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# Adverse Event Monitoring with Imaging: Prognostic Significance in Atezolizumab plus Bevacizumab Therapy for Unresectable Hepatocellular Carcinoma

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**Keywords**
Immunotherapy · Immune-related adverse events · Anti-PD-L1 · Anti-vascular endothelial growth factor · Liver cancer

**Abstract**

***Introduction:*** Immune checkpoint inhibitors (ICIs) have emerged as the first-line systemic therapy for unresectable hepatocellular carcinoma (HCC). Emerging evidence suggests that immune-related adverse events (irAEs) may be associated with improved ICI efficacy. This study evaluated the impact of adverse events during atezolizumab plus bevacizumab therapy on clinical outcomes in patients with unresectable HCC. ***Methods:*** This retrospective study included consecutive patients receiving first-line atezolizumab plus bevacizumab for unresectable HCC. IrAEs and bevacizumab-related adverse events were assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 5.0). Imaging studies conducted during treatment were reviewed to identify asymptomatic, imaging-detected adverse events. Overall survival (OS) was the primary endpoint and was analyzed using time-dependent Cox regression. The secondary endpoint was the disease control rate (DCR). ***Results:*** Among the 198 enrolled patients, 12 had imaging-detected irAEs without symptoms (asymptomatic AE group), whereas 56 experienced clinical symptoms of irAEs ($n$ = 28), bevacizumab-related adverse events ($n$ = 19) or both ($n$ = 9) (symptomatic AE group). The OS rates at 6, 12, 18, and 24 months were 100.0%, 82.5%, 82.5%, and 82.5%, respectively, in the asymptomatic AE group; 89.1%, 64.1%, 41.7%, and 40.5%, respectively, in the symptomatic AE group; and 72.3%, 48.3%, 31.3%, and 19.4%, respectively, for the non-AE group. Compared with the non-AE group, both the asymptomatic and symptomatic AE groups showed significantly improved OS in the inverse probability of treatment weighting-adjusted time-dependent Cox regression analysis ($p$ = 0.02). The DCR was significantly greater in the asymptomatic AE group (100.0%) and the symptomatic

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AE group (91.8%) than in the non-AE group (60.0%) ($p < 0.001$). ***Conclusion:*** Adverse events during atezolizumab plus bevacizumab therapy are associated with improved OS and treatment response in unresectable HCC patients. Asymptomatic imaging-detected irAEs may serve as prognostic factors, highlighting the value of proactive imaging in patient management. 

**Plain Language Summary**

Hepatocellular carcinoma (HCC) is a leading cause of cancer-related deaths worldwide. For patients with unresectable HCC, a combination of two drugs – atezolizumab and bevacizumab – is now widely used as the first-line therapy. These medicines can cause side effects, called adverse events. Some are related to immune system activity, while others are associated with bevacizumab. We aimed to determine whether the occurrence of these adverse events could provide information about treatment outcomes. We studied 198 patients treated with atezolizumab plus bevacizumab. We examined two types of adverse events: (1) those found only on imaging scans without symptoms and (2) those detected by symptoms or laboratory tests. We found that patients who experienced either type of adverse event generally lived longer and responded better to treatment than those without adverse events. In particular, patients with imaging-detected, asymptomatic adverse events showed the most favorable outcomes. Our findings suggest that not all treatment-related side effects are harmful. Instead, their occurrence – especially when detected early on imaging – may indicate that treatment is working effectively. This underlines the value of regular imaging, not only for monitoring tumor response but also for identifying treatment-related adverse events that may predict improved prognosis in patients with HCC.



## Introduction

Hepatocellular carcinoma (HCC) remains the third leading cause of cancer-related death worldwide [1]. Since the success of the IMbrave 150 trial, atezolizumab plus bevacizumab has become the first-line systemic treatment for unresectable HCC [2]. Recently, the HIMALAYA study revealed that the combination of immune checkpoint inhibitors (ICIs) consisting of tremelimumab plus regular-interval durvalumab significantly improved overall survival (OS) compared with sorafenib in patients with unresectable HCC [3]. Therefore, the treatment for unresectable HCC has shifted from tyrosine kinase inhibitors to ICIs, leading to improved survival outcomes. In contrast to other types of cytotoxic chemotherapy, ICIs have distinct adverse events (AEs) related to the immune response [4]. As ICIs have become the dominant therapy for unresectable HCC, the early diagnosis and management of immune-related adverse events (irAEs) are essential for sustaining long-term treatment and improving survival outcomes.

Previous studies have suggested that the occurrence of irAEs can increase the efficacy of ICIs, improve survival rates, and increase response rates in patients with various cancers [5, 6]. In cases of HCC, the combination of atezolizumab and bevacizumab has been notably associated with favorable survival outcomes when mild irAEs occur, suggesting their potential as surrogate markers for HCC prognosis [7–9]. Regarding bevacizumab-related AEs, retrospective studies have suggested that arterial hypertension induced by bevacizumab may also be associated with positive outcomes in liver cancer patients [10, 11]. However, severe irAEs, leading to treatment cessation, have been linked to significantly worse outcomes [8, 12]

With the comprehensive introduction of dual ICI treatments like tremelimumab and durvalumab, and considering the high likelihood of the future development and approval of ICI-centered therapies, the early detection of irAEs and appropriate therapeutic decision-making are crucial for the continuation of successful ICI therapy [13]. However, a comprehensive evaluation of the relationship between the development of AEs during treatment with atezolizumab plus bevacizumab for unresectable HCC and the clinical outcome has not been fully performed. Therefore, our study was conducted with the aim of comprehensively evaluating the effects of treatment-related AEs assessed by both clinical symptoms and imaging studies on the clinical outcomes in patients with unresectable HCC treated with atezolizumab plus bevacizumab.

## Patients and Methods

### *Study Population*

Consecutive patients who received atezolizumab plus bevacizumab as first-line systemic therapy for unresectable HCC between October 2020 and June 2023 at Seoul National University Hospital (Seoul, South Korea) were retrospectively reviewed. HCC was diagnosed

radiologically and/or histologically according to the latest updated guidelines [14, 15]. This study conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki. This study was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. H-2307-071-1448). The requirement to obtain informed consent from patients was waived by the IRB because of the retrospective nature of this study.

Patients were included in the study on the basis of the following criteria: (i) age >18 years; (ii) unequivocal diagnosis of unresectable HCC on the basis of radiological and/or histological findings; (iii) treatment with atezolizumab plus bevacizumab as first-line systemic therapy; and (iv) Eastern Cooperative Oncology Group performance status of 0 or 1. Patients who met any of the following criteria were excluded: (i) the presence of another concurrent malignancy; (ii) failure to conduct initial response assessment after the administration of atezolizumab plus bevacizumab; and (iii) prior recipient of a liver transplant.

*Treatment Regimens*

The atezolizumab plus bevacizumab regimen was administered intravenously. Atezolizumab was given at a dose of 1,200 mg. Bevacizumab was then given at a dose of 15 mg/kg. Both were administered on the same day every 3 weeks [16]. When an AE occurred, treatment was resumed according to the National Comprehensive Cancer Network guidelines [17]. Treatment with atezolizumab plus bevacizumab was discontinued in patients who experienced fatal AEs, disease progression, or liver failure [14, 15, 18].

*Assessments and Outcomes*

IrAEs and bevacizumab-related AEs were evaluated according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, which uses a severity scale ranging from grade 1 to grade 5. Grade 5 represents an AE leading to death, whereas grade 0 indicates the absence of any symptoms or problems. Within the broad spectrum of AEs, irAEs are defined as those with a pathophysiology likely associated with an immunological response or those for which the physicians administer corticosteroids as rescue therapy [19]. The AEs related to bevacizumab have been defined on the basis of clinical symptoms associated with vascular endothelial growth factor (VEGF) inhibition, as identified in previous studies [2, 20]. The occurrence of adverse events in all patients was regularly assessed during outpatient visits, and their occurrence and severity were thoroughly documented in the electronic medical records. All the imaging studies that were conducted during treatment, including contrast-enhanced liver computed tomography (CT) and chest CT scans, were retrospectively reviewed by a single board-certified radiologist specializing in body imaging to identify any imaging manifestations that suggested the occurrence of irAEs. To accurately determine whether the imaging findings represented irAEs, clinical symptoms and laboratory results were evaluated in parallel, with reference to previous literature describing the characteristic radiological features of irAEs [21, 22]. The detailed results of the imaging evaluations are provided in the supplementary data (for all online suppl. material, see https://doi.org/10.1159/000548830). Based on these criteria, AEs in this study were categorized into two groups: asymptomatic AEs, defined as radiological findings suggestive of irAEs without concurrent clinical or laboratory abnormalities, and symptomatic AEs, defined as all other AEs detected by clinical manifestations or laboratory findings, including both irAEs and bevacizumab-related AEs. The detailed results of the imaging evaluations are provided in the supplementary data.

