Research Article

The analysis of muscle volume measured by bioelectrical impedance in patients with hepatocellular carcinoma treated with first-line atezolizumab plus bevacizumab combination therapy or first-line lenvatinib

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Running Head: Body composition in HCC treatment

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Abstract

Introduction:

Measurements of body composition, such as the skeletal muscle index (SMI), are useful for predicting prognosis in hepatocellular carcinoma (HCC). This study aimed to analyze the relationship between skeletal muscle changes during therapy with atezolizumab plus bevacizumab (Atezo + Beva) or lenvatinib (Len) and the association between SMI and prognosis.

Methods:

Patients with advanced HCC and Child-Pugh A status received Atezo + Beva or Len as first-line systemic chemotherapy. We assessed prognosis and body composition obtained by bioelectrical impedance analysis (BIA).

Results:

A total of 109 patients received treatment (Atezo + Beva, n=47; Len, n=62). During treatment, the arm SMI was reduced in the Len group and maintained in the Atezo + Beva group. The extracellular water-to-total body water ratio (ECW/TBW) increased significantly in both groups during treatment. In the Atezo + Beva group, no factor was associated with prognosis. Multivariate analysis showed that in the Len group, the arm SMI (hazard ratio [HR], 0.5; 95% CI, 0.26-0.89; *p*=0.02), ECW/TBW (HR, 2.7; 95%

CI, 1.21-6.01; *p*=0.01) and Child-Pugh score (HR, 2.3; 95% CI, 1.31-6.13; *p*=0.004) were associated with progression-free survival (PFS).

Conclusion:

Assessing body composition with BIA before Atezo + Beva and Len treatment may be useful.

Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death worldwide [1-3]. In recent years, the prognosis of HCC has improved due to progress in imaging technology and therapeutic strategies. However, advanced HCC still has a poor prognosis. Systemic therapy is recommended for patients with Barcelona Clinic Liver Cancer (BCLC) intermediate- or advanced-stage cancer, according to the American Association for the Study of Liver Diseases (AASLD) guideline [4].

Recently, combination therapy with atezolizumab plus bevacizumab (Atezo + Beva) for advanced HCC was shown to be superior to treatment with sorafenib in terms of progression-free survival (PFS) and overall survival (OS) [5]. Atezo + Beva was globally approved for unresectable HCC based on the results of the phase 3 IMbrave150 trial [5].

In March 2018, lenvatinib (Len) was approved for insurance coverage in Japan as a first-line therapy for advanced HCC. The REFLECT study demonstrated the noninferiority of Len to sorafenib [6]. In that study, patients who received Len had a significantly better response, as assessed by the modified Response Evaluation Criteria in Solid Tumors (mRECIST), and a longer PFS than patients who received sorafenib, although OS was similar with both drugs [7].

Sarcopenia is defined by a decrease in both handgrip strength and skeletal muscle mass according to the diagnostic criteria of the Japan Society of Hepatology [8]. The prognosis of cirrhotic patients with sarcopenia is generally poor [9]. Previous studies have demonstrated that in patients with HCC, sarcopenia is associated with a worse prognosis and an increased rate of cancer recurrence [10, 11]. In addition to the collective measure of sarcopenia, a loss of skeletal muscle mass and a decrease in handgrip strength are independently associated with a poor prognosis [12-17]. Low SMI in patients treated with Atezo + Beva has been associated with shorter OS or PFS [18, 19]. Previously, we reported that arm SMI was associated with PFS, and ECW/TBW was associated with OS, PFS, and post-progression survival when body composition was assessed by bioelectrical impedance analysis (BAI) [20]. Nevertheless, most of these studies used single-slice computed tomography (CT), not BIA, to measure skeletal muscle mass.

No study has compared body composition in patients treated with Atezo + Beva and Len. We studied the relationship between body composition assessment by BIA and prognosis in patients treated with Atezo + Beva or Len.

Methods

Patients

Patients eligible for this retrospective cohort study had advanced HCC and Child-Pugh class A liver disease. Patients were treated with Atezo + Beva or Len as first-line systemic chemotherapy at Hiroshima University. Atezo + Beva treatment was started between October 2020 and April 2022, and Len treatment was started between April 2018 and April 2022. Exclusion criteria were as follows: (1) Atezo + Beva administered less than three times or a duration of treatment with Len less than 6 weeks and (2) absence of body composition measurements by BIA before and after the start of treatment. Patients meeting study criteria were classified into the Atezo + Beva group or the Len group.

Treatments

Patients in the Atezo + Beva group received atezolizumab 1200 mg intravenously plus bevacizumab 15 mg/kg once every 3 weeks. Patients in the Len group received lenvatinib 8 mg/ 12 mg once daily based on their body weight. Treatment interruptions and dose reductions were permitted for adverse drug reactions. Patients continued therapy until death or until one of the following criteria for cessation of therapy was

met: adverse events (AEs) that required termination of treatment, deterioration of Eastern Cooperative Oncology Group performance status to 4, worsening liver function, or withdrawal of consent.

