Research Article

Outcomes of patients with Child-Pugh B and unresectable hepatocellular carcinoma undergoing first-line systemic treatment with sorafenib, lenvatinib, or atezolizumab plus bevacizumab.

Chihiro Kikugawa [a,b] Shinsuke Uchikawa [a,b], Tomokazu Kawaoka [a,b], Takahiro Kinami [a,b], Shigeki Yano [a,b], Kei Amioka [a,b], Kensuke Naruto [a,b], Yuwa Ando [a,b], Kenji Yamaoka [a,b], Masataka Tsuge [a,b], Yumi Kosaka[c], Kazuki Ohya[c], Nami Mori[c], Shintaro Takaki[c], Keiji Tsuji[c], Hirotaka Kouno[d], Hiroshi Kohno[d], Kei Morio[e], Takashi Moriya[e], Michihiro Nonaka[f], Yasuyuki Aisaka[f], Keiichi Masaki[g], Yoji Honda[g], Noriaki Naeshiro[h], Akira Hiramatsu[i], Hiroshi Aikata[j], Shiro Oka[a,b]

[a] Department of Gastroenterology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Japan.

[b] Research Center for Hepatology and Gastroenterology, Hiroshima University, Japan.

[c] Department of Gastroenterology, Hiroshima Red Cross Hospital & Atomic Bomb Survivors Hospital, Japan.

[d] Department of Gastroenterology, National Hospital Organization Kure Medical Center

and Chugoku Cancer Center, Hiroshima, Japan.

[e] Department of Gastroenterology, Chugoku Rosai Hospital, Hiroshima, Japan.

[f] Department of Gastroenterology, JA Hiroshima General Hospital, Hiroshima, Japan.

[g] Department of Gastroenterology, Hiroshima City Asa Citizens Hospital, Hiroshima, Japan.

[h] Department of Gastroenterology, National Hospital Organization Higashihiroshima Medical Center, Hiroshima, Japan.

[i] Department of Gastroenterology, Hiroshima Memorial Hospital, Hiroshima, Japan.

[j] Department of Gastroenterology, Hiroshima Prefectural Hospital, Japan

Running Head: Systemic treatment for HCC patients with Child-Pugh B

***Corresponding author**

Tomokazu Kawaoka, MD

Department of Gastroenterology, Applied Life Sciences, Institute of Biomedical and Health Sciences, Hiroshima University Hospital, 1-2-3, Kasumi, Minami-ku, Hiroshima 734-8551, Japan.

TEL: +81-82-257-5192; FAX: +81-82-257-5194

E-mail: kawaokatomo@hiroshima-u.ac.jp

Number of tables: 5

Number of figures: 7

Word count: 4294 words

Key words: hepatocellular carcinoma, Child-Pugh B, atezolizumab plus bevacizumab, lenvatinib, sorafenib

Abstract

Introduction: Systemic therapy is recommended for patients with Child-Pugh A in hepatocellular carcinoma (HCC). We analyzed the outcomes of a cohort of patients with HCC and who received either sorafenib (Sor), lenvatinib (Len) or atezolizumab plus bevacizumab (Atezo + Bev) as first-line systemic therapy for HCC, with the aim of identifying prognostic factors for survival. ***Methods:*** A total of 825 patients with advanced HCC and Child-Pugh A or B received either Sor, Len, or Atezo + Bev as first-line systemic therapy. Liver function was assessed according to the Child-Pugh score and the modified albumin-bilirubin (mALBI) grade. ***Results:*** When prognosis was analyzed according to liver function such as Child-Pugh classifications, scores and mALBI grades, that worsened with a decline in liver function ($p < 0.001$ for all). A Child-Pugh score of 7 was a factor significantly associated with OS. In patients with a Child-Pugh score of 7, a mALBI grade of 3 was an independent predictor of OS. In Child-Pugh B patients with HCC, receiving Atezo + Bev was identified as a factor associated with PFS. ***Conclusion:*** Determining the hepatic reserve of patients with unresectable HCC might be useful for identifying patents suitable for systemic treatment for HCC. Atezo + Bev might prolong the PFS of patients with a Child-Pugh score of 7.

Introduction

Hepatocellular cancer (HCC) is one of the leading causes of cancer-related death [1]. Systemic therapy is recommended for patients with unresectable HCC [2]. Systemic therapies for patients with unresectable HCC are rapidly changing. Sorafenib (Sor), lenvatinib (Len), or atezolizumab plus bevacizumab combination therapy (Atezo + Bev) are recommended as first-line therapies for unresectable HCC. In 2008, Sor was first shown to improve patient outcomes compared with placebo in the SHARP trial [3]. In 2017, Len was reported to be not inferior to Sor for overall survival (OS). Atezo + Bev for unresectable HCC was recently shown to be superior to treatment by Sor for progression-free survival (PFS) and OS [4]. Atezo + Bev was approved worldwide for unresectable HCC based on the results of the phase 3 IMbrave150 trial [4]. That trial wasthe first study to demonstrate the superiority of combination immunetherapy for HCC.

The American Association for the Study of Liver Diseases (AASLD) guidelines have recommended systemic therapy for patients with Barcelona Clinic Liver Cancer (BCLC) intermediate- or advanced-stage cancer [2]. However, patients with Child-Pugh B have generally been excluded from clinical trials for the treatment of HCC. The efficacy and safety of systemic therapies for patients with Child-Pugh B remain unknown. The HCC guidelines of the Japan Society of Hepatology only recommend systemic therapy for

patients with Child-Pugh A.

There have been several reports on studies comparing the outcomes of patients with Child-Pugh A or B and HCC undergoing single treatment with Sor only or Len only [5-10]. However, to our best knowledge, there have not yet been any published studies comparing several types of systemic therapy for HCC. Real-world clarification on the several types of systemic therapy for HCC in patients with Child-Pugh A or B should provide meaningful information for many physicians. In this study, we evaluated the efficacy and safety of different systemic treatments for HCC in patients with Child-Pugh A or B. We analyzed the outcomes of patients with Child-Pugh B undergoing treatment with Sor, Len, or Atezo + Bev as first-line systemic therapies, with the aim of identifying prognostic factors for survival.

Materials and Methods

Patients

Patients eligible for this retrospective cohort study had advanced HCC, Child-Pugh class A or B liver function, and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1. Patients were treated with either Atezo + Bev, Len, or Sor as first-line systemic therapies at Hiroshima University and affiliated institutions from May 2007 to July 2022.

Treatment regimens

Oral Sor was started at 400 mg twice daily and Len was started at respective doses of 8 and 12 mg for patients weighing < 60 and ≥60 kg once daily. Intravenous Atezo (1200 mg) + Bev (15 mg/kg) was administered every three weeks. The Common Terminology Criteria for Adverse Events version 5.0 was used to evaluate adverse events. Each drug was reduced as necessary based on the current dosing guidelines for patients developing drug-related adverse events and discontinued in patients with very serious adverse events. Each treatment was continued in the patients until death or until one of the following criteria was satisfied: disease progression after treatment, the occurrence of an adverse event necessitating treatment discontinuation, deterioration of an ECOG PS to 4

or a decline in hepatic reserve.