The index date was defined as the date on which the patient started treatment with atezolizumab plus bevacizumab. Patients were censored on the earliest of the following dates: the date of the last follow-up, death, or the data cutoff date (August 31, 2024). The date of the first AE, in cases in which both an irAE and a bevacizumab-related AE occurred, was defined as the date of the first of the two events.

The primary endpoint was OS. The secondary endpoints were time-to-progression (TTP), the incidence of AEs during treatment, and the disease control rate (DCR). The radiological response to treatment was evaluated at intervals of three treatment cycles via dynamic CT or magnetic resonance imaging in accordance with the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1). Tumor markers, including the serum levels of alpha-fetoprotein and protein induced by vitamin K absence or antagonist-II (PIVKA-II), were also measured every three treatment cycles.

*Statistical Analysis*

Baseline clinical and demographic characteristics were compared between the groups stratified by the development of AEs. Categorical variables are presented as frequencies (%), and continuous variables are presented as medians with interquartile ranges

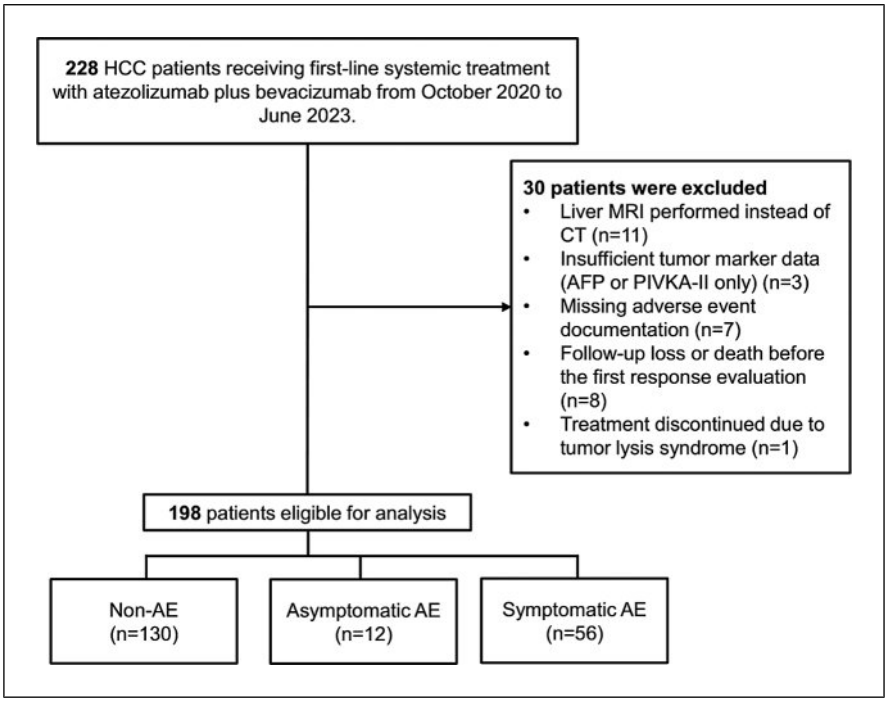


**Fig. 1.** Flow diagram of patient selection for the study.

(IQRs). Categorical variables were compared using Pearson's $\chi^2$ test, whereas continuous variables were compared using analysis of variance (ANOVA) or the Kruskal-Wallis test. Inverse probability of treatment weighting (IPTW) was applied to minimize potential confounding. A propensity score model was constructed to most effectively achieve balance in baseline characteristics between groups by incorporating covariates relevant to treatment assignments, outcome prognosis, or potential confounding effects. The final model included age, sex, the albumin-bilirubin (ALBI) score, the neutrophil-lymphocyte ratio, and alpha-fetoprotein levels [23, 24]. The Kaplan-Meier estimator and log-rank test were used to analyze the time-to-event outcomes, including time to first AE, OS, TTP, and PFS. For OS, TTP, and PFS, time-dependent Cox regression models were additionally applied, in which AE occurrence was modeled as a time-varying covariate [25, 26]. These analyses were conducted both before and after IPTW adjustment to account for potential baseline confounding. A multivariable time-dependent Cox regression model was constructed to identify independent risk factors, incorporating covariates that were significant in univariable analyses or that showed minimal multicollinearity.

All the statistical analyses were performed using R version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria). $p$ values <0.05 indicated statistically significant differences.

## Results

*Study Population*

A total of 198 patients were included in this study (Fig. 1). The following irAEs detected only on CT scans without accompanying symptoms were observed in 12 patients (asymptomatic imaging-detected AEs group): pulmonary infiltration suggesting pneumonitis ($n$ = 8), colon wall thickening suggesting colitis ($n$ = 2), mesenteric infiltration indicating panniculitis ($n$ = 1), and mild enlargement with infiltration of axillary lymph nodes suggesting lymphadenitis ($n$ = 1). None of these 12 patients had any symptoms related to the imaging-detected abnormalities. IrAEs or bevacizumab-related AEs accompanied by clinical symptoms were observed in 56 patients (symptomatic AEs group) with the following distribution: irAEs ($n$ = 28), bevacizumab-related AEs ($n$ = 19), and both ($n$ = 9). AEs were not observed during the follow-up period in the remaining 130 patients (non-AE group). The median follow-up duration was 12.6 months (interquartile range [IQR], 6.6–18.1) in the overall population. In the asymptomatic AE, symptomatic AE, and non-AE groups, the durations were 17.0 months (IQR, 14.0–20.5), 15.7 months (IQR, 9.9–19.9), and 10.2 months (IQR, 5.4–15.6), respectively. The baseline characteristics of the study population are summarized in Table 1. The etiology, Child-Pugh score, neutrophil-lymphocyte ratio (NLR), and PIVKA-II

