



Early experience of atezolizumab plus bevacizumab therapy in Japanese patients with unresectable hepatocellular carcinoma in real-world practice

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Summary

Background. We aimed to investigate the efficacy and safety of atezolizumab plus bevacizumab therapy in patients with unresectable hepatocellular carcinoma (u-HCC) based on whether they had previously received systemic therapy, as well as the association of atezolizumab plus bevacizumab with early alpha-fetoprotein (AFP) response in real-world practice. **Methods.** A total of 52 patients with u-HCC were treated with atezolizumab plus bevacizumab between October 2020 and April 2021. The Response Evaluation Criteria in Solid Tumors (RECIST) and modified RECIST were used to evaluate radiological responses. **Results.** The patients received atezolizumab plus bevacizumab as 1st-line (n = 23), 2nd-line (n = 16), 3rd-line (n = 6), 4th-line (n = 3), 5th-line (n = 3), or 6th-line (n = 1) therapy. According to RECIST, the objective response rate (ORR) and disease control rate (DCR) in all patients were 15.4% and 57.7%. In the 1st-line patients, ORR and DCR based on RECIST 1.1 were 27.3% and 81.8%. The median time to progression (TTP) assessed by RECIST was significantly longer among patients receiving atezolizumab plus bevacizumab as 1st-line therapy than in patients receiving atezolizumab plus bevacizumab as later-line therapy ($P < 0.001$). Patients with an AFP response (reduction $\geq 20\%$ from baseline) at 6 weeks had a significantly longer TTP assessed by RECIST than those without an AFP response ($P = 0.02$). **Conclusion.** Patients who received atezolizumab plus bevacizumab as 1st-line therapy had better clinical outcome than those who received atezolizumab plus bevacizumab in later lines. The AFP response at 6 weeks could be a predictor of disease progression.

Keywords Hepatocellular carcinoma · Atezolizumab · Bevacizumab · Later-line · Alpha-fetoprotein

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver cancer and the fourth most common cause of cancer-related deaths worldwide [1]. HCC is hypervascular, and such angiogenesis is driven by growth factors, such as vascular endothelial growth factor (VEGF). Tyrosine kinase inhibitors targeting VEGF signaling, such as sorafenib [2, 3], regorafenib [4], and lenvatinib [5], have already been approved for the treatment of unresectable HCC (u-HCC) in many countries. Cabozantinib [6] and ramucirumab [7, 8] have been approved as 2nd- or later-line agents for u-HCC in Japan. Ramucirumab was approved for patients with a high alpha-fetoprotein (AFP) level (≥ 400 ng/mL) in July 2019.

VEGF is also associated with cancer immune evasion. Based on this rationale, the combination of programmed cell

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death-ligand 1 (PD-L1) (atezolizumab) and VEGF (bevacizumab) pathway inhibition is believed to be the most effective therapy for advanced HCC. In September 2020, atezolizumab plus bevacizumab [9] was approved for patients with u-HCC in Japan and became the recommended 1st-line therapy. In Japan, agents approved for 1st- and 2nd-line therapies may be used for later-line treatment in real-world practice. In this study, we aimed to investigate the efficacy and safety of atezolizumab plus bevacizumab as 1st-line and later-line therapies in real-world practice. Moreover, we analyzed the factors associated with time to progression (TTP) and the association of atezolizumab plus bevacizumab therapy with the timing of the AFP response and disease progression.

Materials and methods

Patients

A total of 52 patients with u-HCC received atezolizumab plus bevacizumab therapy at the Musashino Red Cross Hospital between October 2020 and April 2021. Atezolizumab plus bevacizumab therapy was administered after discussions by experts at a tumor board in the institution. HCC diagnosis and evaluation of disease progression were based on guidelines proposed by the Japan Society of Hepatology [10], the American Association for the Study of Liver Disease [11], and the European Association for the Study of the Liver [12]. Written informed consent was obtained from all patients, and the ethics committee of the Musashino Red Cross Hospital approved the study in accordance with the Declaration of Helsinki.

Treatment protocol

Patients received intravenous atezolizumab (1200 mg) plus bevacizumab (15 mg/kg) every 3 weeks until disease progression or unacceptable toxicity. Treatment interruption was performed based on the manufacturer's guidelines. Dynamic computed tomography was performed at baseline, 6–8 weeks after atezolizumab plus bevacizumab administration, and every 6–8 weeks thereafter. Treatment response was reported based on the Response Evaluation Criteria in Solid Tumors (RECIST) [13] and the modified RECIST [14]. The AFP level was also evaluated at baseline and every 3 weeks thereafter. Adverse events (AEs) were evaluated according to the Common Terminology Criteria for Adverse Events version 5.0. To assess changes in liver function, the albumin-bilirubin (ALBI) score [15, 16] was analyzed at baseline and at 3, 6, and 9 weeks after treatment. The data cut-off date of clinical response and ALBI score were defined on July 31, 2021.

Statistical analysis

Overall survival (OS) was measured from the date of atezolizumab plus bevacizumab administration to the date of death from any cause. Patients who were lost to follow-up were censored at their last visit or contact. Patients who were still alive on July 31, 2021 were censored. Progression-free survival (PFS) was measured from the date of atezolizumab plus bevacizumab administration to the date of radiological tumor progression or death from any cause. Data are expressed as median (range) or n (%). Fisher's exact test, Mann–Whitney U test, paired t-test, Kaplan–Meier method, and log-rank test were used for statistical analyses. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Shimotsuke, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [17].

