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Rechallenge With Lenvatinib After Atezolizumab Plus Bevacizumab Treatment for Hepatocellular Carcinoma

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Clinical study

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Abstract

Background/Aim: Atezolizumab plus bevacizumab and lenvatinib are the key drugs in the current systemic chemotherapeutic regimen for hepatocellular carcinoma (HCC). Studies have reported the potential effectiveness of lenvatinib introduction after an atezolizumab plus bevacizumab treatment; however, the therapeutic effectiveness of a lenvatinib rechallenge after an atezolizumab plus bevacizumab treatment remains unclear.

Patients and Methods: Thirteen consecutive patients who were rechallenged with lenvatinib after clinical failure following treatments with lenvatinib and atezolizumab plus bevacizumab were included. A comparative study was conducted on the duration and treatment efficacy of the first and second lenvatinib treatments and on the pre- and post-treatment liver function.

Results: The median ratios of the 1-month post-treatment alpha-fetoprotein (AFP) levels to the pretreatment AFP levels were 0.750 and 0.667 for the first and second lenvatinib treatments, respectively, without significant difference (p=0.9327). Meanwhile, the median ratios of the 1-month post-treatment albumin-bilirubin (ALBI) scores to the pretreatment ALBI scores were 1.063 and 0.827 for the first and second lenvatinib treatments, respectively, with significant difference (p=0.015). The median duration of the second lenvatinib treatment was significantly shorter than that of the first lenvatinib treatment [2.8 months (range=0.9–4.7 months) *vs.* 8.7 months (range=3.1–29.7 months)].

Conclusion: Lenvatinib re-administration after atezolizumab plus bevacizumab treatment can act as a double-edged sword, as it exerts an anti-tumor effect while being associated with potential liver function deterioration. However, this treatment sequence can be useful, and requires careful monitoring of the

transitions in the liver function and the patient’s performance status.

Hepatocellular carcinoma (HCC) is the most prevalent primary liver cancer and one of the leading causes of cancer-related deaths worldwide (1, 2). Indications for curative treatments (such as surgical resection and radiofrequency ablation) are limited to the early stages of the cancer (3, 4); paradoxically, a majority of the cases are diagnosed at an advanced stage, and systemic chemotherapy is commonly used for treating these patients. The treatment algorithm of systemic chemotherapy for HCC changed dramatically over time; however, sorafenib remained the only option for advanced-stage HCC until recently (5, 6). Several other systemic treatment options have now emerged; these include lenvatinib, regorafenib, ramucirumab, cabozantinib, and atezolizumab plus bevacizumab (7-11).

Atezolizumab and bevacizumab are antibodies against programmed death-ligand 1 (PD-L1) and the vascular endothelial growth factor (VEGF), respectively. The IMbrave150 trial revealed that a combination of the two was overwhelmingly superior to sorafenib in terms of overall and progression-free survival; thus, this combination was established as the first-line treatment for unresectable HCC, pushing HCC systemic treatment into a multimodal chemotherapeutic era (9). Lenvatinib is a multiple-receptor tyrosine kinase inhibitor (TKI) that mainly targets the VEGF and fibroblast growth factor (12-14). The REFLECT trial revealed that compared to sorafenib, lenvatinib achieved more favorable outcomes for unresectable HCC; (7) the overall survival was comparable between the two, while the progression-free survival after lenvatinib administration was significantly better than that after sorafenib administration.

According to the revised Barcelona Clinic Liver Cancer (BCLC)

classification, atezolizumab plus bevacizumab can be used as the first-line systemic chemotherapy for HCC (15). However, the treatment sequences after atezolizumab plus bevacizumab remain unknown. Several treatment options are available, but without any clear evidence on the most optimal sequence to use, a variety of sequences can be introduced after atezolizumab plus bevacizumab (8, 16). It is theoretically believed, that TKI administration after immune check point inhibitors (ICIs) during the period with sustained effect can exert a synergistic effect by improving the tumor microenvironment (17). Accordingly, a certain consensus has been reached regarding the potential clinical effectiveness of lenvatinib after atezolizumab plus bevacizumab. While a drug rechallenge, wherein the same drug is re-administered for previously refractory tumors, is a standard treatment for many types of cancers, it has been rarely implemented in the treatment of HCC. Only a few studies have assessed rechallenge treatments in HCC systemic chemotherapy, and the effectiveness of a lenvatinib rechallenge in patients refractory to the initial lenvatinib treatment has not yet been determined. Therefore, the present study aimed to investigate the clinical relevance of a lenvatinib rechallenge after the administration of atezolizumab plus bevacizumab in patients with HCC. The present article has described the methods used for achieving this aim, presented the key findings, and discussed the study outcomes with respect to the aim and existing literature.