Assessment of response to treatment

The diagnosis of HCC was based on radiological features of dynamic computed tomography (CT) scans or magnetic resonance imaging (MRI) scans and/or histopathological features of a biopsy specimen.

Assessments of radiological response by dynamic CT or MRI were performed at 4–6 and 8–12 weeks after the start of treatment and then every 4–8 weeks thereafter. The Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and modified Response Evaluation Criteria in Solid Tumors (mRECIST) guidelines were used to assess the response to treatment. An objective response (OR) was defined as the achievement of complete response (CR) or partial response (PR), and a non-OR was defined as stable disease (SD) or progressive disease (PD). OS was defined as the time from the initiation of treatment to death from any cause, with the last follow-up date as the censoring date for surviving patients. PFS was defined as the time from the initiation of treatment to the time of radiological progression according to mRECIST, or time to any cause of death. In patients who were alive without radiological progression, the date of the last radiological evaluation or the date of a change to another treatment was

defined as the censoring date.

Assessment of liver function

Liver function was evaluated in every patient before the start of treatment. The Child-Pugh scoring system and the modified albumin-bilirubin (mALBI) grade were used to assess hepatic reserve. The mALBI grade was developed to provide a more accurate evaluation of patients with conventional ALBI grade 2. The mALBI grading system is based on a 4-point scale (ALBI score ≤ −2.60 is grade 1, > −2.60 to ≤ −2.27 is grade 2a, > −2.27 to ≤ −1.39 is grade 2b, and > −1.39 is grade 3).

Statistical analysis

Continuous variables were expressed as medians (range), while categorical variables were expressed as absolute and relative frequencies. The Mann-Whitney test was used to compare continuous data. Either the Pearson chi-squared test or Fisher exact test was used to compare differences between the distribution of categorical variables. Kaplan-Meier survival curves and the log-rank test were used to estimate OS and PFS.

Logistic regression analysis and Cox regression analysis were carried out for multivariate analysis. Factors with $p < 0.05$ by univariate analysis were subsequently

subjected to multivariate analysis. A p value < 0.05 denoted a statistically significant difference. Predictive Analytics Software R, version 3.5.2 was used for statistical analysis.

Results

Patient background

Table 1 shows the background characteristics of patients. The patients with Child-Pugh B were significantly older than the patients with Child-Pugh A ($p = 0.001$). The serum albumin level, prothrombin activity, and serum α-fetoprotein level were significantly lower in patients with Child-Pugh B than patients with Child-Pugh A ($p < 0.001$, $p < 0.001$, and $p = 0.003$, respectively). The serum total bilirubin level was significantly higher in Child-Pugh B than Child-Pugh A patients ($p < 0.001$). The statistically significant indicators of hepatic reserve such as degree of ascites and encephalopathy, the Child-Pugh score, and mALBI grade showed that the hepatic reserve of patients with Child-Pugh B was lower than the hepatic reserve of patients with Child-Pugh A. ($p < 0.001$, $p < 0.001$, $p < 0.001$ and $p < 0.001$, respectively). A significantly higher proportion of Child-Pugh B patients than Child-Pugh A patients showed macrovascular invasion and a tumor proportion of ≥50% relative to proportion of liver ($p < 0.001$ and $p = 0.009$, respectively). The proportions of Child-Pugh A patients receiving Sor/Len/Atezo + Bev are 58.6%, 26.8% and 14.6%. The proportions of Child-Pugh B patients receiving Sor/Len/Atezo + Bev are 70.9%/13.5%/15.6%. In Sor group, the ratio of the patients who received reduced initial starting dose were 34.0% in Child-Pugh A patients and 29.9% in Child-Pugh B

patitents ($p = 0.433$). In Len group, no patient received reduced initial starting dose.

Table 2 shows the background characteristics of patients with Child-Pugh B in each regimen group. The number of patients received Sor, Len and Atezo + Bev was 100, 19 and 22. No significant differences were observed for indicators of hepatic reserve such as mALBI grade, Child-Pugh score and BCLC stage ($p = 0.278$, $p = 0.212$ and $p = 0.208$, respectively).

Comparison of overall survival rates of patients stratified according to hepatic reserve and treatments

Figure 1a shows that the median survival times (MSTs) of patients with Child-Pugh A and Child-Pugh B were 15.8 and 7.9 months, respectively. Figure 1b shows that the MSTs of patients with Child-Pugh scores of 5, 6, 7, and 8/9 were 17.9, 11.5, 8.4, and 5.4 months, respectively. Figure 1c shows that the MSTs of patients with mALBI grades 1, 2a, 2b, and 3 were 20.6, 15.5and 5.1 months, respectively. The OS was significantly stratified according to Child-Pugh classification, score, and mALBI grade at the start of treatment ($p < 0.001$ for all).

Table 3 shows the results of uni- and multivariate analysis of factors that might be associated with OS in patients with Child-Pugh B. Univariate analysis showed that absence of viral hepatitis, absence of ascites, Child-Pugh scores of 7, mALBI grades 1–

2b, absence of macrovascular invasion, absence of extrahepatic metastases, and size of tumor relative to the liver < 50% were significant favorable factors for OS. Multivariate analysis identified Child-Pugh scores of 7 (hazard ratio [HR], 1.65; 95% confidence interval [CI], 1.08–2.54; $p = 0.022$) and absence of extrahepatic metastases (HR, 1.73; 95% CI, 1.20–2.49; $p = 0.003$) as significant independent factors contributing to OS.

Table 4 shows the results of uni- and multivariate analysis of factors associated with overall survival in patients with a Child-Pugh score of 7. Univariate analysis showed that serum total bilirubin ≤ 1.0 mg/dL, mALBI grades 1–2b, and absence of extrahepatic metastases were favorable factors for OS. Multivariate analysis identified mALBI grades 1–2b (HR, 2.84; 95% CI, 1.23–6.57; $p = 0.015$), and absence of extrahepatic metastases (HR, 1.74; 95% CI, 1.09–2.76; $p = 0.020$) as significant independent factors contributing to OS.

Figure 2 shows bar graphs with the x-axis corresponding to Child-Pugh scores and the y-axis showing the proportions of patients with mALBI grades with that Child-Pugh score. Among a total of 453 patients with a Child-Pugh score of 5, there were 258 (57.0%) mALBI grade 1, 167 (36.9%) mALBI grade 2a, and 28 (6.2%) mALBI grade 2b patients. Among a total of 231 patients with a Child-Pugh score of 6, there were 19 (8.2%) mALBI grade 1, 38 (16.5%) mALBI grade 2a, and 174 (75.3%) mALBI grade

2b patients. Among a total of 87 patients with a Child-Pugh score of 7, there were 3 (3.4%) mALBI grade 1, 9 (10.3%) mALBI grade 2a, 68 (78.2%) mALBI grade 2b, and 7 (8.0%) mALBI grade 3 patients. Among a total of 54 patients with a Child-Pugh score of 8 or 9, there were 2 (3.7%) mALBI grade 2a, 34 (63.0%) mALBI grade 2b, and 18 (33.3%) mALBI grade 3 patients.