Results

Baseline patient characteristics

The baseline characteristics of the 52 patients are presented in Table 1. Atezolizumab and bevacizumab were administered as 1st-line, 2nd-line, 3rd-line, 4th-line, 5th-line, and 6th-line treatments in 23 (44.2%), 16 (30.8%), 6 (11.5%), 3 (5.8%), 3 (5.8%), and 1 (1.9%) patient, respectively. Among the 16 patients who received atezolizumab plus bevacizumab as 2nd-line treatment, 15 were treated with lenvatinib as 1st-line treatment and 1 patient who had been treated with cytotoxic agents as systemic chemotherapy received ramucirumab as the 1st-line molecular targeted agent. Among the 6 patients who received atezolizumab plus bevacizumab as 3rd-line treatment, 3 were previously treated with lenvatinib and sorafenib, 2 received sorafenib and regorafenib, and 1 received axitinib + avelumab (NCT03289533) and lenvatinib. Among the 3 patients who received atezolizumab plus bevacizumab as 4th-line treatment, 2 were treated with sorafenib, regorafenib, and lenvatinib and 1 received lenvatinib, sorafenib, and regorafenib. Among the 3 patients who received atezolizumab plus bevacizumab as 5th-line treatment, 1 was treated with sorafenib, regorafenib, lenvatinib, and ramucirumab, 1 was treated with sorafenib, cabozantinib, lenvatinib, and ramucirumab, and 1 received lenvatinib, sorafenib, ramucirumab, and regorafenib. The 1 patient who received atezolizumab plus bevacizumab as 6th-line treatment was previously treated with axitinib plus avelumab (NCT03289533), cabozantinib, lenvatinib, ramucirumab, and sorafenib.

Table 1 Baseline characteristics

	n = 52
Age (years), median (range)	73 (24–89)
Sex, male/female	42 (80.8)/ 10 (19.2)
Etiology, HBV/HCV/alcohol/others	10 (19.2)/ 20 (38.5)/ 13 (25.0)/ 9 (17.3)
ALBI score, median (range)	−2.24 (−3.28 to −1.37)
Modified ALBI grade, 1/2a/2b/3	12 (23.1)/ 13 (25.0)/ 26 (50.0)/ 1 (1.9)
Child–Pugh class, A/B	48 (92.3)/ 4 (7.7)
ECOG-PS, 0/1	30 (57.7)/ 22 (42.3)
BCLC stage, A/B/C	0 (0)/ 29 (55.8)/ 23 (44.2)
Major portal invasion, yes/no	6 (11.5)/ 46 (88.5)
Extrahepatic spread, yes/no	17 (32.7)/ 35 (67.3)
Baseline AFP concentration (ng/mL), median (range)	192.7 (1.6–79,739.1)
AFP concentration (ng/mL), <20/20–400/>400	15 (28.8)/ 16 (30.8)/ 21 (40.4)
Clinical course, 1st-line/2nd-line/3rd-line/4th-line/5th-line/6th-line	23 (44.2)/ 16 (30.8)/ 6 (11.5)/ 3 (5.8)/ 3 (5.8)/ 1 (1.9)

Data are presented as n (%) unless otherwise indicated

HBV hepatitis B virus, *HCV*, hepatitis C virus, *ALBI* score albumin-bilirubin score, *ECOG-PS* Eastern Cooperative Oncology Group-Performance status, *BCLC* Barcelona Clinic Liver Cancer, *AFP* alpha-fetoprotein

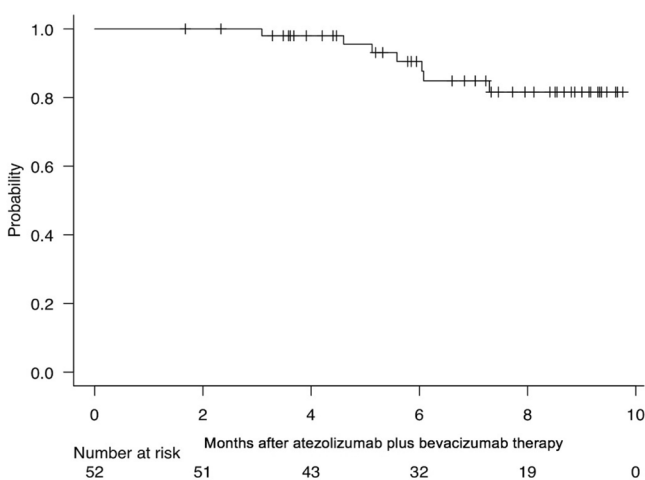
Therapeutic efficacy

At the end of the data cutoff (July 31, 2021), the median duration of follow-up was 221 days (range, 51–297 days). The median number of courses of atezolizumab plus bevacizumab was 5 (range, 1–15). During the observation period, 18 patients continued atezolizumab plus bevacizumab therapy and 34 patients discontinued atezolizumab plus bevacizumab therapy because of progressive disease (PD) (n=28) or AEs (n=6). Six patients died from HCC progression, and one patient died of cerebral hemorrhage. The median OS was not reached, and the median PFS assessed

by the RECIST was 4.7 months (Fig. 1). In 23 patients who received atezolizumab plus bevacizumab as 1st-line treatment, the median OS and PFS were not reached, and the PFS at 3 months was 79.8% (Fig. 2).

Radiological evaluation after atezolizumab plus bevacizumab administration was performed in 46 patients. With regard to the best antitumor response according to the RECIST, 1 patient achieved complete response (CR), 7 patients achieved partial response (PR), 22 patients had stable disease (SD), 16 patients had PD, and 6 patients had no evaluable disease (NE). The objective response

A. Overall survival (n=52)



B. Progression-free survival (n=46)

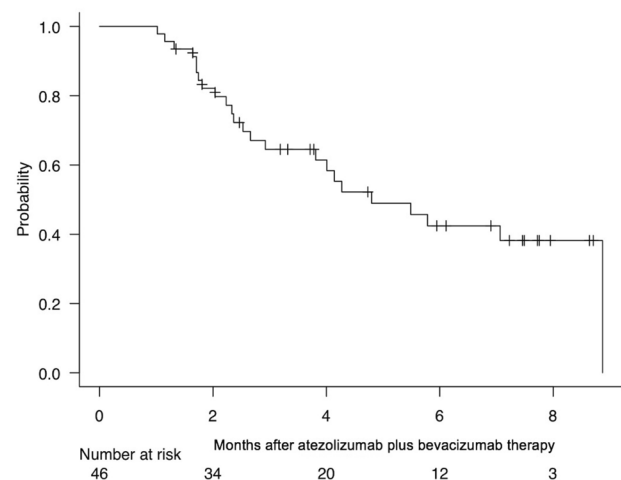


Fig. 1 Overall survival (**A**) and progression-free survival (**B**) in all patients