Patients and Methods

Study design and population

This retrospective study included 13 patients with unresectable HCC who

received lenvatinib rechallenge after failure of lenvatinib and atezolizumab plus bevacizumab treatments at the Kobe University Hospital between May 2018 and May 2022. In this study, all procedures involving human participants were performed in accordance with the ethical standards of our institution and the National Research committee, as well as with the 1964 Declaration of Helsinki (and its later amendments or comparable ethical standards).

The demographic data of all patients were collected. All patients underwent pretreatment laboratory blood tests; these included tests for the viral serology, serum alpha-fetoprotein (AFP), protein induced by vitamin K absence or antagonist II (PIVKAII), serum albumin, total bilirubin, and prothrombin time. HCC was diagnosed on the basis of computed tomography (CT) or magnetic resonance imaging (MRI) findings. The performance status was evaluated using the Eastern Cooperative Oncology Group (ECOG) performance status guidelines. The liver function was assessed using the Child–Pugh classification, albumin–bilirubin (ALBI) grade (18), and modified ALBI (mALBI) grade (19). The transitions of the ALBI score during the treatment course were evaluated. The tumor status was classified according to the BCLC classification (20).

Treatment eligibility criteria and other details

The eligibility criteria for treatment with lenvatinib and atezolizumab plus bevacizumab were as follows: 1) ECOG performance status of 0–2, 2) HCC without indication for locoregional treatments, and 3) Child–Pugh classes A and B. The ineligibility criteria for these treatments were as follows: 1) serious complications, 2) ascites refractory or minimally responsive to therapy, and 3)

severe autoimmune diseases (this criterion was specific to eligibility for atezolizumab plus bevacizumab treatment). Lenvatinib was orally administered at doses of 8 mg/day and 12 mg/day to patients weighing <60 kg and those weighing ≥60 kg, respectively. Conversely, atezolizumab (1,200 mg) and bevacizumab (15 mg/kg) were administered intravenously every 3 weeks.

The serum AFP and PIVKAII levels were determined at the baseline. The follow-up protocol included assessments of these levels every month after the treatment, CT or MRI examinations every 4–12 weeks after the treatment, and assessment of the radiological response and its classification according to the Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1) and the modified RECIST (mRECIST) (21, 22). Adverse events were evaluated by the Common Terminology Criteria for Adverse Events (version 4.0); severe adverse events were defined by grades ≥III.

Statistical analyses

All statistical analyses were performed using the JMP® 14 statistical package (SAS Institute, Cary, NC, USA). Outcomes were given as the median (interquartile range) and categorical variables were expressed as proportions. Categorical variables were analyzed using the χ^2 test, while quantitative continuous variables were analyzed using the Mann–Whitney *U* test. Relationships between quantitative variables were assessed through a Spearman correlation analysis. Overall survival was defined as the period from the start of the first lenvatinib treatment to death or final follow-up. *p* Values of less than 0.05 were considered statistically significant.

Results

Patient baseline characteristics

For all patients, data on the clinical characteristics recorded at the first lenvatinib treatment are presented in Table I. The study cohort comprised 11 men and 2 women [median age: 66 years (range=46–78 years)]. An ECOG performance status of 0 and 1 was observed in 12 and 1 patients, respectively. The Child–Pugh classes were 5A and 6A in 11 and 2 patients, respectively. ALBI grades of 1 and 2 were noted in 10 (77%) and 3 (23%) patients, respectively. Extrahepatic metastases were observed in 8 of the 13 patients (61%). In 12 of the 13 patients, lenvatinib was administered as the first-line systemic chemotherapy; in the remaining one patient, it was administered as second-line therapy after sorafenib treatment.