**Table 1.** Baseline characteristics

| Variables | Non-AE ($n$ = 130) | Asymptomatic AE ($n$ = 12) | Symptomatic AE ($n$ = 56) | $p$ value | SMD |
|---|---|---|---|---|---|
| *A. Before IPTW* | | | | | |
| Age, years | 62.0 (55.0–70.0) | 63.5 (53.0–72.0) | 64.0 (61.0–69.5) | 0.14 | 0.20 |
| Sex, *N* (%) | | | | 1.00 | 0.13 |
| Female | 19 (14.6%) | 1 (8.3%) | 8 (14.3%) | | |
| Male | 111 (85.4%) | 11 (91.7%) | 48 (85.7%) | | |
| Etiology of HCC, *N* (%) | | | | 0.047 | 0.17 |
| HBV | 86 (66.2%) | 5 (41.7%) | 29 (51.8%) | | |
| HCV | 6 (4.6%) | 2 (16.7%) | 4 (7.1%) | | |
| Alcohol | 9 (6.9%) | 3 (25.0%) | 10 (17.9%) | | |
| None | 29 (22.3%) | 2 (16.7%) | 13 (23.2%) | | |
| BCLC stage | | | | 0.10 | 0.38 |
| B | 21 (16.2%) | 5 (41.7%) | 10 (17.9%) | | |
| C | 109 (83.8%) | 7 (58.3%) | 46 (82.1%) | | |
| Child-Pugh score | | | | 0.048 | 0.60 |
| A5 | 93 (71.5%) | 12 (100.0%) | 45 (80.4%) | | |
| A6 | 37 (28.5%) | 0 (0.0%) | 11 (19.6%) | | |
| Albumin, g/dL | 4.0 (3.6–4.2) | 4.0 (3.9–4.5) | 3.8 (3.6–4.2) | 0.12 | 0.48 |
| Total bilirubin, mg/dL | 0.9 (0.6–1.2) | 0.6 (0.5–1.1) | 0.9 (0.7–1.2) | 0.34 | 0.36 |
| PT (INR) | 1.1 (1.0–1.2) | 1.1 (1.0–1.2) | 1.1 (1.0–1.1) | 0.38 | 0.22 |
| ALBI score | −2.6 (−2.9 to −2.2) | −2.8 (−3.1 to −2.6) | −2.6 (−2.8 to −2.2) | 0.05 | 0.59 |
| NLR | 3.0 (2.0–4.5) | 2.0 (1.5–2.6) | 2.2 (1.7–3.3) | 0.008 | 0.32 |
| Fibrosis-4 index | 3.3 (2.1–6.4) | 3.3 (2.5–5.6) | 4.0 (2.3–5.7) | 0.83 | 0.24 |
| Underlying liver status, *N* (%) | | | | 0.05 | 0.38 |
| No cirrhosis | 39 (30.0%) | 1 (8.3%) | 9 (16.1%) | | |
| Cirrhosis | 91 (70.0%) | 11 (91.7%) | 47 (83.9%) | | |
| AFP | | | | 0.72 | 0.08 |
| <400 ng/mL | 73 (56.2%) | 7 (58.3%) | 35 (62.5%) | | |
| ≥400 ng/mL | 57 (43.8%) | 5 (41.7%) | 21 (37.5%) | | |
| PIVKA-II | | | | 0.01 | 0.35 |
| <100 mAU/mL | 32 (24.6%) | 6 (50.0%) | 24 (42.9%) | | |
| ≥100 mAU/mL | 98 (75.4%) | 6 (50.0%) | 32 (57.1%) | | |
| Lymph node metastasis | | | | 0.62 | 0.18 |
| Absent | 97 (74.6%) | 8 (66.7%) | 44 (78.6%) | | |
| Present | 33 (25.4%) | 4 (33.3%) | 12 (21.4%) | | |
| Extrahepatic metastasis | | | | 0.80 | 0.13 |
| Absent | 63 (48.5%) | 7 (58.3%) | 27 (48.2%) | | |
| Present | 67 (51.5%) | 5 (41.7%) | 29 (51.8%) | | |
| PVTT | | | | 0.08 | 0.53 |
| Absent | 77 (59.2%) | 11 (91.7%) | 34 (60.7%) | | |
| Present | 53 (40.8%) | 1 (8.3%) | 22 (39.3%) | | |
| Hepatic vein invasion | | | | 0.46 | 0.11 |
| Absent | 122 (93.8%) | 11 (91.7%) | 50 (89.3%) | | |
| Present | 8 (6.2%) | 1 (8.3%) | 6 (10.7%) | | |
| Prior local treatment | | | | 0.95 | 0.16 |
| Absent | 20 (15.4%) | 1 (8.3%) | 9 (16.1%) | | |
| Present | 110 (84.6%) | 11 (91.7%) | 47 (83.9%) | | |

**Table 1** (continued)

| Variables | Non-AE ($n$ = 130) | Asymptomatic AE ($n$ = 12) | Symptomatic AE ($n$ = 56) | $p$ value | SMD |
|---|---|---|---|---|---|
| *B. After IPTW* | | | | | |
| Age, years | 62.0 (55.0–70.0) | 63.0 (52.0–68.0) | 63.0 (58.0–68.0) | 0.69 | 0.10 |
| Sex, *N* (%) | | | | 0.79 | 0.12 |
| Female | 20 (15.2%) | 1 (9.1%) | 7 (12.4%) | | |
| Male | 110 (84.8%) | 11 (90.9%) | 49 (87.6%) | | |
| Etiology of HCC, *N* (%) | | | | 0.25 | 0.25 |
| HBV | 85 (65.3%) | 5 (36.5%) | 30 (54.2%) | | |
| HCV | 6 (4.7%) | 2 (19.3%) | 3 (6.2%) | | |
| Alcohol | 10 (8.0%) | 2 (20.4%) | 10 (17.0%) | | |
| None | 29 (22.0%) | 3 (23.8%) | 13 (22.6%) | | |
| BCLC stage | | | | 0.19 | 0.35 |
| B | 20 (15.4%) | 3 (27.6%) | 8 (13.5%) | | |
| C | 110 (84.6%) | 9 (72.4%) | 48 (86.5%) | | |
| Child-Pugh score | | | | 0.05 | 0.59 |
| A5 | 94 (72.0%) | 12 (100.0%) | 45 (80.2%) | | |
| A6 | 36 (28.0%) | 0 (0.0%) | 11 (19.8%) | | |
| Albumin, g/dL | 4.0 (3.6–4.3) | 4.0 (3.8–4.4) | 3.8 (3.6–4.2) | 0.20 | 0.36 |
| Total bilirubin, mg/dL | 0.9 (0.6–1.2) | 0.6 (0.5–1.1) | 0.9 (0.7–1.2) | 0.12 | 0.37 |
| PT (INR) | 1.1 (1.0–1.2) | 1.1 (1.0–1.2) | 1.1 (1.0–1.1) | 0.48 | 0.12 |
| ALBI score | −2.6 (−2.9 to −2.2) | −2.7 (−3.1 to −2.6) | −2.6 (−2.8 to −2.3) | 0.06 | 0.48 |
| NLR | 2.8 (1.8–4.2) | 2.1 (1.6–2.5) | 2.4 (1.7–3.7) | 0.28 | 0.22 |
| Fibrosis-4 index | 3.2 (2.1–6.3) | 3.0 (1.8–6.2) | 3.6 (2.3–5.7) | 0.43 | 0.14 |
| Underlying liver status, *N* (%) | | | | 0.13 | 0.41 |
| No cirrhosis | 39 (27.6%) | 1 (5.3%) | 10 (20.0%) | | |
| Cirrhosis | 91 (72.4%) | 11 (94.7%) | 39 (80.0%) | | |
| AFP | | | | 0.75 | 0.12 |
| <400 ng/mL | 75 (57.7%) | 8 (66.6%) | 35 (62.8%) | | |
| ≥400 ng/mL | 55 (42.3%) | 4 (33.4%) | 21 (37.2%) | | |
| PIVKA-II | | | | 0.07 | 0.44 |
| <100 mAU/mL | 37 (28.8%) | 7 (61.3%) | 20 (36.4%) | | |
| ≥100 mAU/mL | 93 (71.2%) | 5 (38.7%) | 36 (63.6%) | | |
| Lymph node metastasis | | | | 0.84 | 0.09 |
| Absent | 94 (72.5%) | 9 (70.9%) | 43 (76.7%) | | |
| Present | 36 (27.5%) | 3 (29.1%) | 13 (23.3%) | | |
| Extrahepatic metastasis | | | | 0.42 | 0.26 |
| Absent | 61 (47.3%) | 8 (66.6%) | 28 (49.7%) | | |
| Present | 69 (52.7%) | 4 (33.4%) | 28 (50.3%) | | |
| PVTT | | | | 0.45 | 0.31 |
| Absent | 80 (61.4%) | 10 (81.5%) | 34 (60.6%) | | |
| Present | 50 (38.4%) | 2 (18.5%) | 22 (39.4%) | | |
| Hepatic vein invasion | | | | 0.52 | 0.11 |
| Absent | 63 (48.1%) | 11 (94.8%) | 51 (90.2%) | | |
| Present | 67 (51.9%) | 1 (5.2%) | 5 (9.8%) | | |

**Table 1** (continued)

| Variables | Non-AE ($n$ = 130) | Asymptomatic AE ($n$ = 12) | Symptomatic AE ($n$ = 56) | $p$ value | SMD |
|---|---|---|---|---|---|
| Prior local treatment | | | | 0.76 | 0.10 |
| Absent | 19 (14.4%) | 2 (18.5%) | 11 (20.1%) | | |
| Present | 111 (85.6%) | 10 (81.5%) | 45 (79.9%) | | |

AE, adverse event; AFP, alpha-fetoprotein; ALBI score, albumin-bilirubin score; BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; IPTW, inverse probability of treatment weighting; NLR, neutrophil-lymphocyte ratio; PIVKA-II, protein induced by vitamin K absence or antagonist-II; PT (INR), international normalized ratio of prothrombin time; PVTT, portal vein tumor thrombosis; SMD, standardized mean difference.



levels initially significantly differed among the groups, but these values were balanced following IPTW adjustment. Accordingly, all variables were appropriately adjusted after IPTW.