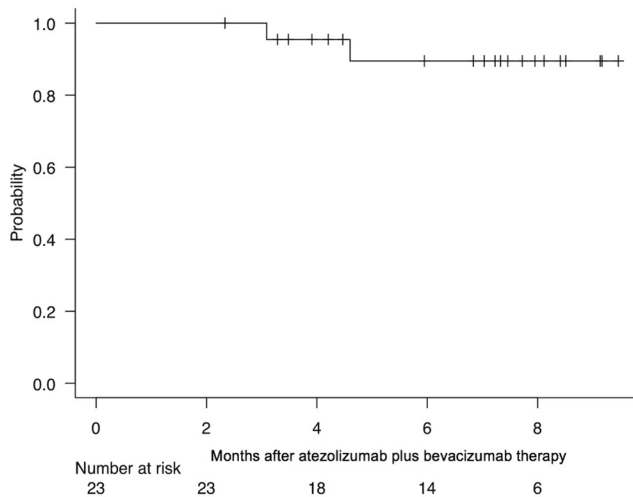
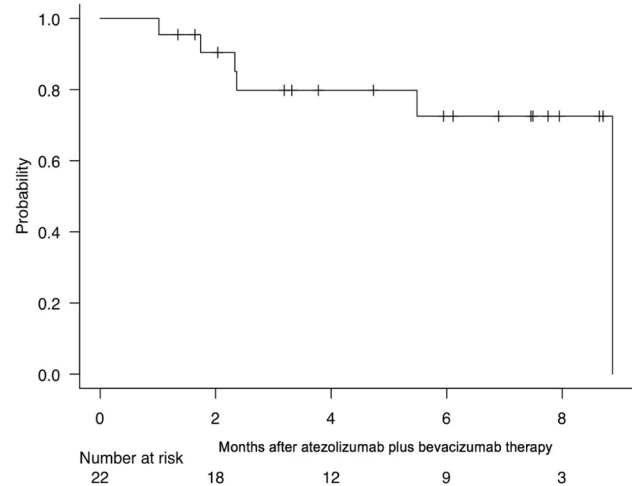
A. Overall survival (n=23)**B. Progression-free survival (n=22)**

Fig. 2 Overall survival (**A**) and progression-free survival (**B**) in patients receiving atezolizumab plus bevacizumab as 1st-line therapy

rate (ORR) and disease control rate (DCR) were 15.4% and 57.7%, respectively. With regard to the best antitumor response according to the modified RECIST, 1 patient achieved CR, 10 patients achieved PR, 21 patients had SD, 14 patients had PD, and 6 patients had NE. The ORR and DCR were 21.2% and 61.5%, respectively.

Treatment after atezolizumab plus bevacizumab

During the observation period, 30 of 34 patients (88.2%) who discontinued atezolizumab plus bevacizumab received further anticancer therapy (Table 2). The other 4 patients (11.8%) received palliative care. The transition rates to post-treatment among patients receiving atezolizumab plus bevacizumab as 1st-line therapy (n=9) and

those receiving atezolizumab plus bevacizumab as later-line therapy (n=25) were 100% and 84%, respectively.

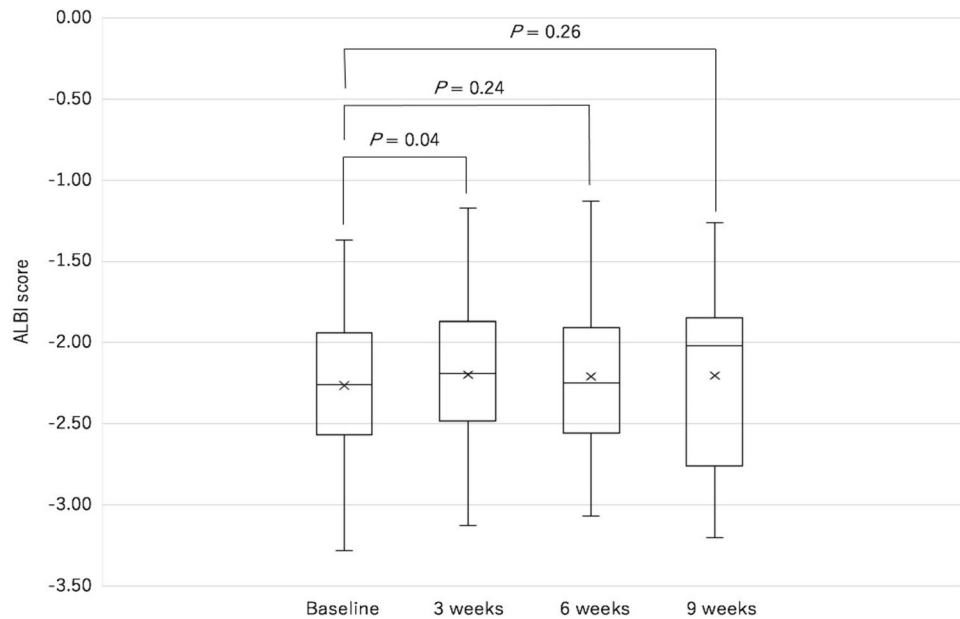
Changes in liver function during atezolizumab plus bevacizumab therapy