Changes in the AFP level and the therapeutic response to each treatment

Table II presents the transitions in the serum AFP level and radiological findings after each treatment. The serum AFP level was higher than 10 ng/ml in seven of the 13 included patients before the first lenvatinib treatment, and the serum AFP level decreased in six of these seven patients (excluding case 7). The serum AFP level also decreased after the second lenvatinib introduction in the same six patients. Regarding treatment with atezolizumab plus bevacizumab, the ratio of the 1-month post-treatment AFP level to the pretreatment AFP level was less than 1 in only four of the 10 patients (40%) whose pretreatment AFP levels were higher than 10 ng/ml. In the remaining six patients, the serum AFP levels

increased 1 month after the atezolizumab plus bevacizumab treatment. Among the 10 patients whose serum AFP levels were higher than 10 ng/ml before the second lenvatinib treatment, the AFP level decreased in nine patients (90%) within 1 month after the second treatment. The median ratios of the 1-month post-treatment AFP level to the pretreatment AFP level were 0.750 and 0.667 for the first and second lenvatinib treatments, respectively; no significant differences were noted between the two (Figure 1; p=0.9327).

According to the mRECIST, the objective response rate (ORR) and the disease control rate (DCR) for the first lenvatinib treatment were 38.5% and 100%, respectively; according to the RECIST, these were 23.0% and 100%, respectively. According to the mRECIST, the ORR and DCR for the atezolizumab plus bevacizumab treatment were 7.7% and 69.2%, respectively; according to the RECIST, these were 0% and 69.2%, respectively. According to the mRECIST, the ORR and DCR for the second lenvatinib treatment were 7.7% and 92.3%, respectively; according to the RECIST, these were 0% and 92.3%, respectively.

Changes in the liver function for each treatment

Table III presents data on the changes in liver function and treatment duration for each treatment. After the first lenvatinib treatment, based on the ratios of the 1-month post-treatment ALBI scores to the pretreatment ALBI scores, liver function deterioration was noted in only five of the 13 included patients; the remaining eight patients maintained the liver function in the first month after the treatment. Furthermore, based on the ratios of the 3-month post-treatment ALBI

scores to the pretreatment ALBI scores, the liver function had been restored to its pretreatment level in 11 of the 13 included patients (ratio >1). Meanwhile, for the second lenvatinib treatment, the ALBI score dropped significantly below its pretreatment value 1 month after the treatment (ratio of the 1-month post-treatment ALBI score to the pretreatment ALBI score <1). Liver function deterioration was seen in 11 patients. Among the nine patients for whom the ALBI score could be recorded at the 3-month follow-up, liver function restoration (ratio of the 3-month post-treatment ALBI score to the pretreatment ALBI score >1) was only observed in one patient; the impaired liver function persisted in the remaining eight patients. The median ratios of the 1-month post-treatment ALBI scores to the pretreatment ALBI scores were 1.063 and 0.827 for the first and second lenvatinib treatments, respectively, a significant difference was observed between the two (Figure 2; p=0.015).

Treatment course

The median survival time of all 13 patients was 36.1 months; the 3-year survival rate was 62.9%. During the first lenvatinib and atezolizumab plus bevacizumab treatments, no patients developed any severe adverse events. Meanwhile, five patients developed severe adverse events during the second lenvatinib treatment; some of these experienced more than one event. Thus, the number of patients who developed grade 3 proteinuria, grade 3 general fatigue, the hand-foot syndrome, and edema were two, two, one, and one, respectively.

The median duration of the second lenvatinib treatment was significantly shorter than that of the first lenvatinib treatment [2.8 months (range=0.9–4.7

months) *vs*. 8.7 months (range=3.1–29.7 months)]. The median duration of the atezolizumab plus bevacizumab treatment was 3.0 months (range=2.3–9.8 months). The median interval from the first lenvatinib treatment to the cessation of the second lenvatinib treatment was 21.8 months (range=11.5–37.4 months).

Discussion

The present study showed that the efficacy of the first lenvatinib treatment could be replicated in the second lenvatinib treatment when it was administered after the atezolizumab plus bevacizumab treatment. The transitions in the tumor marker levels were quite similar between the first and second lenvatinib treatments. The median ratios of the 1-month post-treatment AFP levels to the pretreatment AFP levels were 0.750 and 0.667 for the first and second lenvatinib treatments, respectively. According to the mRECIST, the ORRs of the first and second lenvatinib treatments were 38.5% and 7.7%, respectively; the corresponding DCRs were 100% and 92.3%, respectively. These findings indicated that the tumor could be resensitized to lenvatinib by a second lenvatinib treatment after the atezolizumab plus bevacizumab treatment.