Figure 3a shows the MSTs of patients with liver disease classified as Child-Pugh A. The MSTs of patients treated with Atezo + Bev, Len, or Sor were not reached, 21.9 months, and 11.0 months, respectively. The MSTs were significantly shorter in patients treated with Sor. Figure 3b shows the MSTs of patients with Child-Pugh 7. The MSTs of patients treated with Atezo + Bev, Len, or Sor were 19.5, 9.2, and 7.8 months, respectively. Figure 3c shows the MSTs of patients with Child-Pugh 8/9. The MSTs of patients treated with Atezo + Bev, Len, or Sor were 8.3, 7.2, and 4.3 months, respectively.

Progression-free survival in patients stratified according to hepatic reserve or type of treatment

Figure 4a shows that the median PFS times of patients with Child-Pugh A and Child-Pugh B were 4.8 (95% CI: 4.1-5.1) and 3.4 months (95% CI: 2.7-4), respectively ($p <$

0.001). Figure 4b shows that the median PFS times of patients with Child-Pugh scores of 5, 6, 7, and 8/9 were 5.0 (95% CI: 4.3-5.8), 4.5 (95% CI: 3.5-4.6), 3.6 (95% CI: 2.7-5.1), and 3.4 months (95% CI: 1.9-3.6), respectively ($p < 0.001$). Figure 4c shows that the median PFS times of patients with mALBI grades 1, 2a, 2b, and 3 were 5.9 (95% CI: 4.7-7.2), 4.4 (95% CI: 3.8-4.9), 3.8 (95% CI: 3.1-4.3) and 2.0 months (95% CI: 0.9-3.8), respectively ($p < 0.001$).

Table 5 shows the results of uni- and multivariate analysis of factors that might be associated with PFS in patients with Child-Pugh B. Univariate analysis showed that absence of viral hepatitis and absence of extrahepatic metastases were favorable factors for PFS. Multivariate analysis identified absence of extrahepatic metastases (HR, 2.84; 95% CI, 1.23–6.57; $p = 0.015$), size of tumor relative to the liver < 50% (HR, 1.78; 95% CI, 1.16–2.72; $p = 0.008$) and treatment with Atezo + Bev (HR, 2.12; 95% CI, 1.22–3.67; $p = 0.008$) were independent factors associated with PFS.

Figure 5a shows that the median PFS times of patients with Child-Pugh A treated with Atezo + Bev, Len, or Sor were 11.0 (95% CI: 8.4-13.3), 9.0 (95% CI: 6.5-9.8), and 3.4 months (95% CI: 3-3.6) respectively ($p < 0.001$). Figure 5b shows that the median PFS times of patients with a Child-Pugh score of 7 treated with Atezo + Bev, Len, or Sor were 6.9 (95% CI: 3.7-NA), 4.4 (95% CI: 3-19.7) and 2.7 months (95% CI: 1.8-

3.5), respectively ($p = 0.023$). Figure 5c shows that the median PFS times of patients with Child-Pugh scores of 8/9 treated with Atezo + Bev, Len, or Sor were 7.9 (95% CI: 1.3-21.2), 2.9 (95% CI: 0.4-NA) and 2.1 months (95% CI: 1.8-3.5), respectively ($p = 0.034$). The median PFS times of patients with Child-Pugh A, a Child-Pugh score of 7, or Child-Pugh scores of 8/9 who were treated with Atezo + Bev were significantly longer than the PFS times of patients who were treated with Len or Sor ($p < 0.001$, $p = 0.023$ and $p = 0.034$, respectively).

The rate of discontinuation of treatment in patients stratified by hepatic reserve

Figure 6a shows that the median of time to discontinuation of treatment of patients with Child-Pugh A and Child-Pugh B were 5.8 and 2.6 months, respectively. Figure 6b shows that the median of time to discontinuation of treatment of patients with Child-Pugh scores of 5, 6, 7 and 8/9 were 6.5, 4.3, 3.8 and 2.1 months, respectively. Figure 6c shows that the median time to discontinuation of treatment of patients with mALBI grade 1, 2a, 2b and 3 were 7.4, 5.7, 3.8 and 1.8 months. Significant stratification of times to discontinuation of treatment was confirmed according to Child-Pugh classifications and scores and mALBI grades at the start of treatment ($p < 0.001$ for all).

Figure 6d shows the rate of discontinuation of treatment of each regimen in patients

with Child-Pugh B. The median time to discontinuation of treatment of patients treated with Atezo + Bev, Len and Sor were 6.9, 5.9 and 6.1 months.

Proportions of patients stratified according to reasons for interruption of treatment

Figure 7a shows bar graphs with the horizontal axis representing Child-Pugh scores and the vertical axis representing proportions of patients categorized by reasons for interruption of treatment. The proportion of patients with Child-Pugh 5 with worsening of general condition as a reason for interruption of treatment was 5.1%, with disease progression was 39.3%, with adverse events was 39.5% and with another reason was 16.1%. The proportion of patients with Child-Pugh 6 with worsening of general condition as a reason for interruption of treatment was 11.2%, with disease progression was 44.2%, with adverse events was 33.5% and with another reason was 11.2%. The proportion of patients with Child-Pugh 7 with worsening of general condition as a reason for interruption of treatment was 17.6%, with disease progression was 34.1%, with adverse events was 43.6%, and with another reason was 4.7%. The proportion of patients with Child-Pugh 8 or 9 with worsening of general condition as a reason for interruption of treatment was 23.1%, with disease progression was 42.3%, with adverse events was 30.8%, and with another reason was 3.8%.

Figure 7b shows bar graphs with the horizontal axis representing mALBI grades and

the vertical axis representing proportions of patients categorized by reasons for interruption of treatment. The proportion of patients with mALBI grade 1 with worsening of general condition as a reason for interruption of treatment was 3.2%, with disease progression was 42.6%, with adverse events was 38.6% and with another reason was 15.7%. The proportion of patients with mALBI grade 2a with worsening of general condition as a reason for interruption of treatment was 8.0%, with disease progression was 37.0%, with adverse events was 40.5%, and with another reason was 14.5%. The proportion of patients with mALBI grade 2b with worsening of general condition as a reason for interruption of treatment was 15.2%, with disease progression was 40.5%, with adverse events was 34.6%, and with another reason was 9.7%. The proportion of patients with mALBI grade3 with worsening of general condition as a reason for interruption of treatment was 16.6%, with disease progression was 41.7%, and with adverse events was 41.7%.

Discussion

The efficacy and safety of systemic therapy for patients with poor liver function remains unclear, because patients with Child-Pugh B are generally excluded from major phase III clinical trials.

The results of the GIDEON study, a nonrandomized observational registry study of patients with HCC who were treated with Sor, showed that there was no difference between the safety profiles of Sor for patients with HCC and either Child-Pugh A or B. However, the patients with HCC and Child-Pugh B were in worse general condition and showed a higher rate of treatment discontinuation than the patients with Child-Pugh A. The median OS time of patients with Child-Pugh B was 5.2 (range: 4.6–6.3) months, which was shorter than the median OS time of patients with Child-Pugh A [6]. Ogasawara et al. reported that among patients with HCC treated with Sor, those with Child-Pugh 7 had a similar incidence of adverse events compared with patients with Child-Pugh A, and shorter OS than patients with Child-Pugh A [7].