The changes in the ALBI score in 52 patients who received atezolizumab plus bevacizumab are shown in Fig. 3. The median ALBI scores at baseline, 3 weeks, 6 weeks, and 9 weeks were -2.26 (range, -3.28 to -1.37), -2.19 (range, -3.13 to -1.17), -2.25 (range, -3.07 to -1.13), and -2.02 (range, -3.2 to -1.26), respectively. The median ALBI score was significantly worsened at 3 weeks compared to baseline ($P=0.04$). There were no significant differences in the median ALBI scores at baseline and 6 weeks ($P=0.24$), or at baseline and 9 weeks ($P=0.26$). Among patients receiving atezolizumab plus bevacizumab as 1st-line treatment (n=23), the median ALBI scores at baseline, 3 weeks, 6 weeks, and 9 weeks were -2.28 (range, -3.28 to -1.37), -2.30 (range, -3.13 to -1.17), -2.31 (range, -3.07 to -1.13), and -2.39 (range, -3.2 to -1.26), respectively. In patients receiving atezolizumab plus bevacizumab as 2nd- or later-line therapy (n=29), the median ALBI scores at baseline, 3 weeks, 6 weeks, and 9 weeks were -2.25 (range, -2.99 to -1.48), -2.14 (range, -3.04 to -1.26), -2.14 (range, -2.82 to -1.20), and -1.96 (range, -3.04 to -1.26), respectively. There were no significant differences in the median ALBI scores at baseline and at 3 weeks, at baseline and at 6 weeks or at baseline and at 9 weeks in either group (Fig. 4).

Table 2 Treatment after discontinuation of atezolizumab plus bevacizumab (n=30)

	n (%)
Lenvatinib	11 (32.3)
Cabozantinib	7 (20.6)
Sorafenib	5 (14.7)
Regorafenib	2 (5.9)
Hepatic arterial infusion chemotherapy	2 (5.9)
Transarterial infusion chemotherapy	2 (5.9)
Ramucirumab	1 (2.9)

Fig. 3 Changes in the median ALBI score (n=52) ALBI score, albumin-bilirubin score

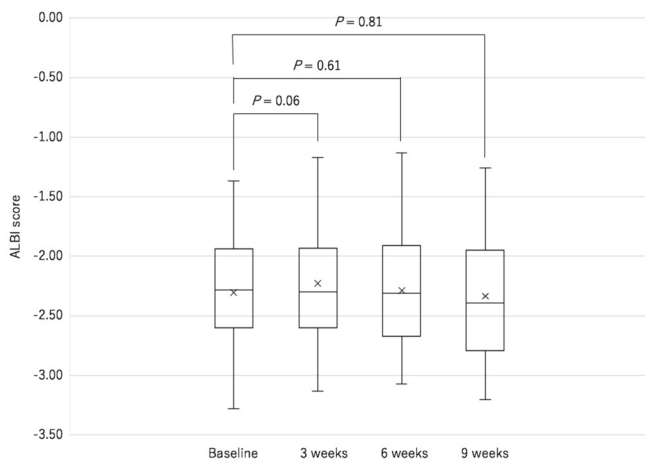


Adverse events during atezolizumab plus bevacizumab therapy

AEs observed during atezolizumab plus bevacizumab therapy are shown in Table 3. Any grade AE was observed in 36 of the 52 patients. The rates of total AEs in patients receiving atezolizumab plus bevacizumab as 1st-line therapy (n = 23) and those receiving atezolizumab plus bevacizumab as 2nd- or later-line therapy (n = 29) were 60.9% and 75.9%, respectively (P = 0.37). When comparing AEs with an incidence of 10% or more, the rates of AEs were 56.5%

in patients receiving atezolizumab plus bevacizumab as 1st-line therapy and 75.9% in patients receiving atezolizumab plus bevacizumab as 2nd- or later-line therapy (P = 0.23). No infusion reaction was reported in any patient. During the observation period, six patients discontinued atezolizumab plus bevacizumab therapy owing to AEs, as follows: two patients with transaminase increase, one patient with interstitial pneumonia, one patient with meningitis and transaminase increase, one patient with renal dysfunction, and one patient with gastrointestinal bleeding. Four of the six patients were treated with corticosteroids. The rates of

A. First-line treatment (n=23)



B. Second- or later-line treatment (n=29)

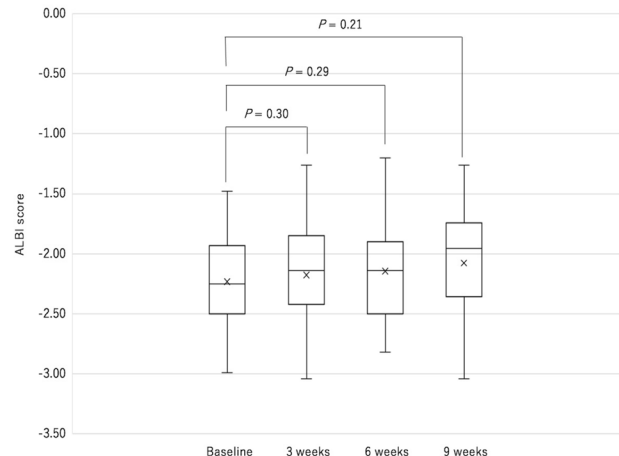


Fig. 4 Changes the in median ALBI score among patients receiving atezolizumab plus bevacizumab as 1st-line treatment (n = 23) (A) and those receiving it as 2nd- or later-line treatment (n = 29) (B)

Table 3 Adverse events

	Any grade n (%)	Grade ≥ 3 n (%)
Hypertension	12 (23.1)	0 (0)
Fatigue	14 (26.9)	1 (1.9)
Diarrhea	5 (9.6)	0 (0)
Decreased appetite	8 (15.4)	1 (1.9)
Fever	11 (21.2)	1 (1.9)
Rash	3 (5.8)	0 (0)
Nausea	5 (9.6)	1 (1.9)
Edema	8 (15.4)	0 (0)
Ascites	3 (5.8)	0 (0)
Transaminase increase	7 (13.5)	3 (5.8)
Total bilirubin increase	4 (7.7)	0 (0)
Proteinuria	7 (13.5)	0 (0)
Thromboembolism	0 (0)	0 (0)
Epistaxis, subcutaneous hemorrhage, or gastrointestinal bleeding	8 (15.4)	1 (1.9)
Interstitial pneumonia	1 (1.9)	1 (1.9)
Renal dysfunction	1 (1.9)	1 (1.9)
Adrenal insufficiency	1 (1.9)	0 (0)
Meningitis	1 (1.9)	1 (1.9)
Infusion reaction	0 (0)	0 (0)

discontinuation due to AEs among patients treated with atezolizumab plus bevacizumab as 1st-line and 2nd- or later-line therapy were 8.7% and 13.8%, respectively ($P=0.68$).

