Clinical effects and emerging issues of atezolizumab plus bevacizumab in patients with advanced hepatocellular carcinoma from Japanese real-world practice

(進行肝細胞癌に対する Atezolizumab/Bevacizumab 併用療法における有効性の検証と新たな臨床的課題の探索を目的とした本邦の実臨床コホートの解析)

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ABSTRACT

Background and Aims: Although the efficacy of atezolizumab has been demonstrated in randomized controlled trials, its long-term efficacy and association with adverse events in real-world practice are unknown. This study was to designed to shed light on these issues.

Methods: In this multicenter retrospective study, data were collected data from patients with advanced hepatocellular carcinoma treated with atezolizumab plus bevacizumab in seven institutions in Japan. The authors focused on the efficacy and adverse events related to vascular endothelial growth factor (VEGF) inhibition.

Results: A total of 123 patients were enrolled in this study. The median progression-free survival (PFS) for the first-line treatment group was 8.0 months (95% confidence interval (CI) 6.1–9.9), whereas the median PFS for the second- or later-line treatment group was 4.1 months (95% CI 2.6–5.7), which was significantly worse than that of the first-line treatment group ($p = 0.005$). Twenty-seven patients had interrupted bevacizumab treatment. Proteinuria accounted for the largest proportion of bevacizumab treatment interruptions. The cumulative incidence rate of bevacizumab interruption due to anti-VEGF-related adverse events was significantly higher in patients with hypertension and/or diabetes mellitus than in those without ($p = 0.026$). The landmark analysis showed that patients experienced bevacizumab interruption by 24 weeks from treatment initiation had poorer PFS than those who did not ($p = 0.013$).

Conclusion: The PFS of atezolizumab plus bevacizumab as first-line treatment mostly replicates that of a global phase 3 trial. Interrupted bevacizumab treatment was more common in patients with hypertension and/or diabetes mellitus, which may be associated with worsening long-term PFS.

Keywords: hepatocellular carcinoma, atezolizumab, bevacizumab, hypertension, diabetes mellitus, proteinuria, anti-VEGF agent

INTRODUCTION

Liver cancer including hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, and its incidence and mortality are still increasing.[1, 2] HCC is the major type of primary liver cancer, and it occurs predominantly in patients with a background of chronic liver disease caused by hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, alcohol abuse, or metabolic syndrome. The incidence rates of HBV- and HCV-related HCCs have reduced in some countries and regions including Japan, because of focused infection prevention measures and significant progress in antiviral treatments over the past few decades.[3–6] However, there has been a marked increase in nonviral hepatitis mostly caused by metabolic syndrome in developed countries. The trend is particularly marked in Japan, where HCC-causing nonviral hepatitis is increasing dramatically.[7] Thus far, unfortunately, many patients with HCC are still diagnosed after having more advanced disease, although several guidelines recommend surveillance of high risk populations for the early detection of HCC.[3, 8, 9] Therefore, progress in systemic therapy is essential to prolong the prognosis of patients with advanced HCC.

Systemic therapies for advanced HCC have gradually improved from the late 2000s to the 2010s, with several molecular target agents showing efficacy. During this period, four tyrosine kinase inhibitors (i.e., sorafenib, regorafenib, lenvatinib, and cabozantinib) and one anti-VEGFR-2 monoclonal antibody (ramucirumab) became the standard treatment options for advanced HCC.[10–15] However, the development of immunotherapy for advanced HCC lagged behind other malignancies due to the failure of two phase 3 trials of anti-PD-1 antibody monotherapy (nivolumab and

pembrolizumab).[16,17] In 2019, a global phase 3 trial (IMbrave 150) demonstrated that atezolizumab plus bevacizumab, combination immunotherapy with anti-PD-L1 antibody and anti-VEGF monoclonal antibody, significantly prolonged the overall survival (OS) compared with sorafenib alone in patients with advanced HCC.[18,19] Nowadays, atezolizumab plus bevacizumab is recommended as the first choice for the first-line treatment of advanced HCC by guidelines worldwide.[20, 21]

In Japan, more than a year has passed since atezolizumab plus bevacizumab was approved by the regulatory authority and made available for administration in real-world practice. When new agents become available in the field practice, it is clinically meaningful to clarify their efficacy and emerging clinical issues in a real-world clinical setting that differs from clinical trials after a certain period since the new agent was approved. Thus, this study aimed to verify the effect and illustrate clinical issues of atezolizumab plus bevacizumab for advanced HCC by using a Japanese cohort of real-world clinical practice.

PATIENTS AND METHODS

Patients

We retrospectively collected data from patients with advanced HCC treated with atezolizumab plus bevacizumab as first-line or second- or later-line between October 2020 and April 2021 at seven institutions in Japan. Data collection was cut off at the end of October 2021. This study was conducted with the approval of the Research Ethics Committee of the Graduate School of Medicine, Chiba University (No. 3091). Patient data were anonymized and decharacterized for analysis.