Body composition analysis

Body composition was measured by BIA using Inbody 720® (until August 2021) or Inbody 770® (from September 2021) (BioSpace Co. Ltd., Seoul, Korea). The BIA used in this study was a 4-pole, 8-point direct segment multifrequency BIA that can evaluate not only total muscle mass, but also muscle mass specifically of the right arm, left arm, trunk, right leg, and left leg. The first body composition measurement was taken within one year of treatment initiation, the second measurement was taken around 2 months after the start of treatment, and the third measurement was taken around 6 months after the start of treatment. Five patients in Atezo + Beva group and four patients in the Len group failed the third measurement. Total SMI (kg/m^2) was calculated by dividing the limb skeletal muscle mass (kg) by the square of the height (m^2). Arm SMI was calculated by dividing the arm's skeletal muscle mass (kg) by the square of the height (m^2). Leg SMI was calculated by dividing the leg's skeletal muscle mass (kg) by the square of the height (m^2). According to the Japan Society of Hepatology criteria,

patients with total SMI values < 7.0 kg/m^2 (males) and < 5.7 kg/m^2 (females) were defined as having loss of skeletal muscle mass. We defined the median of arm SMI value as cutoff value to divide the patients into high or low groups. The cutoff value was as follow: arm SMI (1.86 [males] and 5.7 [females]). The BIA measured the extracellular water to total body water ratio (ECW/TBW), an oedema index. Because excessive ECW results in an oedematous state, the ECW/TBW is an index that reflects the degree of oedema. An ECW/TBW > 0.400 was defined as an overhydrated state.

Assessment of treatment response

Evaluation of response to treatment was performed by image inspection, such as with CT and magnetic resonance imaging (MRI), according to mRECIST and Response Evaluation Criteria in Solid Tumors (RECIST). In the Atezo + Beva group, CT or MRI was performed 4 weeks after treatment initiation and then every 2 months. In the Len group, CT or MRI was performed every 1-3 months. Adverse drug reactions were defined according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE 4.0).

Statistical analysis

In this study, we set the cutoff value for total SMI according to the sarcopenia diagnostic criteria of the Japanese Society of Hepatology, and those for arm SMI and leg SMI were set at the median value. Continuous variables were expressed as median (range), while categorical variables were expressed as absolute and relative frequencies. The student's t test was used to compare continuous data. Either Pearson's chi-square test or Fisher's exact test was used to compare groups for significant differences in the distribution of categorical variables. The OS and PFS were calculated using Kaplan–Meier survival curves and a log-rank test. Cox regression analysis was carried out for multivariate analysis. A p value < 0.05 was considered statistically significant. JMP statistical software version 16.2.0 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

Results

Characteristics of patients treated with first line-line systemic chemotherapy with Atezolizumab plus Bevacizumab or Lenvatinib

A total of 109 patients were analyzed (Atezo + Beva group, n=47; Len group, n=62). The median age was 74 years in the Atezo+ Beva group and 72.5 years in the Len group, and 11/47 patients in the Atezo + Beva group and 11/62 in the Len group were female. Patient characteristics are summarized in Table 1; none differed significantly between treatment groups.

Response to first-line treatment with Atezolizumab plus Bevacizumab or Lenvatinib by mRECIST and RECIST

No significant difference was noted between the Atezo + Beva group and the Len group in objective response rate (ORR) or disease control rate (DCR) according to mRECIST or RECIST v1.1. By mRECIST, the ORR was 51.1% vs 65.6%, respectively (p=0.13), and the DCR was 85.1% vs 88.5%, respectively (p=0.60); by RECIST v1.1, the ORR was 38.3% vs 38.7%, respectively (p=0.97), and the DCR was 85.1% vs 85.5%, respectively (p=0.96) (Table 2).

The Atezo + Beva and Len groups did not differ significantly in terms of median OS

(20.8 vs. 19.1 months, respectively; $p = 0.55$) (Figure 1a) and PFS (12.0 vs. 7.2 months, respectively; $p = 0.15$) (Figure 1b) at the time of this analysis.

Adverse events

A total of 100 patients (91.7%) suffered from any grade AEs. Table 3 shows AEs that occurred during treatment in more than 10% of all patients. Incidence of hypertension (57.4% vs 95.2%, $p<0.0001$), fatigue (34.0% vs 85.5%, $p<0.0001$), anorexia (23.4% vs 80.6%, $p<0.0001$), diarrhea (14.9% vs 45.2%, $p=0.008$), elevated aspartate aminotransferase/alanine aminotransferase (17.0% vs 40.3%, $p=0.009$), thyroid function abnormality (8.5% vs 45.2%, $p<0.0001$), hand-foot skin reaction (0.0% vs 46.8%, $p<0.0001$), hoarseness (0.0% vs 24.2%, $p=0.0003$) and decreased platelet count (4.3% vs 21.0%, $p=0.008$) were more frequently observed in patients treated with Len. Proteinuria (40.4% vs 43.5, $p=0.74$) and fever (10.6% vs 14.5%, $p=0.55$) were similar between the two groups.