No AEs other than those reported in the IMbrave150 trial were observed.

Clinical outcomes in the 1st-line group and the 2nd- or later-line group

We compared TTP between the patients treated with atezolizumab plus bevacizumab as 1st-line ($n=22$) and 2nd or later-line ($n=24$). The baseline characteristics are shown in Table 4. The proportions of patients receiving a full dose of atezolizumab plus bevacizumab in the 1st-line group and the 2nd- or later-line group were 72.7% and 58.3%, respectively ($P=0.23$). Among 22 patients who received atezolizumab plus bevacizumab as 1st-line treatment, 1 patient achieved CR, 5 patients achieved PR, 12 patients had SD, and 4 patients had PD according to the RECIST. The ORR was 27.3% and the DCR was 81.8% according to the RECIST. According to the modified RECIST, 1 patient achieved CR, 6 achieved PR, 11 had SD, and 4 had PD. The ORR was 31.8% and the DCR was 81.8% using the modified RECIST. Among the 24 patients who received atezolizumab plus bevacizumab as 2nd- or later-line treatment, 2 achieved PR, 10 had SD, and 12 had PD according to the RECIST. The ORR was 8.3% and the DCR was 50.0% using the RECIST. According to the modified RECIST, 4 patients achieved PR, 10 had SD, and 10 had PD. The ORR was 16.7% and the DCR was 58.3% using the modified RECIST. The median TTP assessed by the RECIST was significantly longer in

Table 4 Baseline characteristics in the 1st-line group and the 2nd- or later-line group

	1st-line group (n=22)	2nd- or later-line group (n=24)	<i>P</i>
Age (years), median (range)	73 (56–89)	74 (34–86)	0.66
Sex, male (%)	16 (72.7)	22 (91.7)	0.13
Etiology, HBV/HCV/alcohol/others (%)	3 (13.6)/11 (50.0)/6 (27.3)/2 (9.1)	5 (20.8)/7 (29.2)/7 (29.2)/5 (20.8)	0.39
ECOG-PS, 0/1 (%)	15 (68.2)/7 (31.8)	12 (50.0)/12 (50.0)	0.24
BCLC stage B/C (%)	15 (68.2)/7 (31.8)	9 (37.5)/15 (62.5)	0.05
Major portal invasion (%)	3 (13.6)	3 (12.5)	>0.99
Extrahepatic metastasis (%)	4 (18.2)	12 (50.0)	0.06
ALBI score, median (range)	-2.32 (-3.28 to -1.60)	-2.25 (-2.99 to -1.57)	0.47
Child–Pugh A (%)	22 (100)	23 (95.8)	>0.99
Alb (g/dL, median)	3.5 (2.8–4.7)	3.4 (2.8–4.3)	0.31
T-Bil (mg/dL, median)	0.7 (0.4–1.2)	0.6 (0.3–1.8)	0.46
PT (% , median)	95 (72–120)	99 (57–120)	0.84
AST (U/L, median)	44 (19–128)	39 (3–161)	0.49
ALT (U/L, median)	31 (9–123)	25 (14–73)	0.36
eGFR (mL/min/1.73 m ²), median (range)	58.6 (37.3–103.1)	67.1 (37.5–96.0)	0.25
Urine protein-to-creatinine ratio, median (range)	0.06 (0–1.53)	0.08 (0.03–4.14)	0.07
AFP (ng/mL), median (range)	223.2 (1.6–41246.2)	232.5 (4.8–37477.2)	0.75
DCP (mAU/mL), median (range)	482.6 (15.4–313273.7)	927.4(42.9–200499)	0.77

HBV hepatitis B virus, *HCV* hepatitis C virus, *ECOG-PS* Eastern Cooperative Oncology Group-Performance Status, *BCLC* Barcelona Clinic Liver Cancer, *ALBI* albumin-bilirubin, *Alb* albumin, *T-Bil* total bilirubin, *PT* prothrombin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *eGFR* estimated glomerular filtration rate, *AFP* alpha-fetoprotein, *DCP* des- γ -carboxy prothrombin

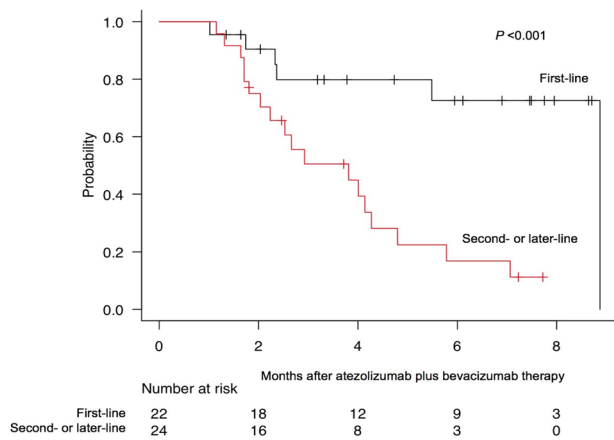


Fig. 5 Time to progression in the 1st-line group and the 2nd- or later-line group

the 1st-line group than in the 2nd- or later-line group (not reached vs. 3.8 months, $P < 0.001$) (Fig. 5).

We next analyzed the factors associated with TTP in patients receiving atezolizumab plus bevacizumab ($n = 46$). In the multivariate analysis, receiving atezolizumab plus bevacizumab as 2nd- or later-line therapy was the only significant factor (hazard ratio 3.16, 95% confidence interval 1.03–9.74, $P = 0.04$) (Table 5).

1st-line group: received atezolizumab plus bevacizumab as 1st-line therapy.