Treatment with atezolizumab plus bevacizumab

Patients were administered 1200 mg of atezolizumab plus 15 mg per kilogram of body weight of bevacizumab every 3 weeks.[18] Although Child–Pugh class A is recommended at the start of atezolizumab plus bevacizumab treatment, Child–Pugh class B was used at the discretion of the specialist and with the patient's full informed consent. Contrast-enhanced computed tomography or magnetic resonance imaging was performed to assess tumor response immediately before the initiation and every 6–9 weeks after the initiation of treatment. Although each physician's decision was final, the starting dose and withdrawal/interruption criteria of atezolizumab plus bevacizumab were determined in this study based on the *Guide for Appropriate Use of Atezolizumab Plus Bevacizumab* in patients with unresectable HCC developed for Japanese Physicians by Chugai Pharmaceutical CO, LTD in accordance with the protocol of IMbrave 150.

Clinical parameters

In this study, the following clinical parameters were retrospectively collected from seven institutions: baseline demographic data of atezolizumab plus bevacizumab (e.g., sex, age, etiology, complications, Eastern Cooperative Oncology Group performance status, Child–Pugh class, radiological assessment, α-fetoprotein (AFP), and treatment before atezolizumab plus bevacizumab initiation), adverse events (AE) after the initiation of atezolizumab plus bevacizumab, date of radiological progression, and date of death or last follow-up. Metabolic dysfunction-associated fatty liver disease (MAFLD) was identified based on the latest definition.[22] Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) was extracted from the medical history in patients both without a history of alcohol consumption and without the diagnosis of other chronic liver diseases including viral hepatitis and autoimmune hepatitis according to the guideline.[23] We also conducted a pathological diagnosis of NASH in patients for whom clinical samples were available for NAFLD/NASH.[22]

Radiological assessments were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[24] The clinical benefit rate (CBR) was defined as the percentage of patients who have achieved complete response, partial response, or stable disease ≥6 months.[25] AEs were evaluated following the Common Terminology Criteria for Adverse Events version 5.0. At least two physicians retrospectively assessed the radiological findings to provide a more unbiased evaluation: the physician in charge at each institution and the physician at Chiba University Hospital, a high-volume

center for advanced HCC (M.N.). Two or more physicians evaluated the radiological assessments at Chiba University Hospital (including M.N.).

We identified immune-related AEs and bevacizumab-related AEs among all AEs associated with atezolizumab plus bevacizumab treatment during the observation period. Immune-related AEs were determined based on a previous report.[26] Bevacizumab-related AEs were assumed to be hypertension, proteinuria, bleeding, and thrombosis, which were typical AEs caused by anti-VEGF agents. We also evaluated the occurrence of hepatic dysfunction, which was defined as ascites, jaundice, or hepatic encephalopathy of grade 3 or higher.

Statistical analysis

Kaplan–Meier plots of medians with 95% confidence intervals (CIs) were used to estimate the OS. The censoring date was defined as the date of the last follow-up. Progression-free survival (PFS) after atezolizumab plus bevacizumab was estimated using Kaplan–Meier plots of medians with 95% CIs, with the progression date defined according to RECIST and the censoring date defined as the date of the last radiological assessment without progression. Cox proportional hazards regression model was used to estimating the hazard ratio of PFS with atezolizumab plus bevacizumab and identify factors that prevent bevacizumab from being administered on schedule while being under atezolizumab plus bevacizumab. All reported p values are two sided, and p value less than 0.05 was considered significant. All statistical analyses were conducted using IBM SPSS Statistics for Windows, version 25 (IBM Corp,

Armonk, New York, USA).

RESULTS

Patient background and characteristics

Between October 2020 and April 2021, 123 patients were identified as receiving atezolizumab plus bevacizumab for advanced HCC in seven Japanese institutions. Table 1 shows the patient background and characteristics. The median age was 73 years, 102 patients (82.9%) were male, and 114 patients (92.7%) were classified as having Child–Pugh A. The most common etiology was HCV in 37 patients (30.1%), followed by HBV in 24 patients (19.5%), and NAFLD/NASH in 21 patients (17.1%). We identified 50 (40.7%) patients with MAFLD and 10 (8.1%) with clinically confirmed NASH. At the start of atezolizumab plus bevacizumab treatment, 82 (66.7%) patients had hypertension and 46 (38.2%) had diabetes as a comorbidity. According to baseline radiological assessments, macrovascular invasion and extrahepatic metastasis were found in 34 (27.6%) and 51 (41.5%) patients, respectively. In the present cohort, atezolizumab plus bevacizumab was introduced in 60 patients (48.8%) as first line, 63 patients (51.2%) as the second- or later-line. We also subdivided the patients into two groups: those who met the eligibility criteria of the IMbrave 150 trial and those who did not (IMbrave 150 trial "in" group: 57 patients [46.3%] and "out" group: 66 patients [53.7%]).[18] The baseline characteristics of both the groups are shown in Table S1. Most patients in the IMbrave 150 "out" group received atezolizumab plus bevacizumab as a second- or later-line of treatment (63 or 66 patients [95.5%]).

The median observation period to data cutoff was 7.6 (95% CI 7.0–8.2) months, and 89 patients (72.3%) had discontinued atezolizumab plus bevacizumab; 58 (47.2%) patients had

discontinued treatment due to disease progression and 24 (19.5%) due to AE.