AEs that occurred during treatment in more than 10% of all patients are summarized in Table 4. Incidence of hand-foot skin reactions (17.2% vs 37.3%, $p=0.03$) were common in patients within the high arm SMI group. Although other AEs are similar in the two groups.

Change in body composition during treatment

The median duration from the start of Atezo + Beva and Len treatment to the second body composition assessment was 67 days. The arm SMI measured 3 and 6 months after the start of treatment decreased significantly from that before treatment in the Len group, whereas there were no significant changes, and the arm SMI was maintained in the Atezo +Beva group (Figure 2a). Both the total SMI and leg SMI increased only in the Atezo + Beva group from before treatment to 6 months after treatment initiation, and the total SMI and leg SMI did not change in the Len group (Figure 2b and c). In both groups, the ECW/TBW increased from before treatment to 2 months and 6 months after treatment initiation (Figure 2d).

Factors associated with progression-free survival and overall survival

No factors were associated with PFS in the Atezo + Beva group (Table 5). Univariate analysis showed that Child-Pugh score 5 and arm SMI ≥ 1.86 (males), ≥ 1.4 (females) were significant factors contributing to an extension of PFS in the Len group. Multivariate analysis showed that the arm SMI (hazard ratio [HR], 0.5; 95% CI, 0.26-0.89; p=0.02), ECW/TBW (HR, 2.7; 95% CI, 1.21-6.01; p=0.01) and Child-Pugh score (HR, 2.3; 95% CI, 1.31-6.13; p=0.004) were associated with PFS in the Len group.

In the Atezo+ Beva group, Child-Pugh score 5 was significant by univariate analysis, but multivariate analysis showed that no factor was significantly associated with OS. Univariate analysis showed that Child-Pugh score 5 and absence of macrovascular invasion (MVI) and AFP < 25 ng/mL were significant factors contributing to an extension of OS in the Len group (Table 6). Multivariate analysis showed that MVI (HR, 3.1; 95% CI, 1.34-6.95; *p*=0.004) and AFP (HR, 3.0; 95% CI, 1.44-6.41; *p*=0.002) were associated with OS in the Len group.

Comparison of prognosis in patients with low or high arm SMI

All Patients were divided into two groups according to their arm SMI values: A low arm SMI group and a high arm SMI group.

In low arm SMI groups, Atezo + Beva and Len groups did not differ significantly in terms of median OS (20.8 vs. 18.8 months, respectively; $p = 0.72$) (Figure 3a) at the time of this analysis. In the high arm SMI group, Atezo + Beva and Len groups did not differ significantly in terms of median OS (not reached vs. 21.5 months, respectively; $p = 0.55$) (Figure 3b) at the time of this analysis. In low arm SMI groups, Atezo + Beva and Len groups did not differ significantly in terms of median PFS (12.0 vs. 5.9 months, respectively; $p = 0.10$) (Figure 3c) at the time of this analysis. In the high arm SMI

group, Atezo + Beva and Len groups did not differ significantly in terms of median PFS (not reached vs. 11.1 months, respectively; $p = 0.61$) (Figure 3d) at the time of this analysis.

Discussion

The loss of skeletal muscle has been reported to be associated with poor prognosis in patients with HCC [21-26]. Patients with HCC treated with molecularly targeted agents had a worse prognosis than patients without sarcopenia in previous reports [27, 28].

With age, the balance between protein synthesis and degradation in skeletal muscle is disrupted, leading to muscle weakness and sarcopenia [24, 25]. Patients with liver disease are similarly prone to sarcopenia, which is known to result from malnutrition [26]. In HCC, skeletal muscle depletion is induced by disease progression and increased expression of inflammatory cytokines [10]. Furthermore, during treatment with antineoplastic agents, AEs such as nausea and loss of appetite reduce oral intake and can cause loss of muscle mass. Sarcopenia is thought to be associated with alterations in the phosphoinositide PI3k/Akt/mTOR signaling pathway, which is associated with muscle protein synthesis [27-30]. Since tyrosine kinase inhibitor (TKI) therapies inhibit this pathway [31-33], there is concern about further loss of muscle mass during treatment in patients with cancer.

We previously reported that loss of skeletal muscle mass during Len treatment is associated with a worse prognosis in HCC [20], and TKI treatment for HCC caused a loss of skeletal muscle [34]. Recently, Matsumoto et al. showed that a decrease in the

SMI was significantly associated with PFS in patients with HCC treated with Atezo + Beva [18]. Hiraoka et al. reported that muscle volume loss was significant factor of OS and PFS in patients with treated Atezo+ Beva [19]. They used CT to calculate the SMI. On the other hand, we assessed changes in body composition, including the SMI, by BIA in patients treated with Atezo + Beva or Len. In this study, the arm SMI decreased only in patients treated with Len; in contrast, it was maintained in patients treated with Atezo + Beva. Furthermore, in patients treated with Len, a decrease in the arm SMI was associated with PFS. We analyzed the OS and PFS of both groups in patients with a low arm SMI and high arm SMI. PFS of patients with treated with Atezo + Beva was longer than patients treated with Len, but there was no significant difference. We think further long-term observation in needed.