In patients with HCC treated with Len, those with Child-Pugh B showed a lower overall response rate (ORR) and shorter OS than patients with Child-Pugh A. Thus physicians should be cautious about administering to and take care when using Len in patients with Child-Pugh B [8, 9].

D'Alessio et al. reported on the safety and efficacy of Atezo + Bev used to treat patients with HCC and Child-Pugh B and found that the adverse events profile in patients with Child-Pugh B was not worse than the adverse events profile of patients with HCC and Child-Pugh A who were treated with Atezo + Bev [11]. However, patients with Child-Pugh B had shorter PFS and OS than Child-Pugh A patients. In another report on the treatment of patients with HCC with Atezo + Bev, there were no differences between the ORRs or disease control rates obtained by either the patients with Child-Pugh A or with B [12].

When choosing systemic therapy for patients with HCC and Child-Pugh B, we compared the outcomes of patients treated with Sor, Len, or Atezo + Bev, which are used as the first-line systemic treatments for unresectable HCC, in accordance with their hepatic reserves. In this study, it was found that the PFS and OS were stratified by the Child-Pugh classification, Child-Pugh score, and mALBI grade. Patients with poor liver function had poor PFS and OS. Previous studies have reported that in patients with HCC, those with Child-Pugh B had shorter OS rates than those with Child-Pugh A, because of poor hepatic reserves and various cirrhotic complications [13]. The stratification of OS and PFS observed in our study may have been affected by prognostic differences in liver function. Our analysis found that a Child-Pugh score of 7 was a factor associated with OS

in patients with Child-Pugh B. And mALBI grade of 3 was an independent predictor of OS in patients with HCC and Child-Pugh score of 7. Patients with a Child-Pugh score of 7 were able to tolerate systemic therapy, which may improve their outcome. However, patients with a Child-Pugh score of 7 who are classified with mALBI grade 3 might consider another type of therapy because they may not benefit from systemic therapy. We think that HCC patients with Child-Pugh score 7 and mALBI 3 who respond well to nutritional therapy may benefit from systemic therapy. The Child-Pugh system has subjective (ascites, hepatic come) and confounding factors (albumin, ascites). However, the ALBI system is calculated by albumin and total bilirubin and does not include subjective factors [16]. With the Child-Pugh system, class A, which is a good indication for systemic therapy, can be extracted. Use of the ALBI system for patients with Child-Pugh B, especially those who score 7, may be useful in identifying patients eligible for systemic therapy. Therefore, when planning the treatment of patients with HCC, it may be useful to combine the Child-Pugh scoring system and ALBI system.

It has been reported that liver function deteriorates during treatment with tyrosine kinase inhibitors such as Sor and Len [15-17]. Vascular endothelial growth factor (VEGF) stimulates the production of nitric oxide (NO), a vasodilator molecule, by endothelial NO synthase [18]. Therefore, the use of a VEGF receptor inhibitor such as Sor and Len leads

to the reduced production of NO. Studies using contrast-enhanced ultrasonography and perfusion CT found that Sor decreased the arterial and portal blood flow to the liver [19, 20]. Whether or not HCC is present in patients with cirrhotic livers, the endothelial dysfunction of liver sinusoidal endothelial cells leads to the decreased production of NO and increased production of vasoconstrictor molecules such as endothelin and thromboxane A2, resulting in the contraction of hepatic stellate cells and increased intrahepatic resistance [21, 22]. Therefore, the use of VEGF receptor inhibitors in patients with cirrhosis may lead to reduced hepatic blood flow and deterioration in liver function. Bev has also been thought to reduce hepatic blood flow, same as Sor and Len. However, our study found that treatment with Atezo + Bev was a significant factor associated with PFS in patients with HCC and Child-Pugh B. Therefore, the degree of reduced hepatic blood flow due to Atezo + Bev might not be extensive. The therapeutic benefits of Atezo + Bev might improve the outcomes of patients with HCC and a Child-Pugh score of 7. No significant difference in OS of each regimen in patients with Child-Pugh B was observed in this study. The fact that Atezo + Bev had a shorter observation period than the other two regimen might have influenced this result.

In our study, the rate of treatment discontinuation was higher in patients with poor hepatic reserve. Patients with poor hepatic reserve at the start of treatment had more

discontinuations due to worsening general condition. These patients may tend to be affected by decreased hepatic blood flow due to VEGF receptor inhibitors.

This study has several limitations, including that it was a retrospective nonrandomized study. We need to perform a prospective and randomized controlled study. Table 2 shows that there were significant differences in the backgrounds of patients with Child-Pugh B among each regimen, which may have influenced the result of this study. The observation period of this study is long, from 2007 to 2022, during this time, there were changes in cirrhosis treatment and strategies for HCC therapy. This historical bias might be effective on the patient background or the prognosis of each treatment group, especially on OS in this study. We need the results of a phase II study of Atezo + Bev for patients with advanced HCC and Child-Pugh B. The results of that study are needed because currently there is no clear evidence for treating patients with HCC and Child-Pugh B with systemic therapies. It will be important to assess the hepatic reserve of patients with HCC and Child-Pugh B before treatment to select patients suitable for systemic therapy. Careful selection of the most suitable patients may lead to better outcomes.

Acknowledgments

We thank the staff of the Division of Nutrition Management at Hiroshima University.

Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki. All study participants gave written informed consent to participate in the study. This study protocol was reviewed and approved by the ethical committee for clinical research of Hiroshima University, approval number [E-882].

Conflicts of Interest Statement

The authors have no relevant financial or non-financial interests to disclose.

Funding Sources

We did not receive any funding.

Author Contributions

Chihiro Kikugawa and Shinsuke Uchikawa: conceptualization, formal analysis,

Tomokazu Kawaoka: conceptualization, formal analysis, writing original draft;

Takahiro Kinami, Shigeki Yano, Kei Amioka, Kensuke Naruto, Kenji Yamaoka, Masataka Tsuge, Yuwa Ando, Yumi Kosaka, Kazuki Ohya, Nami Mori, Shintaro Takaki, Keiji Tsuji, Hirotaka Kouno, Hiroshi Kohno, Kei Morio, Takashi Moriya, Michihiro Nonaka, Yasuyuki Aisaka, Keiichi Masaki, Yoji Honda, Noriaki Naeshiro, Akira Hiramatsu, Hiroshi Aikata and Shiro Oka: data curation.

Data Availability Statement

The data that support the findings of this study are not publicly available, because the datacontain information that could compromise the privacy of the research participants; but are available from C.K (chiroo@hirohshima-u.ac.jp) upon reasonable request.

References

1. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, et al. Cancer statistics for the year 2020: an overview. *Int J Cancer* 2021:149:778–89.

2. Llovet JM, Villanueva A, Marrero JA, Schwartz M, Meyer T, Galle PR, et al. Trial design and endpoints in hepatocellular carcinoma: AASLD consensus conference. *Hepatology* 2021:73:158–91.

3. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008:359: 378–90.

4. Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med* 2020:382:1894–905.

5. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomized, double-blind, placebo-controlled trial. *Lancet Oncol* 2009:10:25–34.

6. Lencioni R, Marrero J, Venook A, Ye SL, Kudo M. Design and rationale for the non-interventional Global Investigation of therapeutic Decision in hepatocellular carcinoma and Of its treatment with sorafenib (GIDEON) study. *Int J Clin Pract* 2010:64:1034–41.

7. Ogasawara S, Chiba T, Ooka Y, Kanogawa N, Saito T, Motoyama T, et al. Sorafenib treatment in child-Pugh a and B patients with advanced hepatocellular carcinoma: safety, efficacy and prognostic factors. *Investig New Drugs* 2015:33:729–739.

8. Ogushi K, Chuma M, Uojima H, Hidaka H, Numata K, Kobayashi S, et al. Safety and efficacy of Lenvatinib treatment in Child-Pugh A and B patients with unresectable hepatocellular carcinoma in clinical practice: A multicenter analysis. *Clin Exp Gastroenterol* 2020:13:385–96.

9. Hiraoka A, Kumada T, Atsukawa M, Hirooka M, Tsuji K, Ishikawa T, et al. Prognostic factor of lenvatinib for unresectable hepatocellular carcinoma in real-world conditions—Multicenter analysis. *Cancer Med* 2019:8:3719–28.

10. Wang DX, Yang X, Lin J, Bai Y, Long JY, Yang XB, et al. Efficacy and safety of Lenvatinib for patients with advanced hepatocellular carcinoma: A retrospective, real-world study conducted in China. *World J Gastroenterol* 2020:26:4465–78.

11. D'Alessio A, Fulgenzi CAM, Nishida N, Schönlein, M, von Felden J, Schulze K, et al. Preliminary evidence of safety and tolerability of atezolizumab plus bevacizumab in patients with hepatocellular carcinoma and Child-Pugh A and B cirrhosis: A real-world study. *Hepatology* 2022:76:1000–12.

12. Tanaka T, Hiraoka A, Tada T, Hirooka M, Kariyama K, Tani J, et al. Therapeutic efficacy of atezolizumab plus bevacizumab treatment for unresectable hepatocellular carcinoma in patients with Child-Pugh class A or B liver function in real-world clinical practice. *Hepatol Res* 2022:52:773–83.

13. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. *J Hepatol* 2006:44:217–31.

14. Hiraoka A, Michitaka K, Kumada T, Izumi N, Kadoya M, Kokudo N, et al. Validation and Potential of Albumin-Bilirubin Grade and Prognostication in a Nationwide Survey of 46,681 Hepatocellular Carcinoma Patients in Japan: The Need for a More Detailed Evaluation of Hepatic Function. *Livier cancer* 2017:6:325-36.

15. Terashima T, Yamashita T, Sunagozaka H, Arai K, Kawaguchi K, Kitamura K, et al. Analysis of the liver functional reserve of patients with advanced hepatocellular carcinoma undergoing sorafenib treatment: prospects for regorafenib therapy. *Hepatol Res* 2018:48:956–66.

16. Hiraoka A, Kumada T, Atsukawa M, Hirooka M, Tsuji K, Ishikawa T, et al. Early relative change in hepatic function with lenvatinib for unresectable hepatocellular carcinoma. *Oncology* 2019:97:334–40.

17. Ueshima K, Kudo M. Comparative analysis on efficacy and change of liver function

between lenvatinib and sorafenib: from experience of REFLECT study. *Kan Tan Sui* 2018:77:278–83.

18. Richard Moreau. VEGF-induced angiogenesis drives collateral circulation in portal hypertension. *J Hepatol* 2005:43:6–8.

19. Sugimoto K, Moriyasu F, Saito K, Rognin N, Kamiyama N, Furuichi Y, et al. Hepatocellular carcinoma treated with sorafenib: early detection of treatment response and major adverse events by contrast-enhanced US. *Liver Int* 2013:33:605–15.

20 Sacco R, Faggioni L, Bargellini I, Ginanni B, Battaglia V, Romano A, et al. Assessment of response to sorafenib in advanced hepatocellular carcinoma using perfusion computed tomography: results of a pilot study. *Dig Liver Dis* 2013:45:776–81.

21. Iwakiri Y. Endothelial dysfunction in the regulation of portal hypertension. *Liver Int* 2012:32:199–213.

22. Anegawa G, Kawanaka H, Yoshida D, Konishi K, Yamaguchi S, Kinjo N, et al. Defective endothelial nitric oxide synthase signaling is mediated by Rho-kinase activation in rats with secondary biliary cirrhosis. *Hepatology* 2008:47:966–77.

Figure legends

Fig. 1. OS in patients stratified by (a) Child-Pugh classification, (b) Child-Pugh score, and (c) by modified ALBI grade.

OS in patients compared by liver function. Patients with Child-Pugh B, Child-Pugh 8/9 and mALBI grade 3 at the start of treatment had significantly shorter OS rates.

Abbreviations: mALBI, modified albumin-bilirubin; MST, median survival time; OS, overall survival

Fig. 2. Proportion of each grade of mALBI in each Child-Pugh score.

Bar graphs with the horizontal axis representing Child-Pugh scores and the vertical axis representing proportions of patients stratified by modified ALBI grade for (a) all patients, (b) patients treated with sorafenib, (c) patients treated with lenvatinib, and (d) patients treated with atezolizumab plus bevacizumab.

(a) The proportions of patients with mALBI grade 3 in patients with Child-Pugh 5, Child-Pugh 6, Child-Pugh 7, and Child-Pugh 8 or 9 were 0%, 0%, 8%, and 33.3%, respectively.

(b) The proportions of patients with mALBI grade 3 in patients with Child-Pugh 5, Child-Pugh 6, Child-Pugh 7, and Child-Pugh 8 or 9 were 0%, 0%, 9.5%, and 37.8%, respectively.

(c) The proportions of patients with mALBI grade 3 in patients with Child-Pugh 5, Child-

Pugh 6, Child-Pugh 7, and Child-Pugh 8 or 9 were 0%, 0%, 7.7%, and 16.7%, respectively. (d) The proportions of patients with mALBI grade 3 in patients with Child-Pugh 5, Child-Pugh 6, Child-Pugh 7, and Child-Pugh 8 or 9 were 0%, 0%, 0%, and 27.3%, respectively.

Abbreviations: mALBI, modified albumin-bilirubin

Fig. 3. Overall survival of patients stratified by treatment regimen with (a) Child-Pugh A, (b) Child-Pugh 7, and (c) Child-Pugh 8/9.

Abbreviations: Atezo + Bev, atezolizumab plus bevacizumab; LEN, lenvatinib; MST, median survival time; OS, overall survival; SOR, sorafenib

Fig. 4. Progression-free survival in patients stratified by (a) Child-Pugh classification (b) Child-Pugh score, and (c) modified ALBI grades.