Efficacy of atezolizumab plus bevacizumab

We assessed the best radiological assessments according to RECIST version 1.1 of 114 patients, excluding nine patients for whom appropriate radiological evaluation was unavailable (Table S2). In the present cohort, the objective response rate (ORR), disease control rate (DCR), and CBR were 15.8% (18 patients), 81.6% (93 patients), and 35.1% (40 patients), respectively. A spider plot of the change in the sum of the tumor diameter of target lesions in 18 patients who achieved objective response is shown in Figure 1A. The median time to response was 3.5 (95% CI 2.7–4.2) months. Additionally, the spider plot of two patients with the pseudo-progression disease is illustrated in Figure 1B.

Figure 2 shows the response rate and PFS by treatment line. The ORR, DCR, and CBR in patients who received atezolizumab plus bevacizumab as the first-line treatment were 28.1%, 89.5%, 43.9%, and those received as second- or later-line treatment were 3.5%, 73.7%, and 26.3%, respectively (Figure 2A). Response rates in patients with second- or later-line treatment were markedly lower than in those with first-line treatment. Furthermore, no obvious difference was found in the response rates by underlying liver disease (Figure S1). The median PFS of patients who received atezolizumab plus bevacizumab as first-line treatment was significantly longer than that of patients with second- or later-line treatment (whole population, 5.9 months (95% CI 4.9–7.0); first-line, 8.0 months (95% CI 6.1–9.9); second- or later-line, 4.1 (95% CI 2.6–5.7), $p = 0.005$) (Figure 2B). Similarly, the comparison of

the ORR, DCR, CBR, and PFS in the IMbrave “in” and “out” groups are shown in Figure S2. The multivariate analysis confirmed the previous history of systemic therapy as an independent poor prognostic factor of PFS in patients with advanced HCC treated with atezolizumab plus bevacizumab (Table S3). The median OS of our cohort was 11.0 months (95% CI not reached). Further analysis by treatment line showed that the median OS for the first-line treatment was not reached and that for the second- and later-line treatments was 8.5 (7.0–10.0) months.

Safety of atezolizumab plus bevacizumab in the present cohort

Table S4 shows the AEs that occurred during the observation period. The most frequently occurring AEs (occurred in >40% of patients) were elevated levels of aspartate aminotransferase (AST; 54.5%), proteinuria (52.0%), fatigue (49.6%), hypoalbuminemia (43.9%), appetite loss (42.3%), and elevated levels of alanine aminotransferase (ALT; 42.3%). The most common AEs of grade 3 or higher AEs (occurred in >5% of patients) were elevated AST levels (9.8%), hypertension (9.8%), and proteinuria (8.1%), elevated ALT levels (6.6%), decreased platelet count (5.7%), and increased blood bilirubin levels (5.7%). In Table S5, we also show the results of AEs for the IMbrave 150 “in" and “out” groups. Figure 3 shows the onset timing of representative immune-related AEs and bevacizumab-related AEs observed in our cohort.

During the observation period, 24 (19.5%) patients required permanent treatment discontinuation due to AEs. Of these, treatment was discontinued in nine and four patients because of

immune-related and anti-VEGF-related AEs, respectively. Various immune-related AEs caused treatment discontinuation. The most common cause of treatment discontinuation due to anti-VEGF-related AEs was severe bleeding (three patients). Moreover, 27 (22.0%) patients had interrupted bevacizumab treatment. Of these, 18 (66.6%) patients had interrupted bevacizumab treatment because of anti-VEGF-related AEs, and the most common causes of interrupted bevacizumab treatment due to anti-VEGF-related AEs were proteinuria (15 patients, 55.6%), bleeding (two patients, 7.4%), and thrombosis (one patient, 3.7%).

We analyzed baseline clinical parameters contributing to interrupted bevacizumab treatment in patients with advanced HCC treated with atezolizumab plus bevacizumab. The multivariate analysis indicated that patients with comorbidities of either or both hypertension and diabetes mellitus at the time of treatment initiation were independent risk factors for interrupted bevacizumab treatment (Table S6). Figure 4A shows the cumulative incidence rate of interrupted bevacizumab treatment in patients with comorbidities of either or both hypertension and diabetes mellitus at the time of atezolizumab plus bevacizumab treatment initiation Furthermore, the cumulative incidence of interrupted bevacizumab treatment due to anti-VEGF-related AEs was significantly higher in patients with either or both hypertension and diabetes mellitus than in patients without both hypertension and diabetes mellitus ($p = 0.026$).

Effect of interrupted bevacizumab treatment on PFS in patients with advanced HCC treated with

atezolizumab plus bevacizumab

We performed landmark analyses of PFS at four time points (6, 12, 18, and 24 weeks) to verify the effect of an interrupted bevacizumab treatment before that time on PFS (Figure 5). No significant difference was found in subsequent PFS between interrupted bevacizumab treatment within 6 or 12 weeks. However, interestingly, PFS after 18 weeks tended to be shorter in patients who had interrupted bevacizumab treatment within 18 weeks than in those who had not, and PFS after 24 weeks was significantly shorter in patients who had interrupted bevacizumab within 24 weeks than in those who could continue bevacizumab ($p = 0.013$).