The SMI is affected by oedema and may be overestimated when it is measured by BIA [20]. In addition, the SMI measured by BIA may be higher than it really is in the presence of fluid overload, and the leg SMI is more susceptible to oedema [8]. In another report, in patients with cirrhosis who were prone to oedema, the arm SMI was more useful for predicting prognosis than the leg SMI due to the susceptibility of the leg SMI to oedema [35]. Decrease of arm SMI in patients treated with Len suggest that patients treated with Len may be more prone to muscle mass loss than those treated with

Atezo + Beva. The frequent appearance AEs in patients treated with Len may have associated with the loss of muscle mass.

In this study, we also examined the total SMI and the leg SMI. Increases in those parameters in the Atezo + Beva group from pre-treatment to 6 months after the start of treatment did not affect prognosis. As the ECW/TBW, an index of oedema, increased in both groups in this study, we expect that this led to an increase in the SMI and the leg SMI in the Atezo + Beva group, which tended to maintain muscle mass, and maintenance in the Len group, which tended to lose muscle mass.

Previously, we reported that the ECW/TBW was associated with OS, PFS [20], maintenance of the relative dose intensity and the duration until reduction or withdrawal of treatment in patients with HCC treated with Len [36]. The ECW/TBW indicates abnormalities related to dehydration, and increases in ECW are often observed among patients with cancer [37] and independently associated with OS and mortality in patients with cancer and sarcopenia [38]. In this study, the pre-treatment ECW/TBW affected PFS in patients treated with Len, as previously reported. Although the ECW/TBW increased during treatment in the Atezo + Beva group, a high pre-treatment ECW/TBW did not affect prognosis. Maesaka et al. reported that Atezo + Beva therapy was superior to Len therapy in the maintenance of hepatic reserve, and lower rates of

severe AEs were observed with Atezo + Beva therapy as compared with Len therapy [39]. Atezo + Beva therapy is associated with fewer AEs than Len, which may have contributed to longer PFS from fewer treatment interruptions or discontinuations due to AEs in patients with a high ECW/TBW.

We found that a low arm SMI was associated with shorter PFS in patients treated with Len. In contrast, the arm SMI was not associated with PFS in patients treated with Atezo + Beva.

This study has several limitations, such its single-center nature and retrospective design. In addition, the observation period was shorter in the Atezo + Beva group. In the future, long-term prospective, multicenter studies are expected.

Conclusion

Patients with unresectable HCC who have a low arm SMI or a high ECW/TBW assessed by BIA before starting systemic chemotherapy with Len may have a poor prognosis. Assessing body composition with BIA before Atezo +Beva or Len treatment may be extremely useful as a prognostic factor.

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Statement of Ethics

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

Conflict of Interest Statement

No author declare Conflict of Interests for this article.

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None to declare.

Author Contributions

Chihiro Kikugawa: conceptualization, formal analysis, writing original draft; Tomokazu Kawaoka: conceptualization, review, editing; Takahiro Kinami, Shintaro Yamasaki,

Masanari Kosaka, Yusuke Johira, Shigeki Yano, Kei Amioka, Kensuke Naruto, Yuwa Ando, Kenji Yamaoka, Yuji Teraoka, Shinsuke Uchikawa, Takuro Uchida, Hatsue Fujino, Takashi Nakahara, Atsushi Ono, Eisuke Murakami, Wataru Okamoto, Masami Yamauchi, Daiki Miki, Masataka Tsuge, Michio Imamura, Hiroshi Aikata and Shiro Oka; data curation.

Data Availability Statement

The data that support the findings of this study are not publicly available due to [their containing information that could compromise the privacy of research participants] but are available from C.K (chiroo@hirohshima-u.ac.jp) upon reasonable request.

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Figure legends

Fig. 1. Overall survival (OS) and progression-free survival (PFS) with atezolizumab + bevacizumab vs lenvatinib.

(a) OS and (b) PFS. Solid line, Atezo + Beva. Dotted line, Len. Treatment choice was not associated with OS and PFS. Treatment choice was not associated with OS and PFS at the time of this analysis.

Abbreviations: Atezo + Beva, atezolizumab plus bevacizumab; Len, lenvatinib; OS, overall survival; PFS, progression-free survival.

Fig. 2. Changes in body composition during treatment.

(a) arm SMI, (b) leg SMI, (c) total SMI and (d) ECW/TBW.