*Development of AEs*

The median time to AE was 3.6 months (95% CI: 1.8–not estimated) in the asymptomatic AE group and 3.1 months (95% CI: 2.3–4.6) in the symptomatic AE group (online suppl. Fig. 1). Nearly half of the AEs occurred within the first 3 months in both groups (41.7% in the asymptomatic group and 50.0% in the symptomatic group). By approximately 6 months after the start of treatment, more than two-thirds of the AEs had occurred (83.3% in the asymptomatic group and 80.4% in the symptomatic group). The median time to the occurrence of irAEs was 4.1 months, with 89.8% of these events occurring within the initial 6 months. In contrast, AEs associated with bevacizumab manifested at a median of 10.6 months, with 42.9% occurring within 6 months (online suppl. Fig. 2). Before IPTW adjustment, a low NLR, low PIVKA-II levels, and the presence of liver cirrhosis were statistically significant independent risk factors for the occurrence of AEs. However, after IPTW, no significant factors associated with the risk of AEs were identified (online suppl. Table 1). Details of the AEs are provided in online supplementary Table 2. In the asymptomatic AE group, irAEs were identified on CT, and pulmonary infiltration suggesting pneumonitis was the most common (66.7%). In the symptomatic AE group, Grade 1 or 2 irAEs primarily manifested as hypothyroidism (42.4%) and dermatitis (33.3%), whereas Grade 3 or 4 irAEs predominantly manifested as hepatitis (50%). Among bevacizumab-related AEs, gastrointestinal bleeding (50.0%) and proteinuria (35.7%) were the most frequently observed. Among the 56 patients in the symptomatic AE group, 8 patients discontinued treatment exclusively because of AEs (atezolizumab, $n$ = 3; bevacizumab, $n$ = 5), independent of disease progression. Excluding the 7 patients who simultaneously demonstrated disease progression, the remaining 41 patients continued atezolizumab plus bevacizumab treatment while receiving management for AEs.

*Overall Survival*

During the follow-up period, 127 of the 198 patients died: 2 (16.7%) in the asymptomatic AE group, 32 (57.1%) in the symptomatic AE group, and 93 (71.5%) in the non-AE group. The median OS was not reached in the asymptomatic AE group ($p$ = 0.007 compared with the non-AE group). In the symptomatic AE group, the median OS was 19.3 months (95% CI: 13.0–not estimated; $p$ = 0.008 compared with the non-AE group). In the non-AE group, the median OS was 11.0 months (95% CI: 8.9–14.4; Fig. 2a). The OS rates at 6, 12, 18, and 24 months were 100.0%, 82.5%, 82.5%, and 82.5%, respectively, in the asymptomatic AE group; 89.1%, 64.1%, 41.7%, and 40.5%, respectively, in the symptomatic AE group; and 72.3%, 48.3%, 31.3%, and 19.4%, respectively, in the non-AE group. Before IPTW, OS was significantly improved in both the asymptomatic AE group (hazard ratio [HR]: 0.15; 95% CI: 0.04–0.60; $p$ = 0.007 compared with the non-AE group) and the symptomatic AE group (HR: 0.58; 95% CI: 0.39–0.86; $p$ = 0.008 compared with the non-AE group). The results of the IPTW-adjusted time-dependent Cox regression analysis were consistent, with hazard ratios of 0.19 (95% CI: 0.05–0.80; $p$ = 0.02) in the asymptomatic AE group and 0.42 (95% CI: 0.21–0.89; $p$ = 0.02) in the symptomatic AE group (Fig. 2d). Time-dependent multivariate Cox analyses consistently revealed that OS was significantly improved in both the asymptomatic (adjusted HR [aHR]: 0.21; 95% CI: 0.05–0.85; $p$ = 0.03) and symptomatic (aHR: 0.45; 95% CI: 0.23–0.90; $p$ = 0.02; Table 2) AE groups after IPTW.

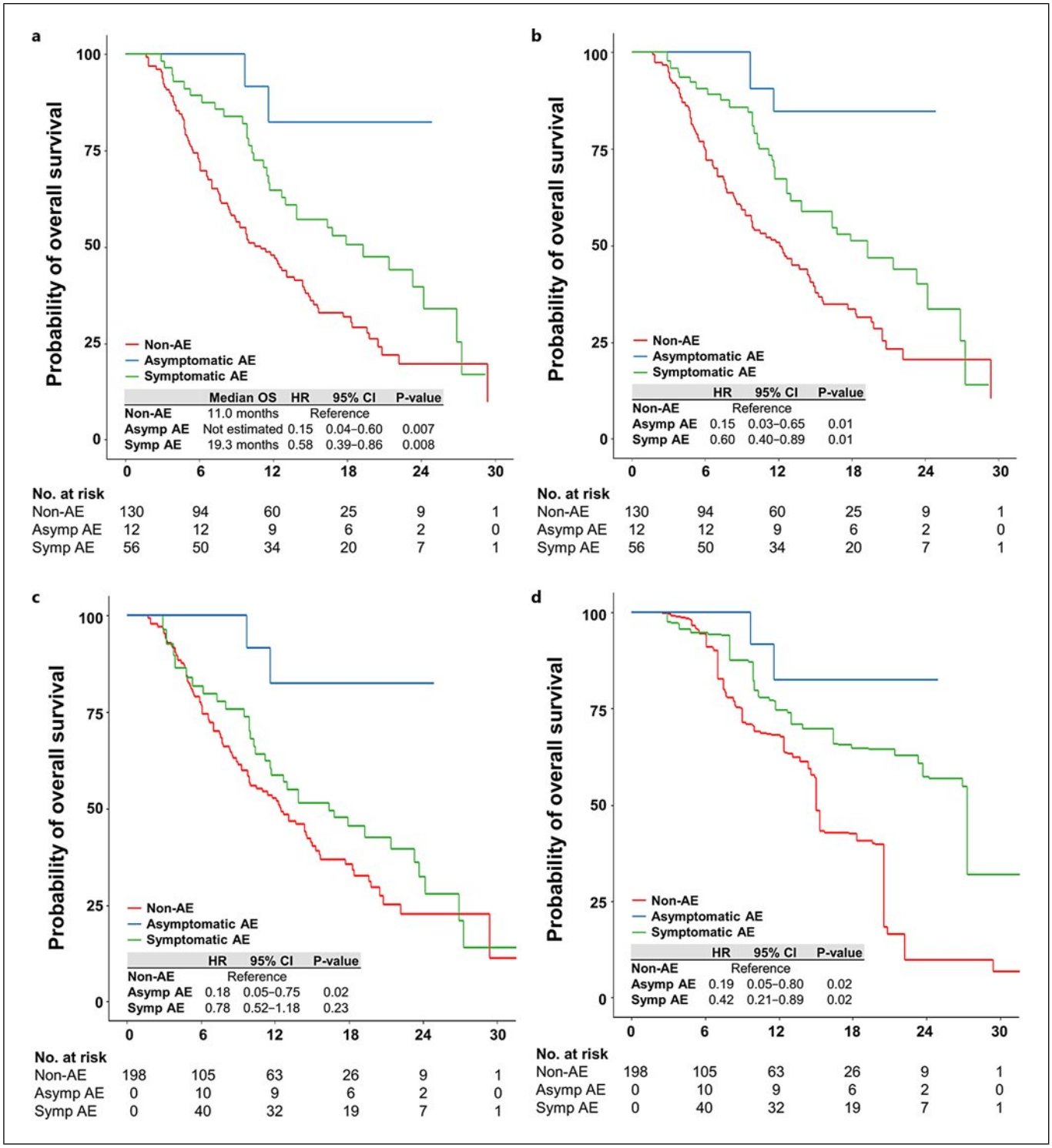


**Fig. 2.** OS according to the occurrence of AEs: Kaplan-Meier estimates before (**a**) and after (**b**) IPTW, and Simon-Makuch plots based on time-dependent Cox regression analysis treating the occurrence of AEs as a time-varying covariate before (**c**) and after (**d**) IPTW.