DISCUSSION

This multicenter retrospective study in Japan verified the safety and efficacy of atezolizumab plus bevacizumab in patients with advanced HCC in real-world practice. We demonstrated that the PFS of patients with advanced HCC who received first-line treatment with atezolizumab plus bevacizumab was significantly longer than that in patients who received it as second- or later-line treatment in Japanese real-world practice. Under the current Japanese health care system, anticancer systemic therapies that have been approved for first-line treatment can be used for patients with coverage under universal health care insurance, regardless of their past treatment history. In the past, many patients received lenvatinib as second- or later-line treatment shortly after it was approved as the first-line agent for advanced HCC.[27] Thus far, immediately after approval, atezolizumab plus bevacizumab has been used in many cases as post-treatment for patients who already received other systemic therapies.

To the best of our knowledge, only a few studies have suggested that the efficacy of immunotherapy was reduced when used after other systemic therapies for other malignancies because immunotherapy is the first-line systemic therapy in most cases. In randomized controlled phase 3 trials of immune checkpoint inhibitor monotherapies, the PFS was almost equivalent to 3.8 months for nivolumab as first-line treatment and 3.0 months for pembrolizumab as second-line treatment after sorafenib.[16, 17] Yamada et al. reported that the efficacy of atezolizumab plus bevacizumab might be limited in patients with advanced HCC with a treatment history of tyrosine kinase inhibitor.[28] The initial report with its short observation period, including 20 patients, showed differences in ORRs according

to RECIST version 1.1 between the first-line treatment group and second- or later-line treatment group (26% VS. 0%). One study of real-world data on non-small cell lung cancer from China demonstrated that the efficacy of immunotherapies was poorer after second- or later-line treatment than after first-line treatment.[29] Taken together with these data and our results, the efficacy of atezolizumab plus bevacizumab may not be expected to be sufficient if atezolizumab plus bevacizumab is used after other systemic therapies. Nowadays, the majority of patients with advanced HCC selected atezolizumab plus bevacizumab as first-line systemic therapy in Japanese clinical practice based on the guidelines. Atezolizumab plus bevacizumab should be administered as a first-line treatment unless there is a particular reason that prevents its use.

In the present cohort, the PFS of the first-line treatment group was 8.0 months (95% CI 6.1–9.9). Our result was concordant with the PFS of a similar population of latest studies from Japan (8.0–8.8 months).[30, 31] Interestingly, the PFS in the first-line setting of real-world data from Japan including ours was slightly longer than that of the updated analysis of IMbrave 150 with a PFS of 6.9 months.[19] The background of patients treated with atezolizumab plus bevacizumab in Japanese clinical practice might be different from those in a global phase 3 trial.[18] Moreover, approximately half of the patients had macrovascular invasion, extrahepatic metastasis, or AFP > 400 ng/mL as tumor aggressiveness. Conversely, the frequencies of the three aforementioned parameters representing tumor aggressiveness were often lower than those in global clinical trials of patients with advanced HCC treated with atezolizumab plus bevacizumab in Japanese clinical practice. We considered that these differences in

patients' background between IMbrave 150 and Japanese clinical practice might be associated with gaps in PFS of the first-line setting in patients with advanced HCC treated with atezolizumab plus bevacizumab.

Our study demonstrated that having comorbidities of hypertension and/or diabetes mellitus at the starting point was significantly correlated to the interruption of bevacizumab during atezolizumab plus bevacizumab treatment. Similarly, we found a significantly higher cumulative incidence of interrupted bevacizumab treatment due to anti-VEGF-related AEs in patients with hypertension and/or diabetes mellitus than in those without both comorbidities. A previous report indicated that hypertension and diabetes mellitus were associated with proteinuria caused by bevacizumab in the pooled analysis of randomized controlled trials of various malignancies.[32] In the present cohort, proteinuria was one of the most common AEs of grade 3 or higher and was the leading cause of interrupted bevacizumab treatment in patients with advanced HCC treated with atezolizumab plus bevacizumab. Proteinuria is a common AE occurring after inhibition of VEGF signaling and reflects severe glomerular damage.[33] Proteinuria due to anti-VEGF agents is one of the leading AEs that make the continuation of systemic treatment with anti-VEGF agents difficult in not only HCC but also other malignancies.[34] Recently, the main cause of HCC in developed countries including Japan has shifted to fatty liver associated with lifestyle-related diseases, and naturally, most of these patients with HCC have comorbid hypertension and diabetes mellitus. Taken together, the management of anti-VEGF-related AEs, mainly proteinuria, during systemic treatment with anti-VEGF agents containing atezolizumab plus bevacizumab in

patients with HCC with comorbid hypertension and diabetes mellitus will be a more focused clinical issue. Anti-VEGF-related AEs were reported to be dose-dependent in a recent study.[35] Considering the future effects of systemic therapies with immune checkpoint inhibitors and anti-VEGF agents on HCC, the dose reduction for populations at a high risk of anti-VEGF-related AEs may be discussed for antibody drugs. Because antibody agents including bevacizumab have a long half-time and moderating the action of anti-VEGF is challenging, treatment of anti-VEGF-related AEs with tyrosine kinase inhibitor, a small molecule compound with the action of anti-VEGF, in combination with an immune checkpoint inhibitor, may be easier.

We also found a significant difference in the PFS 24 weeks from the initiation of atezolizumab plus bevacizumab depending on bevacizumab treatment interruption within 24 weeks. Taken together with the same analyses of data obtained at 6, 12, and 18 weeks, the effect of interrupted bevacizumab treatment on PFS tended to increase with treatment duration. Hatanaka et al. demonstrated a difference in PFS depending on bevacizumab treatment interruption within 9 weeks.[36] Although the number of their patients was larger than in our cohort, they did not demonstrate the effect of interrupted bevacizumab treatment in the long term because of their short observation period. We considered that our results were clinically meaningful, suggesting the possibility that efficacy might decrease if bevacizumab treatment was interrupted, even in cases in which atezolizumab plus bevacizumab was theoretically effective.