2nd- or later-line group: received atezolizumab plus bevacizumab as 2nd-, 3rd-, 4th-, 5th-, or 6th-line therapy.

First-line group: received atezolizumab plus bevacizumab as 1st-line therapy.

Second- or later-line group: received atezolizumab plus bevacizumab as 2nd-, 3rd-, 4th-, 5th-, or 6th-line therapy.

The association between the AFP response and therapeutic efficacy in patients receiving atezolizumab plus bevacizumab therapy.

We investigated the AFP response as a predictor of DCR according to RECIST in patients receiving atezolizumab plus bevacizumab therapy. The AFP response was defined as a reduction in AFP from the baseline of $\geq 20\%$. Thirty-two patients continued atezolizumab plus bevacizumab therapy for more than 6 weeks and were included in the analysis. At 3 weeks, 12 patients showed an AFP response. The AFP response at 3 weeks had a positive predictive value (PPV) of 91.7% and a negative predictive value (NPV) of 40.0%. At 6 weeks, 12 patients showed an AFP response. The AFP response at 6 weeks had a PPV of 91.7% and an NPV of 40.0%. The TTPs of patients with and without an AFP response at 3 weeks and 6 weeks are presented in Fig. 6. There were no significant differences in the median TTP between patients with and without an AFP response at 3 weeks (3.8 months vs. 4.8 months, $P = 0.09$). By contrast, there was a significant difference in the median TTP between patients with and without an AFP response at 6 weeks (2.6 months vs. 4.7 months, $P = 0.02$). The results were similar when patients with a baseline AFP < 20 ng/mL were excluded. Although there were no significant differences in the median TTP between patients with and without an AFP response at 3 weeks (3.8 months vs. 4.1 months, $P = 0.08$), there was a significant difference in the median TTP between patients with and without an AFP response at 6 weeks (2.5 months vs. 4.7 months, $P = 0.001$) (Fig. 7).

We also analyzed the association between the AFP response at 6 weeks and therapeutic efficacy stratified by patients with baseline AFP < 20 ng/mL, 20–400 ng/mL, and > 400 ng/mL (Table 6). Among 10 patients with a baseline AFP < 20 ng/mL, 3 had an AFP response at 6 weeks.

Table 5 Factors associated with time to progression in patients treated with atezolizumab plus bevacizumab ($n = 46$)

	Univariate analysis	Multivariate analysis		
	<i>P</i> value	HR	95% CI	<i>P</i> value
Age ≥ 75 years	0.37			
Sex, male	0.66			
Etiology, non-viral	0.03	2.16	0.91–5.15	0.08
ALBI grade 2b	0.47			
ECOG-PS > 0	0.13			
BCLC stage C	0.02	1.86	0.47–7.39	0.37
Major portal invasion	0.96			
Extrahepatic spread	0.01	1.13	0.29–4.29	0.85
AFP ≥ 400 ng/mL	0.21			
Atezolizumab plus bevacizumab as 2nd- or later-line treatment	0.002	3.16	1.03–9.74	0.04
Dose reduction or discontinuation	0.97			

HR hazard ratio, CI confidence interval, ECOG-PS Eastern Cooperative Oncology Group-Performance Status, BCLC Barcelona Clinic Liver Cancer, ALBI albumin-bilirubin score, AFP alpha-fetoprotein

A. At 3 weeks of treatment

B. At 6 weeks of treatment

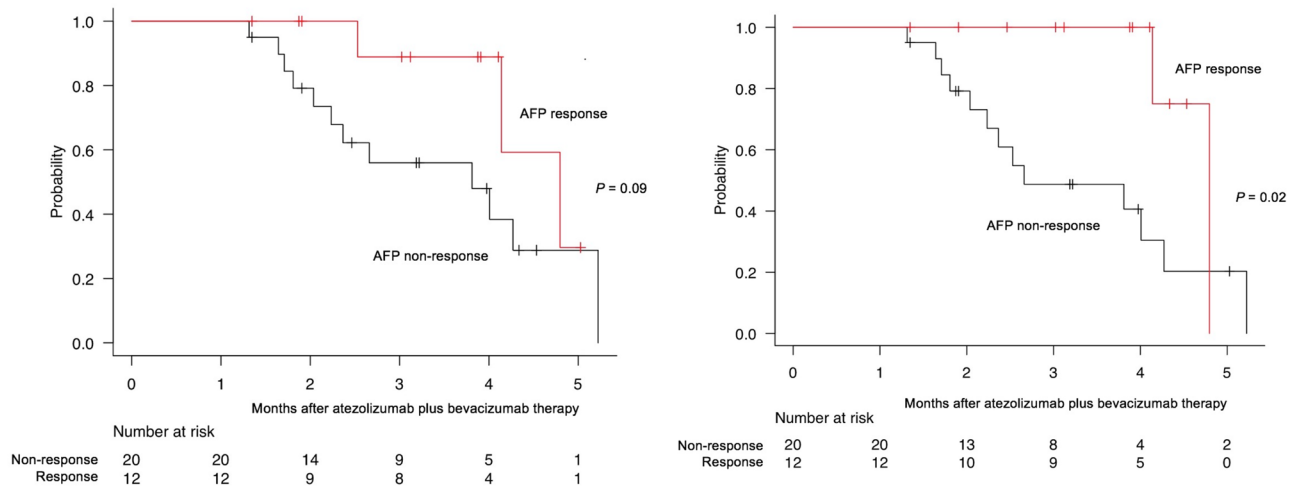


Fig. 6 The comparison of time to progression between patients with and without an AFP response (reduction $\geq 20\%$ from baseline) at 3 weeks (A) and 6 weeks (B) Abbreviations: AFP, alpha-fetoprotein

According to the RECIST, 2 patients achieved PR and 1 had SD. Among 10 patients with a baseline AFP 20–400 ng/mL, 4 had an AFP response at 6 weeks. One patient achieved PR, 2 had SD, and 1 had PD. Among 12 patients with a baseline AFP > 400 ng/mL, 5 had an AFP response at 6 weeks. One patient achieved CR, 1 achieved PR, and 3 patients had SD. There were no significant differences in the median TTP among patients with baseline AFPs < 20 ng/mL, 20–400 ng/mL, and > 400 ng/mL (5.2 months, 4.0 months,

and 4.8 months, respectively; $P=0.19$) in patients with an AFP response at 6 weeks (Fig. 8).