**Table 2.** Time-dependent Cox regression analysis of factors associated with overall survival (A) before and (B) after IPTW

| Variables | Crude HR (95% CI) | *p* value | Adjusted HR (95% CI) | *p* value |
|---|---|---|---|---|
| *A. Before IPTW* | | | | |
| Adverse event | | | | |
| None | 1 [Reference] | | 1 [Reference] | |
| Asymptomatic | 0.18 (0.05–0.75) | 0.02 | 0.32 (0.08–1.32) | 0.12 |
| Symptomatic | 0.78 (0.52–1.18) | 0.23 | 0.83 (0.54–1.28) | 0.41 |
| Age | | 0.64 | | |
| <65 years | 1 [Reference] | | | |
| ≥65 years | 1.09 (0.76–1.55) | | | |
| Sex | | 0.66 | | |
| Female | 1 [Reference] | | | |
| Male | 0.90 (0.55–1.46) | | | |
| Etiology of HCC | | 0.76 | | |
| Other etiology | 1 [Reference] | | | |
| HBV or HCV | 1.06 (0.73–1.54) | | | |
| Child-Pugh score | | 0.002 | | 0.12 |
| A5 | 1 [Reference] | | 1 [Reference] | |
| A6 | 1.85 (1.26–2.70) | | 1.44 (0.91–2.27) | |
| BCLC | | 0.67 | | |
| B | 1 [Reference] | | | |
| C | 0.91 (0.57–1.43) | | | |
| FIB-4 index | | 0.03 | | 0.24 |
| <3.25 | 1 [Reference] | | 1 [Reference] | |
| ≥3.25 | 1.47 (1.03–2.10) | | 1.27 (0.86–1.87) | |
| ALBI score | | <0.001 | | 0.05 |
| ≤−22.60 | 1 [Reference] | | 1 [Reference] | |
| >−2.60 | 1.90 (1.33–2.72) | | 1.52 (0.99–2.34) | |
| NLR | | <0.001 | | <0.001 |
| <3 | 1 [Reference] | | 1 [Reference] | |
| ≥3 | 2.01 (1.41–2.85) | | 2.05 (1.42–2.95) | |
| AFP | | 0.10 | | |
| <400 ng/mL | 1 [Reference] | | | |
| ≥400 ng/mL | 1.35 (0.95–1.92) | | | |
| PIVKA-II | | <0.001 | | <0.001 |
| <100 mAU/mL | 1 [Reference] | | 1 [Reference] | |
| ≥100 mAU/mL | 2.59 (1.70–3.95) | | 2.17 (1.40–3.35) | |
| LN metastasis | | 0.34 | | |
| Absent | 1 [Reference] | | | |
| Present | 0.82 (0.54–1.24) | | | |
| Extrahepatic metastasis | | 0.43 | | |
| Absent | 1 [Reference] | | | |
| Present | 0.87 (0.61–1.23) | | | |
| PVTT | | 0.003 | | 0.38 |
| Absent | 1 [Reference] | | 1 [Reference] | |
| Present | 1.71 (1.20–2.43) | | 1.19 (0.81–1.77) | |
| Hepatic vein invasion | | 0.75 | | |
| Absent | 1 [Reference] | | | |
| Present | 1.11 (0.58–2.12) | | | |
| LC | | 0.07 | | |
| Absent | 1 [Reference] | | | |
| Present | 0.70 (0.47–1.03) | | | |

**Table 2** (continued)

| Variables | Crude HR (95% CI) | *p* value | Adjusted HR (95% CI) | *p* value |
|---|---|---|---|---|
| *B. After IPTW* | | | | |
| Adverse event | | | | |
| None | 1 [Reference] | | 1 [Reference] | |
| Asymptomatic | 0.19 (0.05–0.80) | 0.02 | 0.21 (0.05–0.85) | 0.03 |
| Symptomatic | 0.42 (0.21–0.85) | 0.02 | 0.45 (0.23–0.90) | 0.02 |
| Age | | 0.90 | | |
| <65 years | 1 [Reference] | | | |
| ≥65 years | 1.03 (0.69–1.52) | | | |
| Sex | | 0.42 | | |
| Female | 1 [Reference] | | | |
| Male | 0.80 (0.47–1.37) | | | |
| Etiology of HCC | | 0.56 | | |
| Other etiology | 1 [Reference] | | | |
| HBV or HCV | 1.14 (0.74–1.75) | | | |
| Child-Pugh score | | 0.004 | | 0.11 |
| A5 | 1 [Reference] | | 1 [Reference] | |
| A6 | 1.90 (1.23–2.92) | | 2.06 (0.84–5.08) | |
| BCLC | | 0.35 | | |
| B | 1 [Reference] | | | |
| C | 0.79 (0.49–1.29) | | | |
| FIB-4 index | | 0.12 | | |
| <3.25 | 1 [Reference] | | | |
| ≥3.25 | 1.36 (0.92–2.01) | | | |
| ALBI score | | 0.004 | | 0.71 |
| ≤−2.60 | 1 [Reference] | | 1 [Reference] | |
| >−2.60 | 1.79 (1.21–2.64) | | 1.23 (0.42–3.56) | |
| NLR | | 0.001 | | 0.53 |
| <3 | 1 [Reference] | | 1 [Reference] | |
| ≥3 | 1.90 (1.29–2.80) | | 1.25 (0.62–2.54) | |
| AFP | | 0.17 | | |
| <400 ng/mL | 1 [Reference] | | | |
| ≥400 ng/mL | 1.32 (0.89–1.95) | | | |
| PIVKA-II | | <0.001 | | 0.88 |
| <100 mAU/mL | 1 [Reference] | | 1 [Reference] | |
| ≥100 mAU/mL | 2.56 (1.64–3.99) | | 1.07 (0.46–2.50) | |
| LN metastasis | | 0.32 | | |
| Absent | 1 [Reference] | | | |
| Present | 0.80 (0.52–1.24) | | | |
| Extrahepatic metastasis | | 0.37 | | |
| Absent | 1 [Reference] | | | |
| Present | 1.48 (1.00–2.02) | | | |
| PVTT | | 0.05 | | 0.37 |
| Absent | 1 [Reference] | | 1 [Reference] | |
| Present | 1.48 (1.00–2.02) | | 0.77 (0.44–1.36) | |
| Hepatic vein invasion | | 0.46 | | |
| Absent | 1 [Reference] | | | |
| Present | 1.23 (0.71–2.11) | | | |

**Table 2** (continued)

| Variables | Crude HR (95% CI) | *p* value | Adjusted HR (95% CI) | *p* value |
|---|---|---|---|---|
| LC | | 0.10 | | |
| Absent | 1 [Reference] | | | |
| Present | 0.68 (0.43–1.07) | | | |

Time-dependent Cox regression analysis was performed using the occurrence of adverse events as a time-varying covariate. All other covariates were treated as time-fixed and analyzed using standard Cox regression. AFP, alpha-fetoprotein; ALBI, albumin-bilirubin score; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; FIB-4, fibrosis-4 score; IPTW, inverse probability of treatment weighting; LC, liver cirrhosis; LN, lymph node; NLR, neutrophil to lymphocyte ratio; PIVKA-II, protein induced by vitamin K absence or antagonist-II; PVTT, portal vein tumor thrombosis.

In the subgroup analysis, patients who experienced grade 3 or higher irAEs demonstrated significantly worse OS than did those who experienced grade 1 or 2 irAEs after IPTW (HR: 25.4; 95% CI 8.40–76.77; $p < 0.001$; online suppl. Fig. 4). In addition, the OS of patients experiencing AE before the first response evaluation was shown in online supplementary Figure 5.

*Time-To-Progression*

Disease progression was observed in 146 of the 198 patients, including 9 patients (75.0%) in the asymptomatic AE group, 34 patients (60.7%) in the symptomatic AE group, and 103 patients (79.2%) in the non-AE group. The median TTP was 11.9 months in the asymptomatic AE group (95% CI: 10.4–not estimated, $p = 0.01$ compared with the non-AE group). In the symptomatic AE group, the median TTP was 14.1 months (95% CI: 9.7–21.1; $p < 0.001$ compared with the non-AE group). In the non-AE group, the median TTP was 4.8 months (95% CI: 3.5–6.6; Fig. 3a). According to the IPTW-adjusted time-dependent Cox regression analysis, both the asymptomatic AE group (HR: 0.52; 95% CI: 0.28–0.95; $p = 0.03$) and the symptomatic AE group (HR: 0.49; 95% CI: 0.24–0.99; $p = 0.047$) showed a significantly prolonged TTP compared with the non-AE group (Fig. 3d). Time-dependent multivariate Cox analyses after IPTW revealed that only asymptomatic AEs were independently associated with prolonged TTP (aHR: 0.52; 95% CI: 0.28–0.97; $p = 0.04$; online supplementary Table 3B). The TTP for patients who experienced AEs prior to the first response evaluation was presented in online supplementary Figure 7.