In conclusion, the PFS of atezolizumab plus bevacizumab for the first-line treatment group

was shown to mostly replicate that of IMbrave 150 in Japanese patients with advanced HCC; however, the PFS of the second- or later-line treatment group was significantly worse than that of the first-line treatment group. Bevacizumab was often interrupted in patients with either or both hypertension and diabetes mellitus. Additionally, interrupted bevacizumab treatment might be a risk for impaired treatment efficacy of atezolizumab plus bevacizumab over the long term in patients with advanced HCC. We hope that these results will be confirmed by further large numbers of cases, extended observation periods, and prospective studies, and will be useful for the treatment of advanced HCC.

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TABLES

Table 1. Baseline characteristics of advanced hepatocellular carcinoma patients who received atezolizumab plus bevacizumab.

Supplementary Table 1. Baseline characteristics of patients with advanced hepatocellular carcinoma receiving atezolizumab plus bevacizumab (IMbrave 150 “in” and “out” groups).

Supplementary Table 2. Radiological response according to RECIST version 1.1.

Supplementary Table 3. Cox regression analysis of factors for PFS in this cohort.

Supplementary Table 4. Adverse events due to atezolizumab plus bevacizumab.

Supplementary Table 5. Adverse events due to atezolizumab plus bevacizumab (IMbrave 150 “in” and “out” groups).

Supplementary Table 6. Cox regression analysis of factors for discontinuation of bevacizumab in this cohort.

FIGURE LEGENDS

Figure 1. Spider plots of sum of tumor diameters based on RECIST1.1. (A) The red line shows patients who achieved an objective response. (B) The red line shows patients with confirmed pseudo-progression.

Figure 2. Comparison of efficacy by treatment line. (A) Tumor response according to RECIST 1.1 in the first-line and second- or later-line treatment group. (B) Kaplan–Meier curve of the progression-free survival of the first-line and second- or later-line treatment group with advanced hepatocellular carcinoma treated with atezolizumab plus bevacizumab.

Figure 3. Onset of adverse events caused by atezolizumab plus bevacizumab in patients with advanced hepatocellular carcinoma. The black lines show immune-related adverse events. The blue lines show anti-VEGF-related adverse events. The red line shows hepatic failure.

Figure 4. Association of bevacizumab interruption and baseline comorbidities. (A) Cumulative incidence rate of interrupted bevacizumab treatment (patients with comorbidities of either or both hypertension and diabetes mellitus at the time of treatment initiation vs. patients without comorbidities of both hypertension and diabetes mellitus at the time of treatment initiation). (B) Cumulative incidence rate of interrupted bevacizumab treatment due to anti-VEGF-related adverse events (patients with

comorbidities of either or both hypertension and diabetes mellitus at the time of treatment initiation vs. patients without comorbidities of both hypertension and diabetes mellitus at the time of treatment initiation). VEGF, vascular endothelial growth factor.

Figure 5. Effect of interrupted bevacizumab treatment before 6 weeks (A), 12 weeks (B), 18 weeks (C), and 24 weeks (D) on progression-free survival.

Supplementary Figure 1. Tumor response according to etiologies at the initiation of atezolizumab plus bevacizumab.

Supplementary Figure 2. Comparison of efficacy between the IMbrave 150 “in” and “out” groups. (A) Tumor response according to RECIST 1.1. (B) Kaplan–Meier curve of the progression-free survival of the IMbrave 150 “in” and “out” groups with advanced hepatocellular carcinoma treated with atezolizumab plus bevacizumab.