Discussion

Atezolizumab plus bevacizumab is recommended as a 1st-line therapy for advanced HCC in many guidelines, including the ASCO [18] and ESMO guidelines [19]. Some recent

A. At 3 weeks of treatment

B. At 6 weeks of treatment

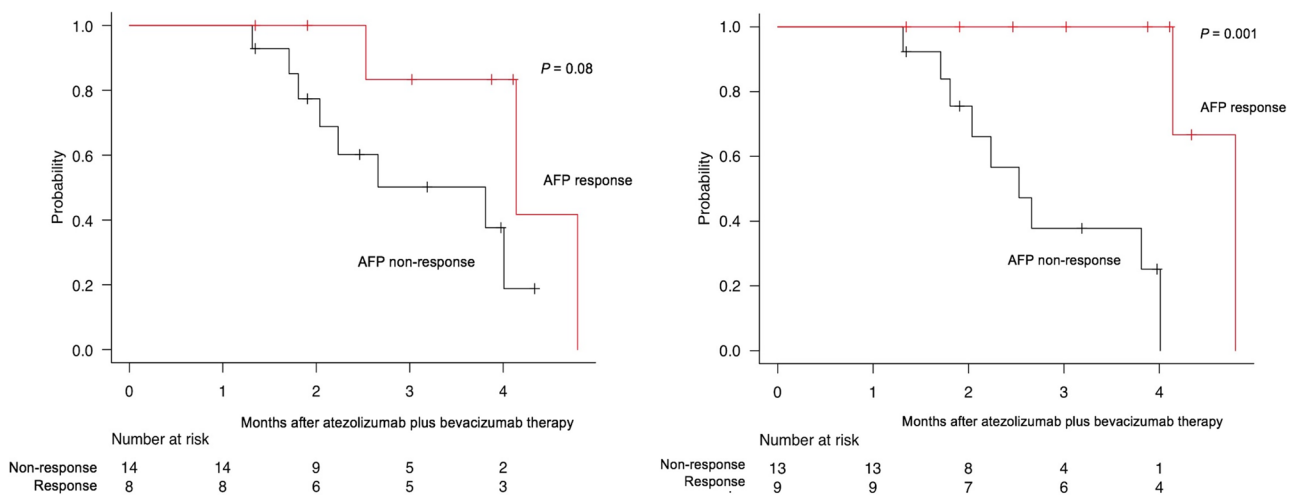


Fig. 7 The comparison of time to progression between patients with and without an AFP response (reduction > 20% from baseline and baseline AFP ≥ 20 ng/mL) at 3 weeks (A) and 6 weeks (B)

Table 6 Positive predictive value and negative predictive value of the AFP response at 6 weeks classified by baseline AFP

Baseline AFP	Positive predictive value (PPV)	Negative predictive value (NPV)
< 20 ng/mL (n = 10)	100%	28.6%
20–400 ng/mL (n = 10)	75%	50%
> 400 ng/mL (n = 12)	100%	42.9%

AFP alpha-fetoprotein

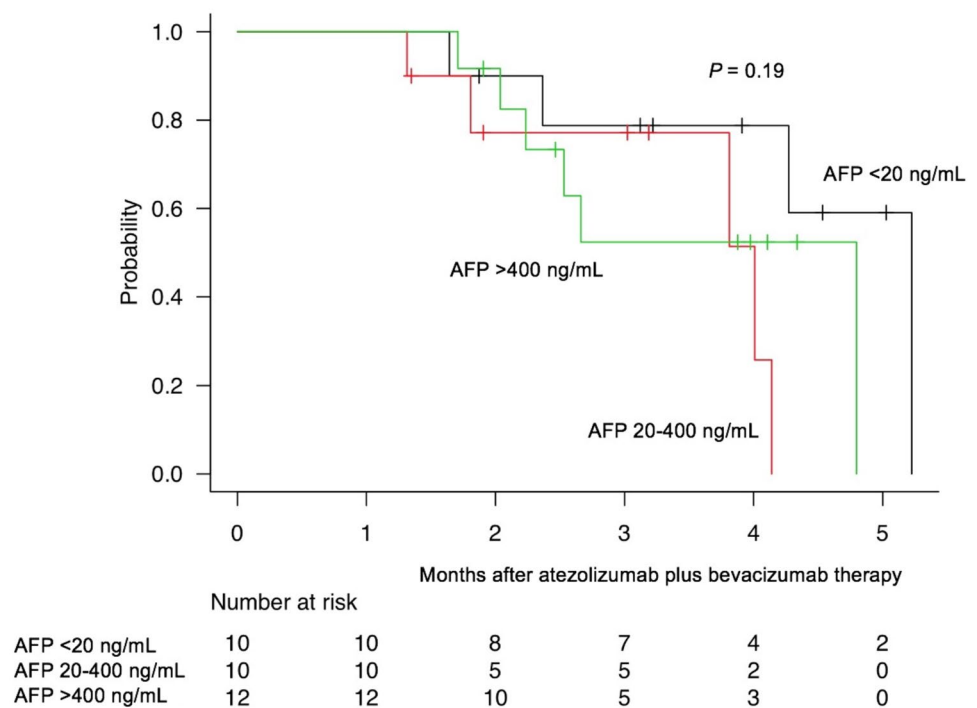
studies have reported the efficacy and safety of atezolizumab plus bevacizumab in Japanese patients with u-HCC in real-world practice [20–22]. To the best of our knowledge, this is the first report to reveal the difference in clinical outcome between patients receiving atezolizumab plus bevacizumab as 1st-line and 2nd- or later-line therapies and the association between the timing of the AFP response and therapeutic efficacy.

