached in patients with hypertension as an AE and 24.6 (14.9–34.3) months in those without. For fatigue, the median OS was 33.2 (25.2–41.1) months in patients without fatigue as an AE and 11.4 (7.7–15.0) months in those with. For rash, the median OS was 33.2 (25.2–41.1) months in patients without rash as an AE and 11.7 (0.3–23.0) months in those with. AE, adverse event; mALBI, modified albumin-bilirubin; OS, overall survival.

efficacy. However, proteinuria did not emerge as a significant factor in our landmark analysis, suggesting that its impact may depend on timing, severity, or cohort-specific characteristics. Hypertension and proteinuria were considered markers of VEGF inhibition but also potential causes of early bevacizumab interruption. We included bevacizumab interruption within 9 weeks as an adjustment factor in the multivariable analysis. Notably, the absence of interruption itself was independently associated with prolonged PFS, suggesting that maintaining continuous VEGF inhibition during the early treatment period may be critical for achieving better disease control.

Furthermore, antihypertensive medications themselves may influence the tumor immune microenvironment and thereby enhance the efficacy of immune checkpoint inhibitors (ICIs) [28, 29]. Calcium channel blockers have been reported to modulate tumor-associated macrophage polarization, favoring a more immunostimulatory phenotype and reducing immunosuppressive signaling. Renin-angiotensin system inhibitors, such as angiotensin converting enzyme inhibitors or angiotensin receptor blockers, may improve T-cell infiltration and activation within the tumor microenvironment, partly by reducing tissue hypoxia and fibrosis, thereby potentially enhancing ICI effectiveness.

Interestingly, our study observed that the absence of irAEs, such as diarrhea, was associated with better OS, contrasting with reports that irAEs often predict favorable outcomes in ICI therapies for other cancers. Cook et al. [30] demonstrated that clinically meaningful irAEs significantly improved OS in patients with non-small cell lung cancer (NSCLC) treated with ICIs, with a median OS of 23.7 months for patients with irAEs compared with 9.8 months for those without. Similarly, Dupont et al. [31] reported a significant association between irAEs and enhanced OS in patients with melanoma or NSCLC, with early and late irAEs independently linked to better outcomes. In our study, rash as an irAE was associated with poorer OS, but not with PFS. The patients who developed rash had a relatively low rate of transition to subsequent treatment following the discontinuation of atezolizumab plus bevacizumab. This limited access to further therapy may have contributed to the observed reduction in OS. Importantly, rash was frequently accompanied by concurrent immune-related hepatic AEs, which likely had a more direct impact on worsening liver function and overall clinical condition. Conversely, HCC is characterized by a distinct immunosuppressive environment, often exacerbated by underlying liver dysfunction or viral hepatitis, which may alter the dynamics of irAEs and their prognostic implications [8, 32]. In particular, liver-related irAEs, such as immune-mediated hepatitis, can have a profound impact on prognosis. Hepatic irAEs may exacerbate pre-existing liver damage, compromise liver function, and limit the ability to continue treatment, thereby negatively affecting survival outcomes [33–35].

Overall, our results emphasize the importance of hypertension as a positive prognostic marker while highlighting the need for careful management of fatigue, rash, and other AEs to optimize treatment outcomes. The use of landmark analysis further strengthens the reliability of these findings as it allows for a more accurate assessment of the timing and significance of AEs.

The limitations of this study include its small sample size and potential for selection bias. Moreover, variations in patient populations and methodologies between studies may account for some differences in findings. Landmark analysis does not account for the dynamic nature of AEs that may occur beyond the predefined time point. Late-onset AEs, which may also have prognostic significance, are not captured within this framework, potentially underestimating the full impact of AEs on therapeutic outcomes. To address multiple comparisons and minimize immortal time bias, we limited the primary analysis to AEs occurring within 9 weeks using a landmark approach. However, formal correction was not applied; hence, these exploratory analyses should be interpreted with caution. Future studies are needed to validate these observations and explore the underlying mechanisms driving the relationships between AEs and therapeutic outcomes.