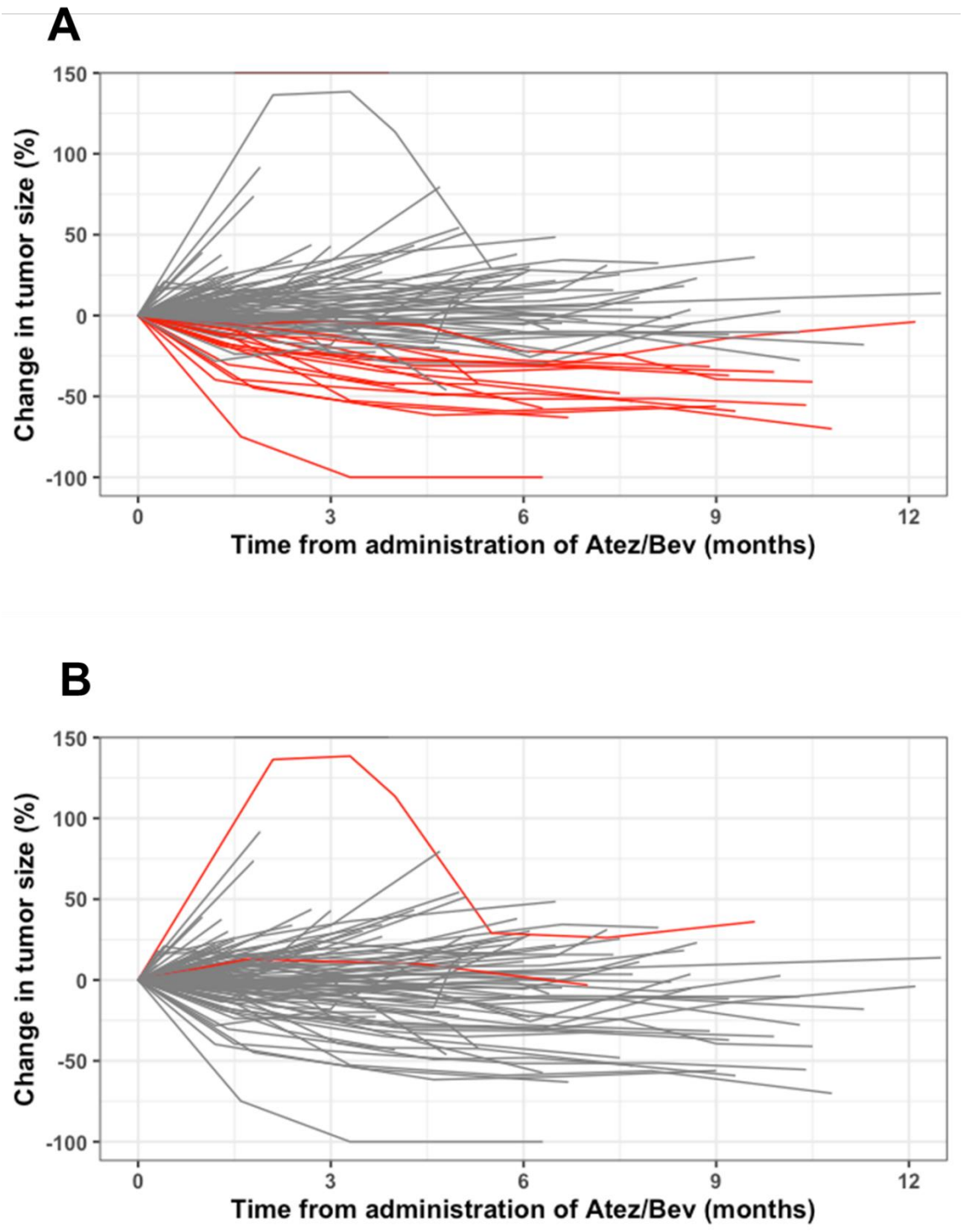

Figure 1. Spider plots of sum of tumor diameters based on RECIST1.1. (A) The red line shows patients who achieved an objective response. (B) The red line shows patients with confirmed pseudo-progression.

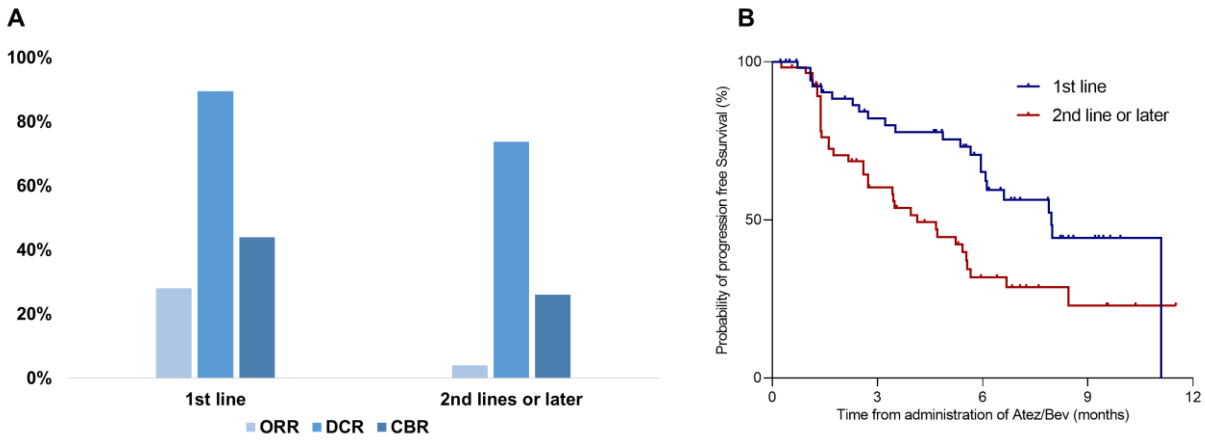

Figure 2. Comparison of efficacy by treatment line. (A) Tumor response according to RECIST 1.1 in the first-line and second- or later-line treatment group. (B) Kaplan–Meier curve of the progression-free survival of the first-line and second- or later-line treatment group with advanced hepatocellular carcinoma treated with atezolizumab plus bevacizumab.