Patients with Child-Pugh B, Child-Pugh 8/9, and mALBI grade 3 at the start of treatment had significantly shorter PFS than other patients.

Abbreviations: mALBI, modified albumin-bilirubin; PFS, progression-free survival

Fig. 5. Progression-free survival in patients stratified by treatment regimen with (a) Child-Pugh A, (b) Child-Pugh 7, and (c) Child-Pugh 8/9.

Abbreviations: Atezo + Bev, atezolizumab plus bevacizumab; LEN, lenvatinib; MST, median survival time; PFS, progression free survival; SOR, sorafenib

Fig. 6. The rate of discontinuation of treatment comparison by (a) Child-Pugh classification, (b) Child-Pugh score and (c) modified ALBI grade. (d) The rate of discontinuation of treatment comparison by regimen in patients with Child-Pugh B.

Abbreviations: ALBI, albumin-bilirubin; Atezo + Bev, atezolizumab plus bevacizumab; LEN, lenvatinib; SOR, sorafenib

Fig. 7. Proportions of patients stratified by Child-Pugh scores or modified ALBI grades according to reasons for interruption of treatment.

Bar graphs with the horizontal axis representing (a) Child-Pugh scores or (b) modified ALBI grade and the vertical axis representing proportions of patients categorized by reasons for interruption of treatment.

(a) The proportions of patients with worsening of general condition accounting for interruption of treatment in patients with Child-Pugh 5, Child-Pugh 6, Child-Pugh 7, and Child-Pugh 8 or 9 were 5.1% 11.2%, 17.6%, and 23.1%, respectively. (b) The proportions of patients with worsening of general condition accounting for interruption of treatment

in patients with modified ALBI grades 1, 2a, 2b, and 3 were 3.2% 8.0%, 15.2%, and 16.7%, respectively.

“other” includes complete response or at the request of the patient.