*Progression-Free Survival*

Disease progression or death occurred in 175 of the 198 patients, including 10 patients (83.3%) in the asymptomatic AE group, 45 patients (80.4%) in the symptomatic AE group, and 120 patients (92.3%) in the non-AE group. The median PFS was 11.4 months in the asymptomatic AE group (95% CI: 9.7–not estimated, $p < 0.001$ compared with the non-AE group) and 11.8 months in the symptomatic AE group (95% CI: 8.6–14.5; $p = 0.005$ compared with the non-AE group). In the non-AE group, the median PFS was 4.1 months (95% CI: 3.5–5.9; online suppl. Fig. 3A). According to the IPTW-adjusted time-dependent Cox regression analysis, only the asymptomatic AE group showed a significant improvement in PFS compared with the non-AE group (HR: 0.53; 95% CI: 0.30–0.93; $p = 0.03$; online suppl. Fig. 3D). Improved progression-free survival was independently associated with both the asymptomatic (HR: 0.51; 95% CI: 0.30–0.85; $p = 0.01$) and symptomatic AE groups (HR: 0.43; 95% CI: 0.22–0.84; $p = 0.01$; online suppl. Table 4), as demonstrated by IPTW-adjusted time-dependent multivariable Cox regression.

*Treatment Response*

Among the 12 patients with asymptomatic AEs, 8.3%, 33.3%, 58.3%, and 0.0% achieved complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), respectively. Among the 56 patients with symptomatic AEs, 3.6%, 23.2%, 66.1%, and 7.1% achieved CR, PR, SD, and PD, respectively. Among the 130 patients without AEs, 1.5%, 12.3%, 46.2%, and 40.0% achieved CR, PR, SD, and PD, respectively. These differences were statistically significant ($p < 0.001$; Table 3). The objective response rates (ORRs) also significantly differed among the groups, with rates of 41.7% in patients with asymptomatic AEs, 26.8% in those with symptomatic AEs, and 13.8% in patients without AEs ($p = 0.01$). Similarly, the DCR was significantly greater in patients with asymptomatic and symptomatic AEs than in those without AEs, with rates of 100%, 92.9%, and 60.0%, respectively ($p < 0.001$).

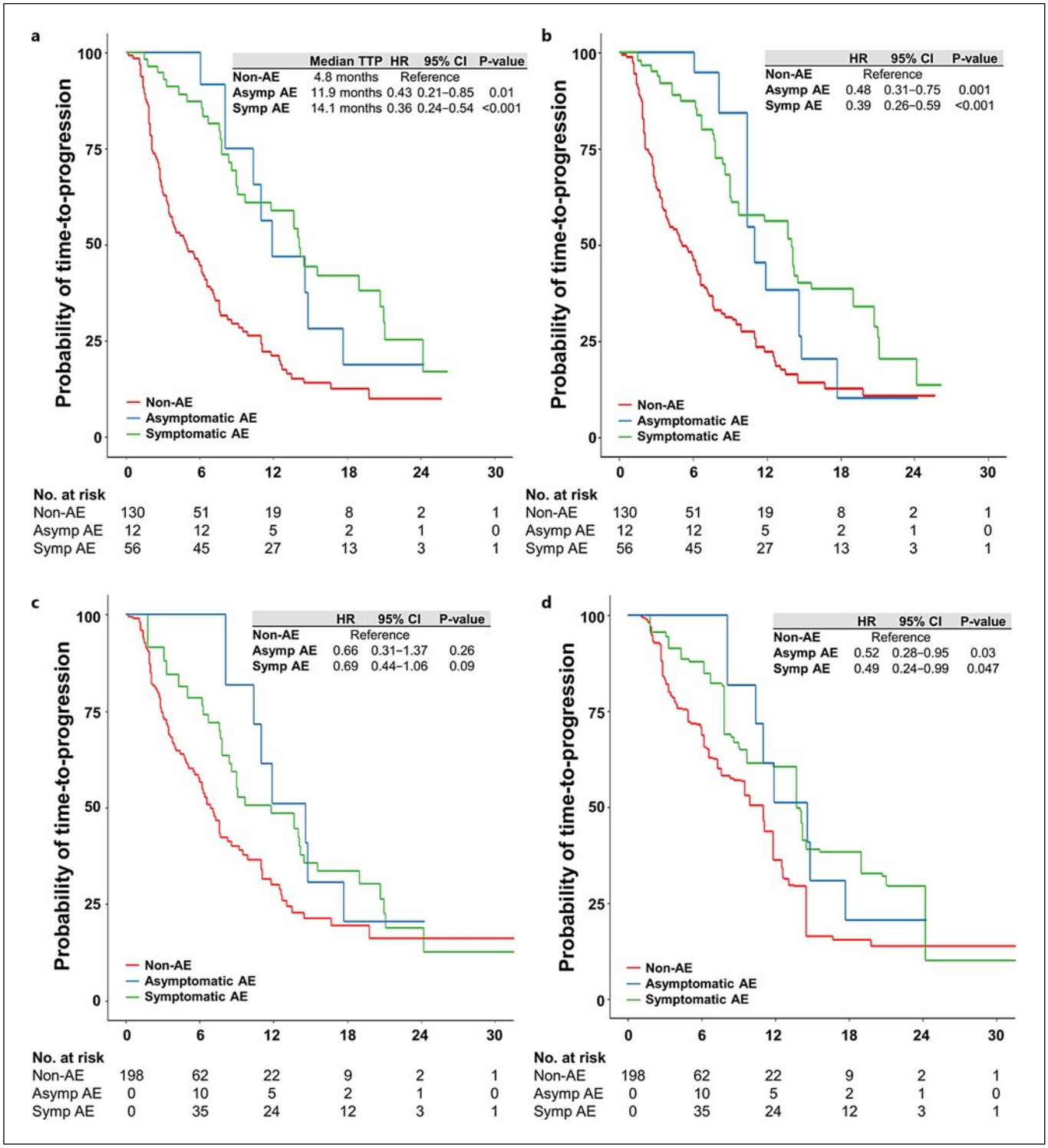


**Fig. 3.** TTP according to the occurrence of AEs: Kaplan-Meier estimates before (**a**) and after (**b**) IPTW, and Simon-Makuch plots based on time-dependent Cox regression analysis treating the occurrence of AEs as a time-varying covariate before (**c**) and after (**d**) IPTW.

**Table 3.** Treatment responses in HCC according to the atezolizumab plus bevacizumab related adverse events

| Parameter | Non-AE ($n$ = 130) | Asymptomatic AE ($n$ = 12) | Symptomatic AE ($n$ = 56) | $p$-value |
|---|---|---|---|---|
| Best objective response, *N* (%) | | | | <0.001 |
| Complete response | 2 (1.5%) | 1 (8.3%) | 2 (3.6%) | |
| Partial response | 16 (12.3%) | 4 (33.3%) | 13 (23.2%) | |
| Stable disease | 60 (46.2%) | 7 (58.3%) | 37 (66.1%) | |
| Progressive disease | 52 (40.0%) | 0 (0.0%) | 4 (7.1%) | |
| Objective response rate, *N* (%) | 18 (13.8%) | 5 (41.7%) | 15 (26.8%) | 0.01 |
| Disease control rate, *N* (%) | 78 (60.0%) | 12 (100.0%) | 52 (92.9%) | <0.001 |

AE, adverse events; HCC, hepatocellular carcinoma.

## Discussion

Atezolizumab plus bevacizumab was the first immunotherapy approved as the first-line systemic treatment for unresectable HCC, followed by the dual ICI combination of tremelimumab plus durvalumab [2, 3]. These advancements have established immunotherapy as a cornerstone in systemic treatment for unresectable HCC. However, the importance of AEs associated with immunotherapy has increased, with some studies suggesting that they may indicate better clinical outcomes [7–9, 27, 28]. Our study not only classified AEs into two categories – asymptomatic AEs, which were detected only on imaging, and symptomatic AEs, which were clinically apparent – but also included both irAEs and bevacizumab-related AEs to comprehensively evaluate their associations with the treatment outcomes. In this study, the occurrence of AEs was treated as a time-varying covariate, and clinical outcomes were analyzed using a time-dependent Cox proportional hazards model. After IPTW adjustment, both the asymptomatic and symptomatic AE groups had significantly improved OS, TTP, and PFS compared with the non-AE group. Approximately half of the AEs associated with atezolizumab plus bevacizumab occurred within the first 3 months of treatment, which is consistent with findings from previous studies [8, 29, 30]. In terms of treatment response, both the DCR and ORR were significantly greater in the asymptomatic and symptomatic AE groups than in the non-AE group. These findings suggest that AEs associated with atezolizumab plus bevacizumab may be indicative of better clinical outcomes. Moreover, asymptomatic AEs detected only through imaging studies could serve as factors suggesting an improved prognosis.