(a) The arm SMI measured by bioelectrical impedance analysis (BIA) decreased significantly from pre-treatment to 6 months after treatment initiation in the Len group. (b) and (c) The leg SMI and total SMI measured by BIA increased significantly from pre-treatment to 6 months after treatment initiation in the Atezo + Beva group. (c) The ECW/TBW measured by BIA increased in both groups.

The symbols represent the individual data. The boxes show the interquartile ranges (IQR); the upper, middle, and lower lines represent the 75^{th} percentiles, median values and 25^{th}

percentiles, respectively. The bars show the ranges of the data from the 25th percentile −(1.5×IQR) to the 75th percentile +(1.5×IQR).

Abbreviations: Atezo + Beva, atezolizumab plus bevacizumab; Len, lenvatinib; SMI, skeletal muscle mass index; ECW/TBW, extracellular water to total body water ratio.

Fig. 3. *Comparison of prognosis in patients with low or high arm SMI*

(a) OS in patients with low arm SMI and (b) OS in patients with high arm SMI. (c) PFS in patients with low arm SMI and (d) PFS in patients with high arm SMI. Solid line, Atezo + Beva. Dotted line, Len.

Abbreviations: Atezo + Beva, atezolizumab plus bevacizumab; Len, lenvatinib; OS, overall survival; PFS, progression-free survival; SMI, skeletal muscle mass index.