Abbreviations: ALBI, albumin-bilirubin

Figure 1

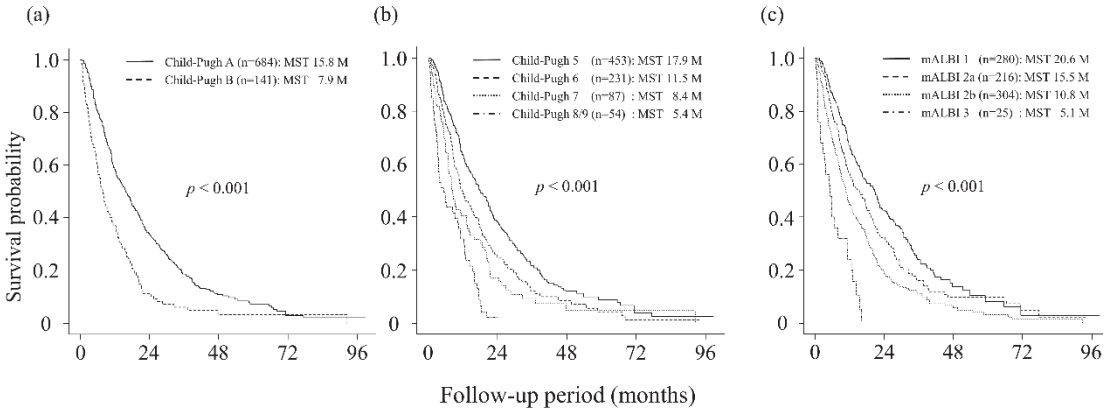

Figure 2

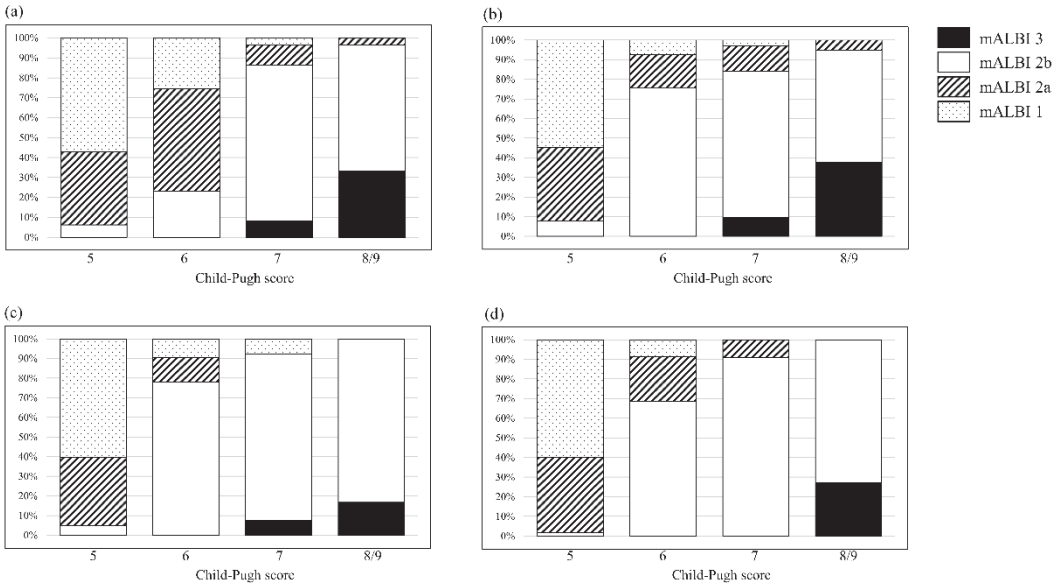

Figure 3

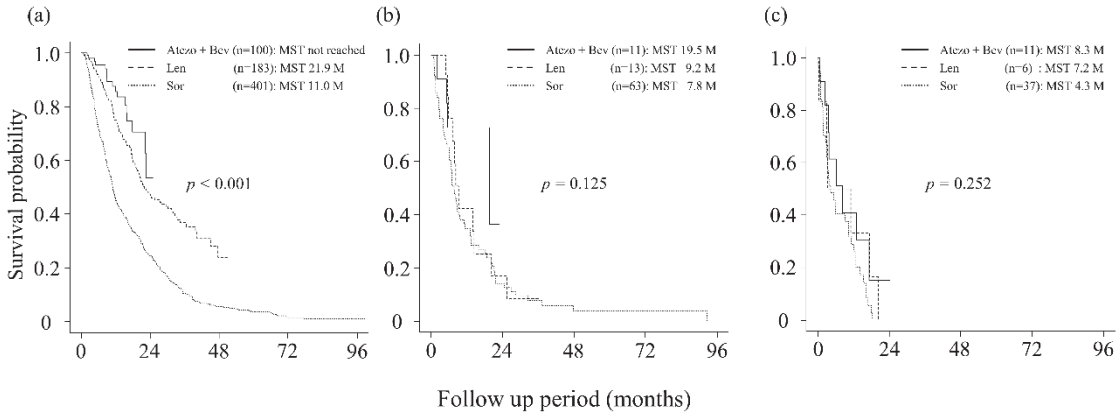

Figure 4

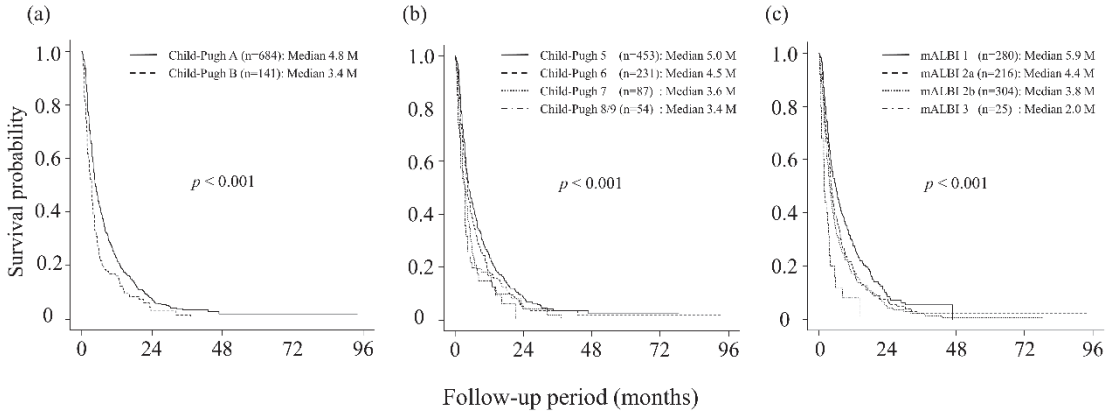

Figure 5

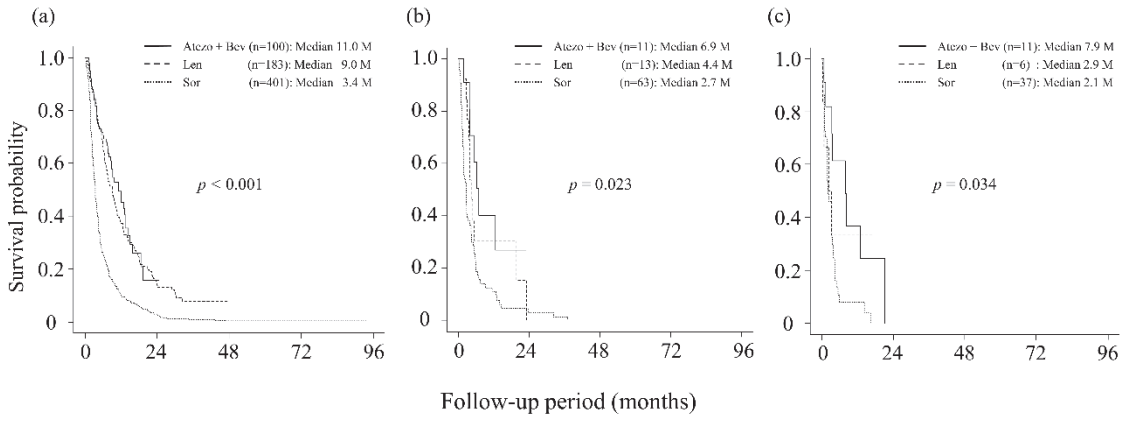

Figure 6

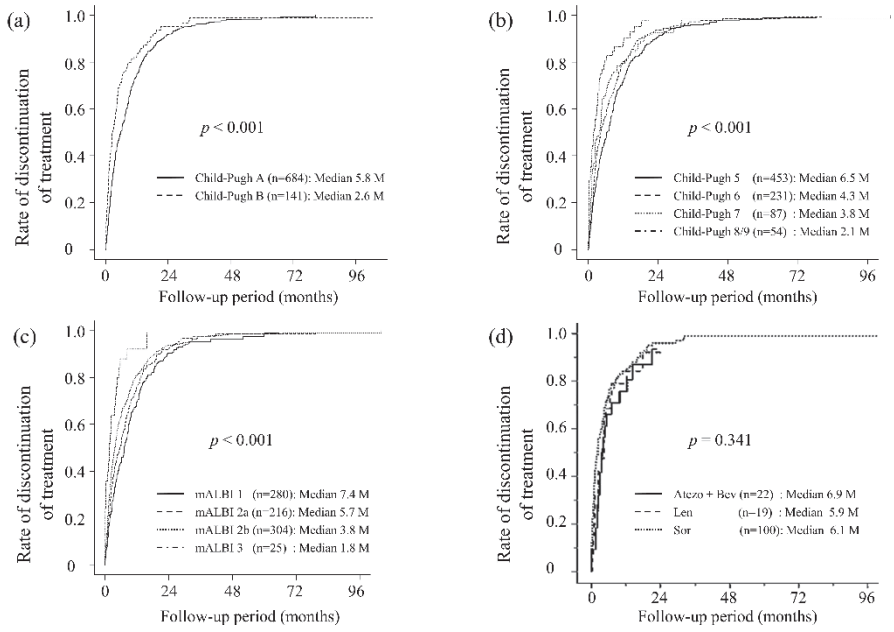

Figure 7

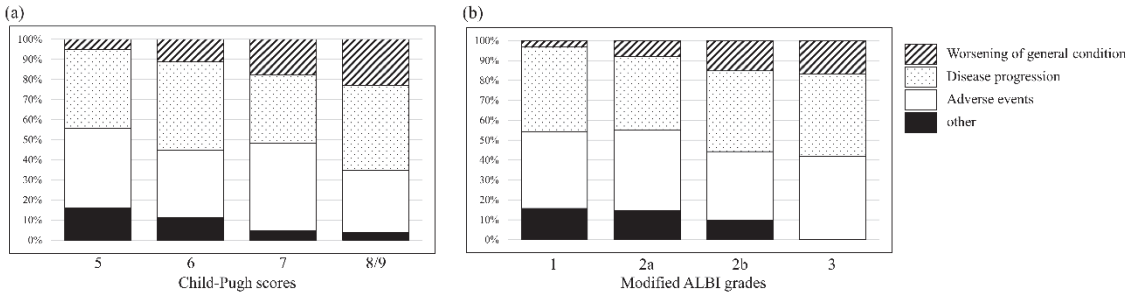
(a)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
5
6
7
8/9
Child-Pugh scores
(b)
1
2a
2b
3
Modified ALBI grades
Worsening of general condition
Disease progression
Adverse events
other

Table 1. Patients background

Variable	Child-Pugh A (*n* = 684)	Child-Pugh B (*n* = 141)	*p*-value
Age, y*	73 (67–79)	70 (62–77)	0.001
Sex, male/female, *n*	564/120	119/22	0.626
Etiology, HBV/HCV/NBNC/B+C, *n*	125/290/260/9	28/55/58/0	0.543
Serum albumin, g/dL*	3.8 (3.5–4.1)	3.1 (2.8–3.4)	<0.001
Serum total bilirubin, mg/dL*	0.8 (0.6–1.0)	1.1 (0.8–1.7)	<0.001
Prothrombin activity, %*	87 (80–96)	69 (63–80)	<0.001
Ascites, none/mild/moderate	671/13/0	75/60/6	<0.001
Encephalopathy, none/mild/moderate	684/0/0	136/5/0	<0.001
Modified ALBI grade, 1/2a/2b/3, *n*	277/205/202/0	3/11/102/25	<0.001
Child-Pugh score, 5/6/7/8/9, *n*	453/231/0/0/0	0/0/87/42/12	<0.001
BCLC stage, A/B/C	28/280/376	3/38/100	0.002
No. of intrahepatic tumors, ≤3/≥4, *n*	252/425	46/94	0.337
Macrovascular invasion, absent/present, *n*	525/159	77/64	<0.001
Extrahepatic metastasis, absent/present, *n*	367/317	69/72	0.31
Tumor size relative to the liver, <50%/≥50%, *n*	594/90	110/31	0.009
Serum α-fetoprotein, ng/mL*	47.9 (6.6–1216.5)	174.1 (11–7044.6)	0.003
Regimen: Sor/Len/Atezo +Bev, *n*	401/183/100	100/19/22	0.002

*median, value in paretheses show interquartile range, unless otherwise indicated.