Immune functions, which are regulated by mechanisms of self-tolerance and the prevention of autoimmunity, are disrupted by the administration of ICIs [31]. This disruption results in excessive T-cell activation and proliferation [32, 33]. Concurrently, B cells are stimulated to produce autoantibodies [34, 35]. This sequence of events leads to the inadvertent targeting and damage of not only tumor cells but also normal cells, resulting in the development of irAEs [31]. Thus, the occurrence of irAEs, as demonstrated in this and several previous studies, indicates that the immune reaction caused by ICIs effectively exerts antitumor activity and is associated with better ICI efficacy and clinical outcomes [6, 8, 31]. However, not all irAEs are associated with a favorable prognosis. Grade 3 or higher irAEs have been linked to poor outcomes, whereas grade 1 or 2 irAEs, or those that are manageable, allow the continuation of ICI therapy, thus suggesting a better prognosis [8, 12]. In addition, when we analyzed irAEs that were asymptomatic and detectable only on imaging studies, we observed that compared with non-AEs, asymptomatic irAEs tended to improve OS and significantly prolonged the TTP. Asymptomatic irAEs detected only on imaging studies might be considered the mildest form of AE related to ICI therapy. On the basis of the results of this study, we cautiously suggest that meticulous monitoring of the occurrence of asymptomatic irAEs through imaging studies, even in the absence of clinical symptoms, is essential. Additionally, these findings indicate that both symptomatic and asymptomatic irAEs can serve as surrogate markers of a potentially favorable prognosis.

Bevacizumab inhibits angiogenesis by neutralizing all isoforms of human VEGF-A and preventing their interaction with VEGF receptors [36, 37]. Consequently, it blocks the formation of the vascular supply

of the tumor, thereby decelerating tumor growth [37, 38]. While irAEs vary on the basis of individual immunity [31, 39], bevacizumab-related AEs are known to be dose dependent [40, 41]. In a similar context, previous studies have suggested that titrating the dose of bevacizumab until the onset of arterial hypertension caused by its antiangiogenic effect may enhance antitumor efficacy and improve outcomes [27, 28]. In colorectal cancer, retrospective studies have demonstrated that bevacizumab-induced arterial hypertension may be correlated with improved clinical outcomes [10, 27, 28]. Our findings indicate that bevacizumab-related AEs, which appear progressively throughout the treatment period in proportion to dose accumulation, may enhance antitumor efficacy and improve outcomes.

As has been extensively investigated in previous studies, our study also revealed that hypothyroidism was the most common irAE associated with atezolizumab [31], whereas the most frequent asymptomatic irAE was pulmonary infiltration, suggesting pneumonitis. The AEs associated with bevacizumab in HCC patients predominantly include gastrointestinal bleeding, notably variceal bleeding, which likely results from bevacizumab-induced impairment of the vascular wall and alterations in the coagulation system [11, 42, 43]. Despite considerable efforts to identify risk factors associated with the occurrence of AEs, the diversity of mechanisms and side effects inherent to various diseases and anticancer agents has resulted in a persistent scarcity of data [5, 11, 31]. This is particularly the case for HCC patients treated with atezolizumab plus bevacizumab, where data on risk factors for AEs are markedly scarce [39]. In our study, univariable and multivariate Cox regression analyses were conducted to identify factors independently associated with the occurrence of AEs. Before IPTW adjustment, a low NLR, low PIVKA-II levels, and the presence of liver cirrhosis were identified as independent risk factors. However, after IPTW, no significant factors associated with the risk of AEs were found.

This study has several limitations as it was a retrospective study conducted at a single center. Nevertheless, this center is a major tertiary cancer center in South Korea that participated in the IMbrave 150 trial [2]. As such, this study included a substantial number of Korean patients who were treated with atezolizumab plus bevacizumab and benefited from a longer follow-up period than those reported in other real-world cohorts. In addition, given the overall limited sample size, we used IPTW adjustment to mitigate confounding and enhance the robustness of the analysis while preserving as much of the available data as possible [23, 24]. Korea, with its HBV-dominant HCC etiology, similar to that of other Asia–Pacific countries, may represent the region, but its distinct etiology from that of Western countries highlights the need for a globally integrated analysis of the results. Accordingly, future validation in larger scale, multicenter, and multinational cohorts is necessary to confirm the generalizability and global applicability of our findings. Furthermore, although irAEs can involve various organ systems, previous studies on radiological findings have focused mostly on specific organs, such as the lungs. In our study, imaging abnormalities alone were classified as asymptomatic irAEs only after thorough exclusion of other causes; however, the lack of established criteria for such radiological presentations alone remains a limitation. Further studies may be warranted to systematically explore and validate the radiological features of asymptomatic irAEs.

In conclusion, when appropriately managed, the AEs associated with atezolizumab plus bevacizumab in patients with unresectable HCC lead to significant improvements in OS, the TTP, and treatment response. Additionally, asymptomatic irAEs detected only on imaging may indicate a favorable prognosis, suggesting that proactive imaging studies could be advantageous.

## Statement of Ethics

This study involves human participants and was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. H-2307-071-1448). The requirement to obtain informed consent from patients was waived by the IRB due to the retrospective nature of this study.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


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## Author Contributions

The corresponding author, S.J.Y., has full access to all study data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. J.P., D.H.L., and S.J.Y. contributed to study concept, design, data analysis, and

interpretation and wrote the manuscript. J.P. and D.H.L. contributed to provision of study materials or patients. J.P., D.H.L., Y.K., H.S., M.H.H., Y.B.L., E.J.C., J.-H.L., Y.J.K., J.-H.Y., and S.J.Y. collected and managed the study data. J.P., D.H.L., and S.J.Y. contributed to data analysis and interpretation and wrote the manuscript.

## Data Availability Statement

All data generated or analyzed during this study are included in this article and its supplementary material files. Further inquiries can be directed to the corresponding author.

## References


1 Singal AG, Kanwal F, Llovet JM. Global trends in hepatocellular carcinoma epidemiology: implications for screening, prevention and therapy. Nat Rev Clin Oncol. 2023;20(12):864–84. https://doi.org/10.1038/s41571-023-00825-3

2 Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. N Engl J Med. 2020;382(20):1894–905. https://doi.org/10.1056/NEJMoa1915745

3 Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. NEJM Evid. 2022;1(8):EVIDoa2100070. https://doi.org/10.1056/EVIDoa2100070

4 Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378(2):158–68. https://doi.org/10.1056/NEJMra1703481

5 Matsuoka H, Hayashi T, Takigami K, Imaizumi K, Shiroki R, Ohmiya N, et al. Correlation between immune-related adverse events and prognosis in patients with various cancers treated with anti PD-1 antibody. Bmc Cancer. 2020;20:656–8. https://doi.org/10.1186/s12885-020-07142-3

6 Daniello L, Elshiaty M, Bozorgmehr F, Kuon J, Kazdal D, Schindler H, et al. Therapeutic and prognostic implications of immune-related adverse events in advanced non-small-cell lung cancer. Front Oncol. 2021;11:703893. https://doi.org/10.3389/fonc.2021.703893

7 Tada T, Kumada T, Hiraoka A, Hirooka M, Kariyama K, Tani J, et al. Adverse events as potential predictive factors of therapeutic activity in patients with unresectable hepatocellular carcinoma treated with atezolizumab plus bevacizumab. Cancer Med. 2023;12(7):7772–83. https://doi.org/10.1002/cam4.5535

8 Nam H, Lee J, Han JW, Lee SK, Yang H, Lee HL, et al. Analysis of immune-related adverse events of atezolizumab and Bevacizumab in patients with hepatocellular carcinoma: a multicentre cohort Study. Liver Cancer. 2024;13(4):413–25. https://doi.org/10.1159/000535839

9 Persano M, Rimini M, Tada T, Suda G, Shimose S, Kudo M, et al. Adverse events as potential predictive factors of activity in patients with advanced HCC treated with Atezolizumab plus Bevacizumab. Target Oncol. 2024;19(4):645–59. https://doi.org/10.1007/s11523-024-01061-0