Figure 1

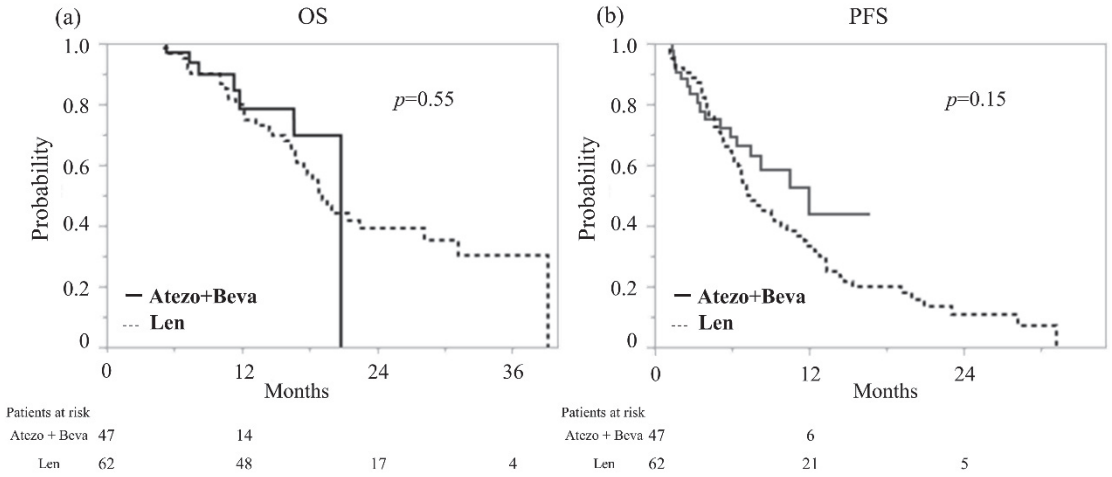

Figure 2

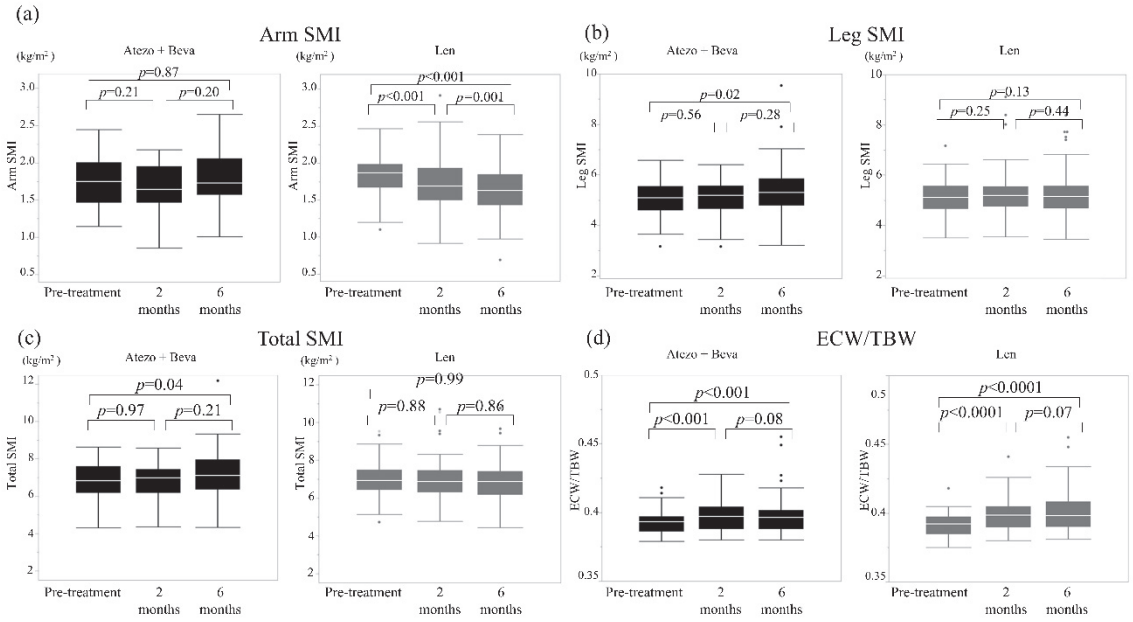

Figure 3

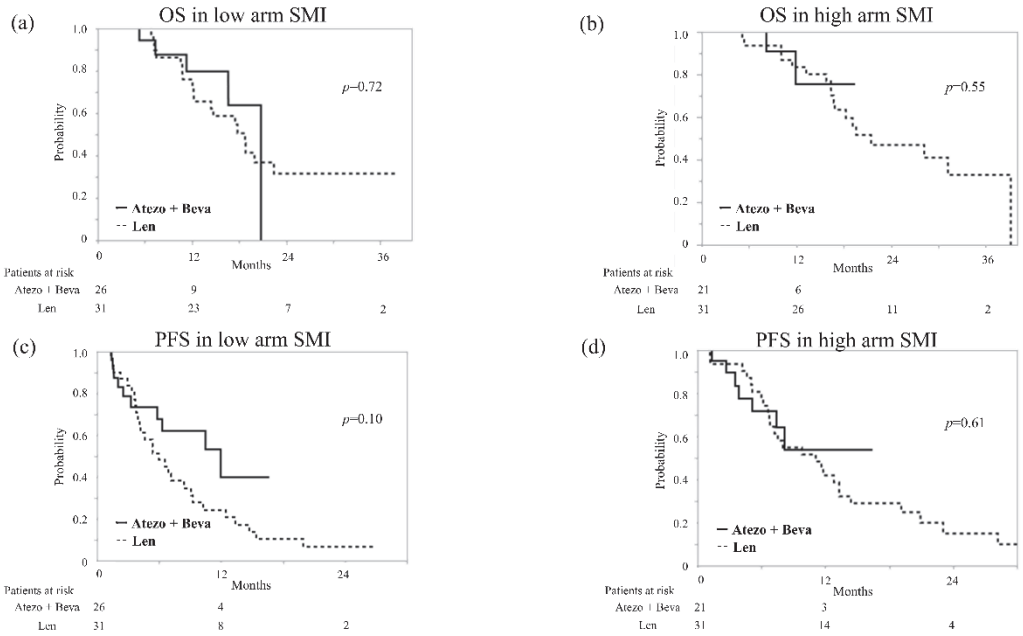
(a)
OS in low arm SMI
p=0.72
Probability
Atezo + Beva
Len
Months
Patients at risk
Atezo + Beva 26 9
Len 31 23 7 2
(b)
OS in high arm SMI
p=0.55
Probability
Atezo + Beva
Len
Months
Patients at risk
Atezo + Beva 21 6
Len 31 26 11 2
(c)
PFS in low arm SMI
p=0.10
Probability
Atezo + Beva
Len
Months
Patients at risk
Atezo + Beva 26 4
Len 31 8 2
(d)
PFS in high arm SMI
p=0.61
Probability
Atezo + Beva
Len
Months
Patients at risk
Atezo + Beva 21 3
Len 31 14 4

Table 1. Patient characteristics

	Atezo + Beva (*n*=47)	Len (*n*=62)	*p* value
Gender, females/males	11/36	11/51	0.47
Age, years	74 (55-90)	72.5 (46-90)	0.54
Etiology, non-viral/viral	21/26	35/27	0.22
Total bilirubin, mg/dL	0.8 (0.3-1.4)	0.7 (0.4-1.6)	0.84
Albumin, g/dL	3.9 (2.8-4.6)	3.7 (2.9-4.9)	0.34
Prothrombin activity, %	93 (62-120)	88 (57-131)	0.20
Platelet count, /μL	13.6 (3.2-26.4)	14.4 (4.8-27.5)	0.81
Child-Pugh score, 5/6	35/12	37/25	0.10
BCLC, A and B/C	23/24	32/30	0.78
Extrahepatic metastasis, -/+	33/14	41/21	0.65
Macrovascular invasion, -/+	36/11	51/11	0.47
TNM stage, II and III/IV	10/37	11/51	0.64
Hepatic tumor size, mm	23 (0-130)	32 (0-120)	0.27
No. of hepatic tumors, ≤3/≥4	25/22	25/37	0.18
Alpha-fetoprotein, ng/mL	27.6 (1.2-35780)	23 (9.5-121590)	0.23
DCP, mAU/mL	351 (822-186190)	194.5 (1142-1083990)	0.48
SMI Males, kg/m^2	7.0 (5.5-8.3)	7.1 (5.3-9.5)	0.27
SMI Females, kg/m^2	5.7 (4.3-8.6)	5.8 (4.7-6.9)	0.64
Arm SMI Males, kg/m^2	1.8 (1.1-2.3)	1.9 (1.1-2.1)	0.11
Arm SMI Females, kg/m^2	1.5 (1.2-2.4)	1.3 (1.3-2.0)	0.66
Leg SMI, Males, kg/m^2	5.3 (4.1-6.1)	5.3 (3.9-7.2)	0.45
Leg SMI, Females, kg/m^2	4.3 (3.2-6.6)	4.4 (3.5-4.9)	0.68
ECW/TBW, <0.400/≥0.400	39/8	52/10	0.90