ALBI, albumin-bilirubin; Atezo + Bev, atezolizumab plus bevacizumab; HBV, hepatitis B virus; HCV, hepatitis C virus; Len, lenvatinib; NBNC, non-B non-C hepatitis; Sor, sorafenib

Table 2. Patients with Child-Pugh B background

Variable	Sor (n = 100)	Len (n = 19)	Atezo + Bev (n = 22)	p-value
Age, y*	70 (61.3-76)	64 (58-79)	69.5 (63.8-78)	0.694
Sex, male/female, *n*	82/18	18/1	19/3	0.290
Etiology, HBV/HCV/NBNC, *n*	23/44/33	3/4/12	2/7/13	0.037
Serum albumin, g/dL*	3.1 (2.8-3.4)	3.2 (2.9-3.4)	3.1 (2.8-3.4)	0.791
Serum total bilirubin, mg/dL*	1.1 (0.8-1.7)	1.0 (0.7-1.5)	1.3 (0.9-1.9)	0.610
Prothrombin activity, %*	68.9 (61.6-79)	79 (69-87)	68 (64-84)	0.157
Ascites, none/mild/moderate	57/40/3	9/10/0	9/10/3	0.160
Encephalopathy, none/mild/moderate	98/2/0	16/3/0	22/0/0	0.030
Modified ALBI grade, 1/2a/2b/3, *n*	2/10/68/20	1/0/16/2	0/1/18/3	0.278
Child-Pugh score, 7/8/9, *n*	63/29/8	13/6/0	11/7/4	0.212
BCLC stage, A/B/C	3/22/75	0/7/12	0/9/13	0.208
No. of intrahepatic tumors, $\leq$3/$\geq$4, *n*	29/71	6/12	11/11	0.179
Macrovascular invasion, absent/present, *n*	56/44	9/10	12/10	0.787
Extrahepatic metastasis, absent/present, *n*	42/58	10/9	17/5	0.009
Tumor size relative to the liver, <50%/$\geq$50%, *n*	77/23	13/6	20/2	0.167
Serum α-fetoprotein, ng/mL*	268.5 (14.7-8597.1)	237.7 (5.3-40990)	12.7 (3.6-99.8)	0.003

*median, value in paretheses show interquartile range, unless otherwise indicated.

ALBI, albumin-bilirubin; Atezo + Bev, atezolizumab plus bevacizumab; HBV, hepatitis B virus; HCV, hepatitis C virus; Len, lenvatinib; NBNC, non-B non-C hepatitis; Sor, sorafenib

Table 3. Univariate and multivariate analysis of factors associated with overall survival in patients with Child-Pugh B

Variable	Univariate analysis	Multivariate analysis		
	p-value	HR	95% CI	*p*-value
Sex, male/female	0.394			
Etiology, non-viral/viral	0.043			
Serum albumin, ≤3.5/>3.5, g/dL	0.569			
Serum total bilirubin, >1.0/≤1.0, mg/dL	0.078			
Prothrombin activity, ≤70%/>70%	0.505			
Ascites, present/absent, n	0.040			
Encephalopathy, present/absent, n	0.132			
Child-Pugh score 7/8 or 9	0.002	1.65	1.08–2.54	0.022
Modified ALBI grade 1 to 2b/3	0.002			
No. of intrahepatic tumors, ≤3/≥4	0.765			
Macrovascular invasion, present/absent	0.031			
Extrahepatic metastasis, present/absent	0.002	1.73	1.20–2.49	0.003
Tumor size relative to the liver, ≥50%/<50%	0.002			
Regimen, Atezo + Bev/TKI	0.059			

ALBI, albumin-bilirubin; Atezo + Bev, atezolizumab plus bevacizumab; CI, confidence interval; HR, hazard risk; TKI, tyrosine kinase inhibitors

Table 4. Univariate and multivariate analysis of factors associated with overall survival in patients with a Child-Pugh score of 7

Variable	Univariate analysis	Multivariate analysis		
	p-value	HR	95% CI	*p*-value
Sex, male/female	0.752			
Etiology, non-viral/viral	0.126			
Serum albumin, ≤3.5/>3.5, g/dL	0.819			
Serum total bilirubin, >1.0/≤1.0, mg/dL	0.027			
Prothrombin activity, ≤70%/>70%	0.752			
Ascites, absent/present, n	0.23			
Encephalopathy, absent/present, n	0.101			
Modified ALBI grade 1 to 2b/3	0.001	2.84	1.23–6.57	0.015
No. of intrahepatic tumors, ≤3/≥4	0.858			
Macrovascular invasion, absent/present	0.113			
Extrahepatic metastasis, absent/present	0.014	1.74	1.09–2.76	0.020
Tumor size relative to the liver, <50%/≥50%	0.104			
Regimen, Atezo + Bev/ TKI	0.125			

ALBI, albumin-bilirubin; Atezo + Bev, atezolizumab plus bevacizumab; CI, confidence interval; HR, hazard ration; TKI, tyrosine kinase inhibitors

Table 5. Univariate and multivariate analysis of progression free survival in patients with Child-Pugh B

Variable	Univariate analysis	Multivariate analysis		
	p-value	HR	95% CI	*p*-value
Sex, male/female	0.334			
Etiology, non-viral/viral	0.008			
Serum albumin, ≤3.5/>3.5, g/dL	0.947			
Serum total bilirubin, >1.0/≤1.0, mg/dL	0.463			
Prothrombin activity, ≤70%/>70%	0.699			
Ascites, present/absent, n	0.252			
Encephalopathy, present/absent, n	0.165			
Child-Pugh score 7/8 or 9	0.276			
Modified ALBI grade 1 to 2b/3	0.514			
No. of intrahepatic tumors, ≤3/≥4	0.079			
Macrovascular invasion, present/absent	0.105			
Extrahepatic metastases, present/absent	<0.001	2.00	1.40–2.87	<0.001
Tumor size relative to the liver, ≥50%/<50%	0.004	1.78	1.16–2.72	0.008
Regimen, Atezo + Bev/TKI	0.002	2.12	1.22–3.67	0.008

ALBI, albumin-bilirubin; Atezo + Bev, atezolizumab plus bevacizumab; CI, confidence interval; HR, hazard ratio; TKI, tyrosine kinase inhibitors