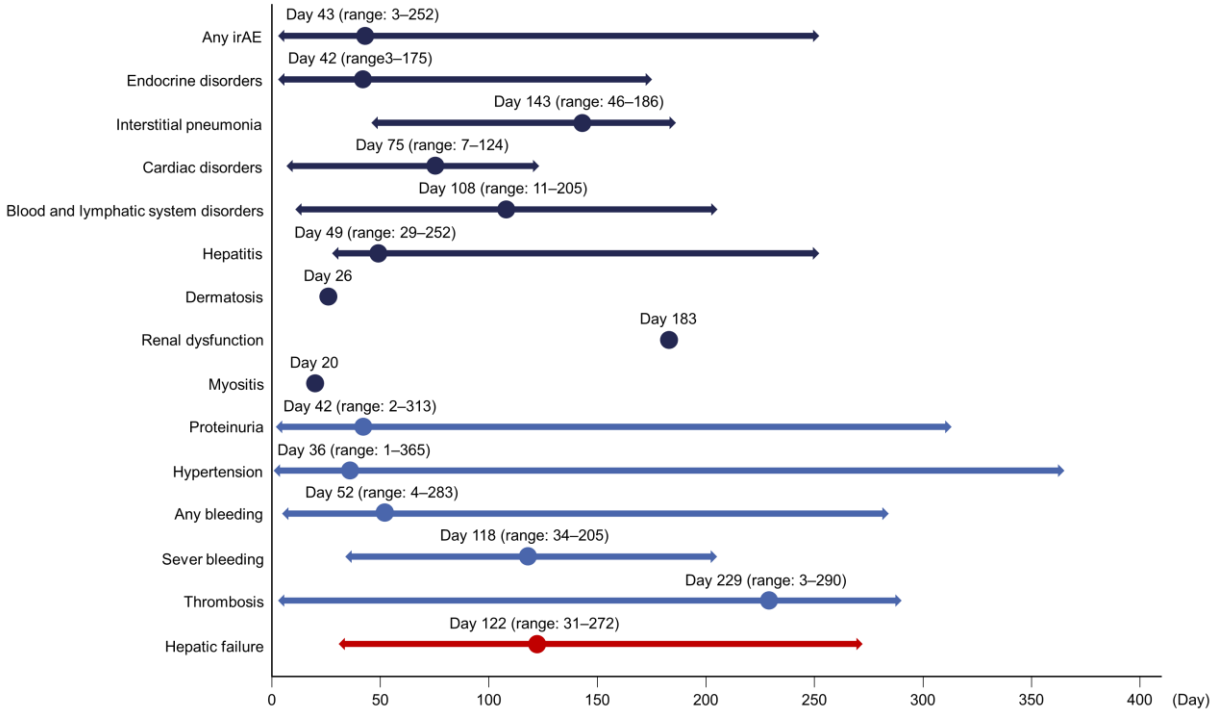

Figure 3. Onset of adverse events caused by atezolizumab plus bevacizumab in patients with advanced hepatocellular carcinoma. The black lines show immune-related adverse events. The blue lines show anti-VEGF-related adverse events. The red line shows hepatic failure.

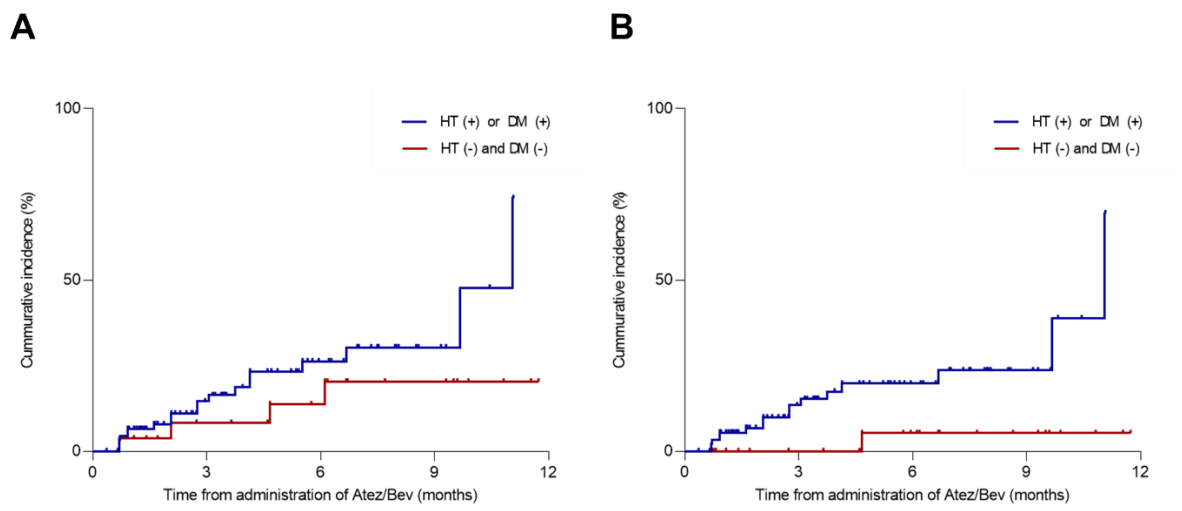

Figure 4. Association of bevacizumab interruption and baseline comorbidities. (A) Cumulative incidence rate of interrupted bevacizumab treatment (patients with comorbidities of either or both hypertension and diabetes mellitus at the time of treatment initiation vs. patients without comorbidities of both hypertension and diabetes mellitus at the time of treatment initiation). (B) Cumulative incidence rate of interrupted bevacizumab treatment due to anti-VEGF-related adverse events (patients with comorbidities of either or both hypertension and diabetes mellitus at the time of treatment initiation vs. patients without comorbidities of both hypertension and diabetes mellitus at the time of treatment initiation). VEGF, vascular endothelial growth factor.