We included patients who received atezolizumab plus bevacizumab as 2nd- or later-line therapy in this study. The IMbrave150 trial [23] included only patients who had not previously received systemic therapy, and the ORR and DCR were 27.3% and 73.6%, respectively, according to the RECIST. Recent studies [20–22] showed there were no significant differences in radiological responses to atezolizumab plus bevacizumab between 1st-line and 2nd- or later-line patients. In our study, the median TTP was significantly shorter in the 2nd- or later-line group than in the first-line

group. In patients previously treated with other agents, dose modification and interruption of bevacizumab were more frequent than in patients receiving atezolizumab plus bevacizumab as 1st-line therapy. However, there were no significant differences in the rate of AEs between the two groups.

Previous reports reported deterioration in liver function during the early period among patients treated with sorafenib [24] and lenvatinib [25]. Sangro et al. [26] reported that patients receiving nivolumab were more likely to have preserved liver function than patients receiving sorafenib. Kudo et al. [27] reported that ramucirumab did not worsen the ALBI score during the early treatment period. Changes in liver function during atezolizumab plus bevacizumab therapy were not examined in the IMbrave150 trial. Recent studies [20, 21] showed the liver function was slightly worsened after 2–3 weeks and recovered at 6 weeks during atezolizumab plus bevacizumab therapy. In our study, the ALBI score at 3 weeks transiently worsened compared to baseline but improved at 6 weeks and 9 weeks. The temporary worsening of liver function may be related to the therapeutic response, which leads to appetite loss and fatigue during the early treatment period. Liver function and these AEs improved spontaneously at 6 and 9 weeks. Atezolizumab plus bevacizumab therapy can be maintained while preserving liver function in many patients.

In this study, we focused on the AFP response at 3 and 6 weeks after the administration of the combination therapy. There were no significant differences in the median TTP between patients with and without an AFP response at 3 weeks. By contrast, there was a significant difference in

Fig. 8 The comparison of time to progression among baseline AFP in patients with an AFP response at 6 weeks Abbreviation: AFP, alpha-fetoprotein

the median TTP between patients with and without an AFP response at 6 weeks. Previous studies reported early AFP response is useful to predict response to sorafenib [28, 29], lenvatinib [30] and checkpoint inhibitor therapy [31]. However, in patients receiving atezolizumab plus bevacizumab therapy, the antitumor response is delayed in some patients, and early treatment decisions based on the AFP response should be avoided.

In Japan, five regimens (sorafenib, regorafenib, lenvatinib, ramucirumab if AFP \geq 400 ng/mL, and cabozantinib) can be administered after atezolizumab plus bevacizumab therapy based on the national health insurance guidelines. Because of the small cohort and short observation period, we could not examine the established clinical outcomes of post-combination therapies in real-world practice. Among the patients who received lenvatinib after combination therapy, the ORR and DCR were 50% and 75%, respectively. Aoki et al. [32] revealed that lenvatinib demonstrated considerable antitumor effects with acceptable safety in patients with progressive and u-HCC when administered immediately after PD-1/PD-L1 blockade failure (ORR 55.6%, DCR 86.1%). Further multicenter studies on treatment after atezolizumab plus bevacizumab therapy are necessary to develop an effective treatment strategy for patients with u-HCC.

There are certain limitations to our study. The study was a retrospective single-center study with a small number of patients and a short observation period, and tumor response was not evaluated in all patients.

To our knowledge, our report is the first to reveal the difference in clinical outcome between 1st-line and 2nd- or later-line atezolizumab plus bevacizumab therapy and the association between the timing of the AFP response and therapeutic efficacy. Our data can provide useful information to develop useful therapeutic strategies for patients with u-HCC and effectively administer combination therapy.

Conclusion

Atezolizumab plus bevacizumab therapy was found to have similar radiological responses to the phase III IMbrave150 trial regimen in u-HCC patients when administered as 1st-line therapy. Patients receiving atezolizumab plus bevacizumab therapy as 1st-line therapy tended to have longer TTP than those receiving atezolizumab plus bevacizumab as 2nd- or later-line therapy. The AFP response at 6 weeks could be a predictive indicator of disease progression.

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Author's contribution Study design: Yuka Hayakawa and Kaoru Tsuchiya Data collection: Yuka Hayakawa, Kaoru Tsuchiya, Masayuki Kurosaki, Yutaka Yasui, Shun Kaneko, Yuki Tanaka, Shun Ishido, Kento Inada, Sakura Kirino, Koji Yamashita, Tsubasa Nobusawa, Hiroaki Matsumoto, Tatsuya Kakegawa, Mayu Higuchi, Kenta Takaura, Shohei Tanaka, Chiaki Maeyashiki, Nobuharu Tamaki, Hiroyuki Nakanishi, Jun Itakura, Yuka Takahashi and Namiki Izumi Data analysis: Yuka Hayakawa and Kaoru Tsuchiya Data interpretation: Yuka Hayakawa, Kaoru Tsuchiya, Masayuki Kurosaki, Shun Kaneko, Yutaka Yasui, Yasuhiro Asahina, Ryuichi Okamoto and Namiki Izumi Manuscript writing: Yuka Hayakawa and Kaoru Tsuchiya Manuscript revision: Masayuki Kurosaki, Shun Kaneko, Yutaka Yasui, Yasuhiro Asahina, Ryuichi Okamoto and Namiki Izumi All authors have read and agreed to the published version of the manuscript.

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Data availability The data presented in this study are available upon request from the corresponding author.

Code availability Not applicable.

Declarations

Ethical approval The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Musashino Red Cross Hospital (No. 28077).

Informed consent Informed consent was obtained from all subjects involved in the study.

Conflict of interest Kaoru Tsuchiya, Masayuki Kurosaki, and Namiki Izumi received advisory board fees and honoraria from the speakers' bureau from Bayer, Eisai, Eli Lilly Japan, and Roche. The Japanese Ministry of Health, Labour and Welfare had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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