10 Dewdney A, Cunningham D, Barbachano Y, Chau I. Correlation of bevacizumab-induced hypertension and outcome in the BOXER study, a phase II study of capecitabine, oxaliplatin (CAPOX) plus bevacizumab as perioperative treatment in 45 patients with poor-risk colorectal liver-only metastases unsuitable for upfront resection. Br J Cancer. 2012;106(11):1718–21. https://doi.org/10.1038/bjc.2012.152

11 Taugourdeau-Raymond S, Rouby F, Default A, Jean-Pastor MJ, French Network of Pharmacovigilance Centers. Bevacizumab-induced serious side-effects: a review of the French pharmacovigilance database. Eur J Clin Pharmacol. 2012;68(7):1103–7. https://doi.org/10.1007/s00228-012-1232-7

12 Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. JAMA Oncol. 2018;4(12):1721–8. https://doi.org/10.1001/jamaoncol.2018.3923

13 Gosangi B, McIntosh L, Keraliya A, Irugu DVK, Baheti A, Khandelwal A, et al. Imaging features of toxicities associated with immune checkpoint inhibitors. Eur J Radiol Open. 2022;9:100434. https://doi.org/10.1016/j.ejro.2022.100434

14 Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018;67(1):358–80. https://doi.org/10.1002/hep.29086

15 Korean Liver Cancer Association KLCA and National Cancer Center NCC Korea. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. Clin Mol Hepatol. 2022;28(4):583–705. https://doi.org/10.3350/cmh.2022.0294

16 Casak SJ, Donoghue M, Fashoyin-Aje L, Jiang X, Rodriguez L, Shen YL, et al. FDA approval summary: atezolizumab plus bevacizumab for the treatment of patients with advanced unresectable or metastatic hepatocellular carcinoma. Clin Cancer Res. 2021;27(7):1836–41. https://doi.org/10.1158/1078-0432.CCR-20-3407

17 Benson AB, D'Angelica MI, Abbott DE, Anaya DA, Anders R, Are C, et al. Hepatobiliary cancers, version 2.2021, NCCN Clinical Practice Guidelines in oncology. J Natl Compr Canc Netw. 2021;19(5):541–65. https://doi.org/10.6004/jnccn.2021.0022

18 Cheng AL, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. J Hepatol. 2022;76(4):862–73. https://doi.org/10.1016/j.jhep.2021.11.030

19 Sangro B, Chan SL, Meyer T, Reig M, El-Khoueiry A, Galle PR. Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma. J Hepatol. 2020;72(2):320–41. https://doi.org/10.1016/j.jhep.2019.10.021

20 Gordon MS, Cunningham D. Managing patients treated with bevacizumab combination therapy. Oncology. 2005;69(Suppl 3):25–33. https://doi.org/10.1159/000088481

21 Tang YZ, Szabados B, Leung C, Sahdev A. Adverse effects and radiological manifestations of new immunotherapy agents. Br J Radiol. 2019;92(1093):20180164. https://doi.org/10.1259/bjr.20180164

22 Shroff GS, Strange CD, Ahuja J, Altan M, Sheshadri A, Unlu E, et al. Imaging of immune checkpoint inhibitor immunotherapy for non-small cell lung cancer. Radiographics. 2022 Nov-Dec;42(7):1956–74. https://doi.org/10.1148/rg.220108

23 Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015;34(28):3661–79. https://doi.org/10.1002/sim.6607

24 Austin PC. Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. Stat Med. 2016;35(30):5642–55. https://doi.org/10.1002/sim.7084

25 D'Agostino RB, Lee ML, Belanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. Stat Med. 1990;9(12):1501–15. https://doi.org/10.1002/sim.4780091214

26 Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. Ann Transl Med. 2018;6(7):121. https://doi.org/10.21037/atm.2018.02.12
27 Scartozzi M, Galizia E, Chiorrini S, Giampieri R, Berardi R, Pierantoni C, et al. Arterial hypertension correlates with clinical outcome in colorectal cancer patients treated with first-line bevacizumab. Ann Oncol. 2009;20(2):227–30. https://doi.org/10.1093/annonc/mdn637
28 Österlund P, Soveri L, Isoniemi H, Poussa T, Alanko T, Bono P. Hypertension and overall survival in metastatic colorectal cancer patients treated with bevacizumab-containing chemotherapy. Br J Cancer. 2011;104(4):599–604. https://doi.org/10.1038/bjc.2011.2
29 Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M, et al. Management of immune-related adverse events in patients treated with immune Checkpoint Inhibitor Therapy: ASCO Guideline update. J Clin Oncol. 2021;39(36):4073–126. https://doi.org/10.1200/JCO.21.01440
30 Tang SQ, Tang LL, Mao YP, Li WF, Chen L, Zhang Y, et al. The pattern of time to onset and resolution of immune-related adverse events caused by immune checkpoint inhibitors in cancer: a pooled analysis of 23 clinical trials and 8,436 patients. Cancer Res Treat. 2021;53(2):339–54. https://doi.org/10.4143/crt.2020.790
31 Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chávez A, Keegan N, Khamashta MA, et al. Immune-related adverse events of checkpoint inhibitors. Nat Rev Dis Primers. 2020;6(1):38. https://doi.org/10.1038/s41572-020-0160-6
32 Latchman YE, Liang SC, Wu Y, Chernova T, Sobel RA, Klemm M, et al. PD-L1-deficient mice show that PD-L1 on T cells, antigen-presenting cells, and host tissues negatively regulates T cells. Proc Natl Acad Sci U S A. 2004;101(29):10691–6. https://doi.org/10.1073/pnas.0307252101
33 Weber J. Immune checkpoint proteins: a new therapeutic paradigm for cancer—preclinical background: CTLA-4 and PD-1 blockade. Elsevier; 2010. Vol. 37; p. 430–9. https://doi.org/10.1053/j.seminoncol.2010.09.005. Semin Oncol5.
34 Das R, Bar N, Ferreira M, Newman AM, Zhang L, Bailur JK, et al. Early B cell changes predict autoimmunity following combination immune checkpoint blockade. J Clin Investig. 2018;128(2):715–20. https://doi.org/10.1172/JCI96798
35 Petersone L, Edner NM, Ovcinnikovs V, Heuts F, Ross EM, Ntavli E, et al. T Cell/B cell Collaboration and autoimmunity: an intimate relationship. Front Immunol. 2018;9:1941. https://doi.org/10.3389/fimmu.2018.01941
36 Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med. 2003;9(6):669–76. https://doi.org/10.1038/nm0603-669
37 Garcia J, Hurwitz HI, Sandler AB, Miles D, Coleman RL, Deurloo R, et al. Bevacizumab (Avastin®) in cancer treatment: a review of 15 years of clinical experience and future outlook. Cancer Treat Rev. 2020;86:102017. https://doi.org/10.1016/j.ctrv.2020.102017
38 Ferrara N, Hillan KJ, Gerber HP, Novotny W. Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer. Nat Rev Drug Discov. 2004;3(5):391–400. https://doi.org/10.1038/nrd1381
39 Chennamadhavuni A, Abushahin L, Jin N, Presley CJ, Manne A. Risk factors and biomarkers for immune-related adverse events: a practical guide to identifying high-risk patients and rechallenging immune checkpoint inhibitors. Front Immunol. 2022;13:779691. https://doi.org/10.3389/fimmu.2022.779691
40 Kabbinavar FF, Schulz J, McCleod M, Patel T, Hamm JT, Hecht JR, et al. Addition of bevacizumab to bolus fluorouracil and leucovorin in first-line metastatic colorectal cancer: results of a randomized phase II trial. J Clin Oncol. 2005;23(16):3697–705. https://doi.org/10.1200/JCO.2005.05.112
41 Maitland ML, Ratain MJ. Terminal ballistics of kinase inhibitors: there are no magic bullets. Ann Intern Med. 2006;145(9):702–3. https://doi.org/10.7326/0003-4819-145-9-200611070-00015
42 Shord SS, Bressler LR, Tierney LA, Cuellar S, George A. Understanding and managing the possible adverse effects associated with bevacizumab. Am J Health Syst Pharm. 2009;66(11):999–1013. https://doi.org/10.2146/ajhp080455
43 Hapani S, Sher A, Chu D, Wu S. Increased risk of serious hemorrhage with bevacizumab in cancer patients: a meta-analysis. Oncology. 2010;79(1–2):27–38. https://doi.org/10.1159/000314980