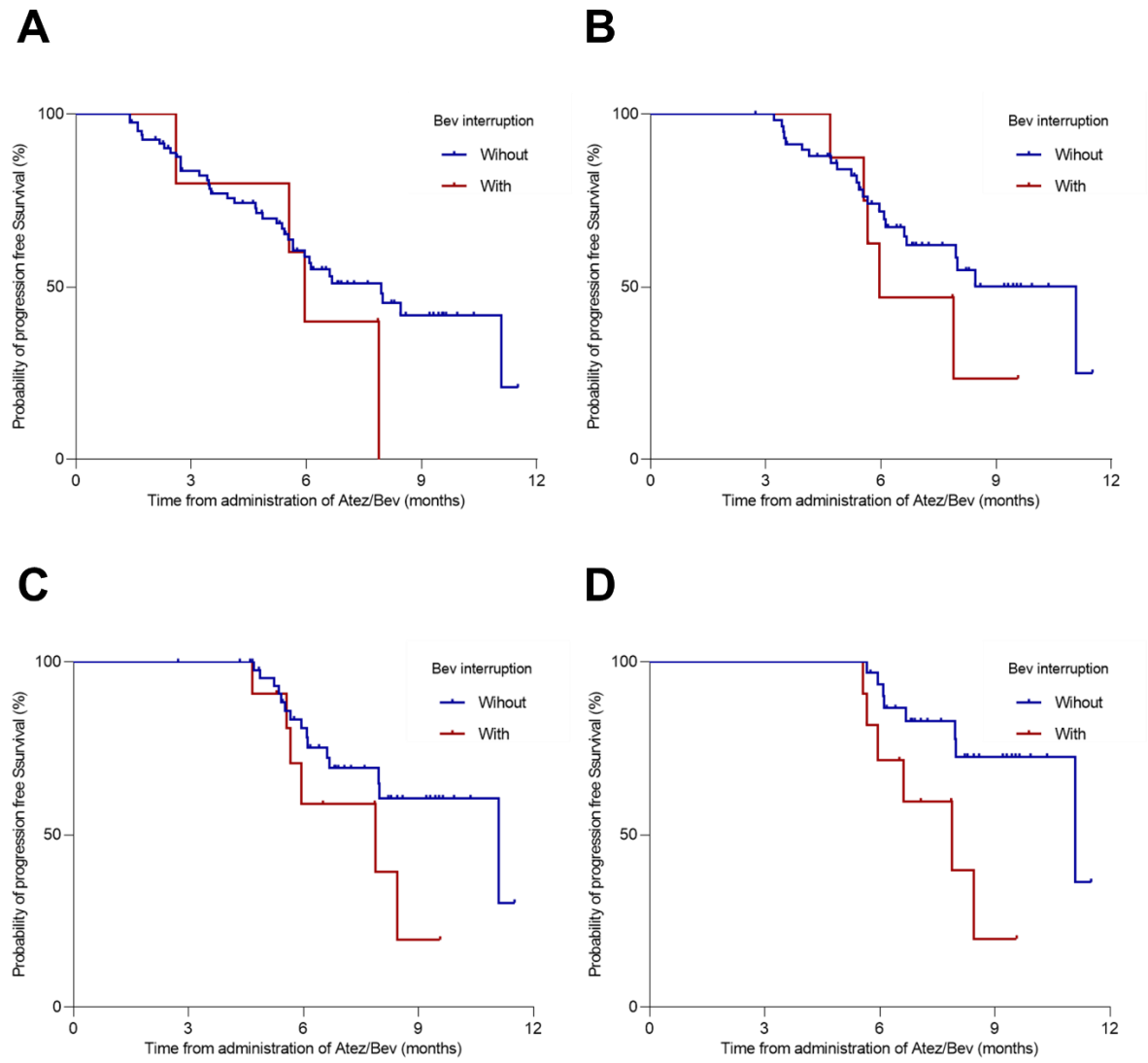

Figure 5. Effect of interrupted bevacizumab treatment before 6 weeks (A), 12 weeks (B), 18 weeks (C), and 24 weeks (D) on progression-free survival.

Table 1. Baseline characteristics of advanced hepatocellular carcinoma patients who received atezolizumab plus bevacizumab.

Variable	N (%)
Age, >73 years old	61 (49.6%)
Sex, male	102 (82.9%)
Child-Pugh class A	114 (92.7%)
HBV positive	24 (19.5%)
HCV positive	37 (30.1%)
NAFLD/NASH (clinically diagnosed)	21 (17.1%)
NASH (pathologically confirmed)	10 (8.1%)
MAFLD	50 (40.7%)
Complication of hypertension	82 (66.7%)
Complication of diabetes	47 (38.2%)
ECOG-PS >0	21 (17.1%)
Macrovascular invasion	34 (27.6%)
Extrahepatic metastasis	51 (41.5%)
BCLC stage C	82 (66.7%)
AFP >400 ng/mL	45 (36.6%)
Previous history of systemic therapies	63 (51.2%)

Abbreviation: HBV, hepatitis B virus; HCV, hepatitis C virus; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; MAFLD, Metabolic associated fatty liver disease; ECOG-PS, Eastern Cooperative Oncology Group performance status; BCLC, Barcelona Clinic liver cancer; AFP, alfa-fetoprotein.

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