Categorical data are represented as number of patients, and continuous data are represented as median (range).

Abbreviation: Atezo + Beva, atezolizumab plus bevacizumab; BCLC, Barcelona Clinic Liver Cancer; DCP, des-gamma-carboxyprothrombin; ECW/TBW, extracellular water/total body water; Len, lenvatinib; SMI, skeletal muscle mass index; TNM, tumor-node-metastasis classification.

Table 2. Best response to first-line systemic chemotherapy

	mRECIST			RECIST v1.1		
	Atezo + Beva	Len	*p* value	Atezo + Beva	Len	*p* value
CR	7	6		1	0	
PR	17	34		17	24	
SD	16	15		22	29	
PD	7	6		7	9	
NE	0	1		0	0	
ORR (%)	51.1	65.6	0.13	38.3	38.7	0.97
DCR (%)	85.1	88.5	0.60	85.1	85.5	0.96

Abbreviation: Atezo + Beva, atezolizumab plus bevacizumab; CR, complete response; DCR, disease control rate; Len, Lenvatinib; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NE, not evaluated; ORR, objective response rate; PD, progressive disease; PR partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1, SD, stable disease.

Table3. Comparison of adverse events observed in patients treated with Atezo + Bev and patients treated with Len.

n (%)	Total	Atezo + Bev (*n*=47)		LEN (*n*=62)		*P value**
		Any grade	Grade 3	Any grade	Grade 3	
Hypertension	86 (79.0)	27 (57.4)	11 (23.4)	59 (95.2)	5 (8.1)	<0.0001
Fatigue	69 (63.3)	16 (34.0)	0 (0.0)	53 (85.5)	8 (13.0)	<0.0001
Anorexia	61 (56.0)	11 (23.4)	0 (0.0)	50 (80.6)	10 (16.1)	<0.0001
Proteinuria	46 (42.2)	19 (40.4)	11 (23.4)	27 (43.5)	11 (17.7)	0.74
Diarrhea	35 (32.1)	7 (14.9)	0 (0.0)	28 (45.2)	6 (9.7)	0.008
Elevated AST/ALT	33 (30.3)	8 (17.0)	3 (6.4)	25 (40.3)	3 (4.8)	0.009
Thyroid function abnormality	32 (29.4)	4 (8.5)	0 (0.0)	28 (45.2)	1 (1.6)	<0.0001
Hand-foot skin reaction	29 (26.6)	0 (0.0)	0 (0.0)	29 (46.8)	1 (1.6)	<0.0001
Hoarseness	15 (13.8)	0 (0.0)	0 (0.0)	15 (24.2)	0 (0.0)	0.0003
Decreased PLT count	15 (13.8)	2 (4.3)	0 (0.0)	13 (21.0)	1 (1.6)	0.008
Fever	14 (12.8)	5 (10.6)	0 (0.0)	9 (14.5)	0 (0.0)	0.55

Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Atezo + Beva, atezolizumab plus bevacizumab; Len, Lenvatinib; PLT, platelet.

Table 4. Comparison of adverse events observed in patients with low arm SMI and patients with high arm SMI.

	Total	Low arm SMI (Males < 1.86, Females < 1.4) (*n*=58)		High arm SMI (Males ≥ 1.86, Females ≥ 1.4) (*n*=51)		*P value**
n (%)		Any grade	Grade 3	Any grade	Grade 3	
Hypertension	86 (79.0)	45 (77.6)	11 (19.0)	41 (80.4)	5 (9.8)	0.99
Fatigue	69 (63.3)	36 (62.1)	2 (3.4)	33 (64.7)	6 (11.8)	0.97
Anorexia	61 (56.0)	34 (58.6)	2 (3.4)	27 (52.9)	8 (15.7)	0.42
Proteinuria	46 (42.2)	23 (39.7)	12 (20.7)	23 (45.1)	10 (19.6)	0.68
Diarrhea	35 (32.1)	15 (25.9)	2 (3.4)	20 (39.2)	4 (7.8)	0.17
Elevated AST/ALT	33 (30.3)	17 (29.3)	4 (6.9)	15 (29.4)	2 (3.9)	0.76
Thyroid function abnormality	32 (29.4)	17 (29.3)	0 (0.0)	15 (29.4)	1 (2.0)	0.91
Hand-foot skin reaction	29 (26.6)	10 (17.2)	1 (1.7)	19 (37.3)	0 (0.0)	0.03
Hoarseness	15 (13.8)	9 (15.5)	0 (0.0)	6 (11.8)	0 (0.0)	0.52
Decreased PLT count	15 (13.8)	8 (13.8)	1 (1.7)	7 (13.7)	0 (0.0)	0.93
Fever	14 (12.8)	5 (8.6)	0 (0.0)	9 (17.6)	0 (0.0)	0.18

Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Atezo + Beva, atezolizumab plus bevacizumab; Len, Lenvatinib; PLT, platelet; SMI, skeletal muscle mass index.

Table 5. Univariate and multivariate analysis of progression-free survival

		Atezo + Beva				Len			
		Univariate analysis	Multivariate analysis			Univariate analysis	Multivariate analysis		
			p value	95% CI	HR		*p* value	95% CI	HR
Gender	Female								
	Male	0.06	0.06	0.11-1.03	0.3	0.82	0.75	0.42-1.86	0.9
Age, years	< 70								
	≥ 70	0.49	0.64	0.42-4.06	1.3	0.40	0.07	0.27-1.04	0.5
Etiology	non-viral								
	viral	0.74				0.12			
Platelets, μL	< 140000								
	≥ 140000	0.66				0.08			
Child-Pugh score	5								
	6	0.52	0.49	0.49-4.45	1.5	0.002	0.004	1.31-6.13	2.3
Extrahepatic metastasis	-								
	+	0.18				0.70			
Macrovascular invasion	-								
	+	0.14				0.44			
No. of tumors	< 4								
	≥ 5	0.20				0.45			
Alpha-fetoprotein, ng/mL	< 25								
	≥ 25	0.45				0.59			
SMI before treatment, kg/m^2	Males < 7, Females < 5.7								
	Males ≥ 7, Females ≥ 5.7	0.35				0.29			
Arm SMI before treatment, kg/m^2	Males < 1.86, Females < 1.4								

	Males ≥ 1.86, Females ≥ 1.4	0.71	0.55	0.24-2.12	0.7	0.04	0.02	0.26-0.89	0.5
Leg SMI before treatment, kg/m^2	Males < 5.3, Females < 4.4								
	Males ≥ 5.3, Females ≥ 4.4	0.46				0.58			
ECW/TBW before treatment	< 0.400								
	≥ 0.400	0.61	0.82	0.19-3.8	0.8	0.13	0.01	1.21-6.01	2.7

Abbreviation: Atezo + Beva, atezolizumab plus bevacizumab; CI, confidence interval; ECW/TBW, extracellular water/total body water; HR, hazard ratio; Len, lenvatinib; SMI, skeletal muscle mass index.

Table 6. Univariate and multivariate analysis of overall survival

		Atezo + Beva				Len			
		Univariate analysis	Multivariate analysis			Univariate analysis	Multivariate analysis		
			p value	95% CI	HR		*p* value	95% CI	HR
Gender	Female								
	Male	0.57				0.45			
Age, years	< 70								
	≥ 70	0.57				0.38			
Etiology	non-viral								
	viral	0.43				0.35			
Platelets, μL	< 140000								
	≥ 140000	0.23				0.53			
Child-Pugh score	5								
	6	0.04	0.10	0.72-40.50	5.4	0.09	0.27	0.73-3.18	1.5
Extrahepatic metastasis	-								
	+	0.73				0.25			
Macrovascular invasion	-								
	+	0.96	0.42	0.28-20.84	2.4	0.004	0.008	1.34-6.95	3.1
No. of tumors	< 4								
	≥ 5	0.79				0.56			
Alpha-fetoprotein, ng/mL	< 25								
	≥ 25	0.50	0.64	0.09-4.26	0.6	0.002	0.004	1.44-6.41	3.0
SMI before treatment, kg/m^2	Males < 7, Females < 5.7								
	Males ≥ 7, Females ≥ 5.7	0.51				0.19			
Arm SMI before treatment, kg/m^2	Males < 1.86, Females < 1.4								

	Males ≥ 1.86, Females ≥ 1.4	0.58	0.91	0.13-0.16	0.9	0.33	0.94	0.45-2.10	1.0
Leg SMI before treatment, kg/m^2	Males < 5.3, Females < 4.4								
	Males ≥ 5.3, Females ≥ 4.4	0.64				0.26			
ECW/TBW before treatment	< 0.400								
	≥ 0.400	0.50	0.54	0.20-21.4	2.1	0.26	0.21	0.70-4.96	1.9

Abbreviation: Atezo + Beva, atezolizumab plus bevacizumab; CI, confidence interval; ECW/TBW, extracellular water/total body water; HR, hazard ratio; Len, lenvatinib; SMI, skeletal muscle mass index.