In conclusion, this study reinforces the dual role of AEs as both biomarkers of efficacy and challenges in the clinical management of uHCC. The application of landmark analysis provides a nuanced understanding of these relationships, guiding personalized strategies for improving outcomes in patients undergoing atezolizumab plus bevacizumab therapy for uHCC.

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Ethics Statement

The Ethics Committee of Osaka University Hospital and each participating institution approved the study protocol. All study participants provided written informed consent before enrollment.

Conflicts of Interest

Tetsuo Takehara has received research grants and lecture fees from Chugai Pharmaceutical Co. Ltd, Eisai, MSD K. K., and AstraZeneca. Hayato Hikita has received lecture fees from Chugai Pharmaceutical Co. Ltd. Takahiro Kodama has received research grants from AstraZeneca and lecture fees from Chugai Pharmaceutical Co. Ltd, Eisai, MSD K. K., and AstraZeneca. All other authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Flowchart of study enrollment. A total of 292 patients with uHCC who received atezolizumab plus bevacizumab were initially assessed. Of these, 14 patients were excluded because their observation period was less than 6 weeks, 13 were excluded due to lack of contrast-enhanced imaging because HCC could not be reliably diagnosed without contrast media, one was excluded due to participation in another clinical trial, and 77 were excluded because they received the treatment as second-line or later therapy. Hence, 187 patients were included in the primary analysis cohort. Furthermore, a total of 138 patients whose disease was controlled and who continued treatment with atezolizumab plus bevacizumab 9 weeks after treatment initiation were included in the landmark analysis. Abbreviation: HCC, hepatocellular carcinoma. **Figure S2:** The onset time of AEs after the initiation of atezolizumab plus bevacizumab. Fatigue, diarrhea, hypertension, proteinuria, liver injury, and interstitial pneumonia had a median onset period of 6 weeks or less after treatment initiation. In contrast, rash, thyroid dysfunction, and adrenal insufficiency occurred at a relatively later period after treatment initiation. Diarrhea, hypertension, proteinuria, and liver injury as AEs were found to occur at 5.3–9.0 weeks, 3.0–6.0 weeks, 3.0–9.0 weeks, and 3.0–6.8 weeks (IQR), respectively. Most AEs were determined to have occurred within 9 weeks of treatment initiation. Abbreviation: AE, adverse event. **Figure S3:** Comparisons of PFS (A) and OS (B) in the 9-week landmark analysis according to the presence of any irAE occurring within 9 weeks. Abbreviations: PFS, progression-free survival; OS, overall survival; irAE, immune-related adverse event. **Figure S4:** Comparisons of PFS (A) and OS (B) in the 9-week landmark analysis among patients without hypertension as an AE, patients with hypertension as an AE

and a history of hypertension (pre-existing hypertension), and patients with hypertension as an AE but no history of hypertension (new-onset hypertension). Abbreviations: PFS, progression-free survival; OS, overall survival; AE, adverse event. **Figure S5:** Comparisons of PFS (A) and OS (B) in the 9-week landmark analysis according to hypertension grade according to CTCAE version 5.0 among patients who experienced hypertension as an AE within 9 weeks. Among patients who experienced hypertension as an AE within 9 weeks, six had Grade 1, 35 had Grade 2, and nine had Grade 3 hypertension. There were no cases of Grade 4 hypertension. We compared survival outcomes across these severity groups; no significant differences in PFS or OS according to hypertension grade were observed. Abbreviations: PFS, progression-free survival; OS, overall survival; CTCAE, Common Terminology Criteria for Adverse Events; AE, adverse event. **Table S1:** Patient characteristics and AEs occurring within 9 weeks in landmark analysis. **Table S2:** Comparison of patient characteristics between patients who experienced hypertension as an AE within 9 weeks and those who did not in the landmark cohort. **Table S3:** Factors associated with OS in the 9-week landmark analysis added pre-existing or new-onset hypertension during treatment to patients who experienced hypertension as an AE within 9 weeks. **Table S4:** Factors associated with PFS in the 6-week landmark analysis. **Table S5:** Factors associated with OS in the 6-week landmark analysis.