Conversely, the changes in the ALBI score were completely different between the first and second lenvatinib treatments. The median ratios of the 1-month post-treatment ALBI scores to the pretreatment ALBI scores were 1.063 and 0.827 for the first and second lenvatinib treatments, respectively, with a significant difference between the two. The aggravation in the ALBI score was remarkable when lenvatinib was administered for the second time (*i.e*., after the atezolizumab plus bevacizumab treatment). Accordingly, lenvatinib

re-administration after atezolizumab plus bevacizumab treatment can act as a double-edged sword; it can exert a significant anti-tumor effect while being associated with potential liver function deterioration.

Based on the current consensus on administering atezolizumab plus bevacizumab as the first-line treatment, future studies must determine the treatment sequence to be administered thereafter. Based on the favorable outcomes of lenvatinib demonstrated in the REFLECT trial (7) and its favorable anti-tumor impact reported by several clinical real-world studies (23), lenvatinib may be established as a basic second-line drug (24). Several reports have suggested that a sequential therapy (comprising ICI followed by lenvatinib) can exert a synergic effect and achieve a favorable anti-tumor response (17, 24, 25).

VEGF induces the Treg cells, tumor-associated macrophages, and myeloid-derived suppressor cells; these contribute to an immunosuppressive tumor microenvironment (26). Lenvatinib selectively inhibits VEGF receptors 1–3 and other proangiogenic and oncogenic pathway-related receptor tyrosine kinases (27, 28). The anti-VEGF activity of lenvatinib suppresses tumor PD-L1 expression and reduces the tumor Treg cells, thereby improving the immunosuppressive microenvironment (29) and enhancing the antitumor activity of ICIs (28). It has been reported that the anti-programed cell death-1 (PD-1) antibodies continue to bind to the CD8+ T cells for more than 20 weeks; (30) thus, during this period, T-cell activation can be restored by a PD-1/PD-L1 blockade and an improvement in the tumor microenvironment. It can be speculated that lenvatinib exerts a synergistic effect when administered during the sustained-effect period following an atezolizumab plus bevacizumab

treatment. The favorable outcomes of lenvatinib, administered as the second- or later line treatment, have also been reported clinically (17).

Drug rechallenges have been reported for various malignancies. In case of several malignant tumor types, resensitization following a TKI rechallenge of a tumor previously refractory to the TKI has been reported (31-35). A study has also demonstrated the effectiveness of a lenvatinib rechallenge after sorafenib in patients with thyroid carcinoma once refractory to the initial lenvatinib treatment (36). We have also reported the potential effectiveness of a lenvatinib rechallenge after ramucirumab in patients with HCC refractory to the initial lenvatinib treatment (37). A chemotherapy-induced alteration of the tumor microenvironment can lead to the resensitization of a tumor that was previously refractory to the chemotherapy regimen; this can become a potential treatment option. In the present study, all cases achieved disease control during the first lenvatinib treatment (stable disease, partial response, and complete response, as indicated by a radiological assessment); thus, a lenvatinib rechallenge after atezolizumab plus bevacizumab treatment can be regarded as reasonable. Future studies should discuss the indications of a lenvatinib rechallenge in HCC cases refractory to the initial lenvatinib treatment.

The median duration of the first and second (rechallenge) lenvatinib treatments was 8.7 and 2.8 months, respectively (Table III). In the REFLECT trial, lenvatinib was administered as the first-line treatment in all cases, and the median duration of treatment was 5.7 months (7). In the present study, lenvatinib was administered as the first-line treatment in 12 out of 13 patients. The nearly same duration of the initial lenvatinib treatment between the present study and

the REFLECT trial suggests that the patient population of the present study represented the real-world patient cohort. Liver function deterioration after a lenvatinib rechallenge may shorten the duration of the second lenvatinib treatment. Therefore, careful patient selection and appropriate medication protocol may help achieve a longer administration; this must be confirmed through future studies.

With the availability of several chemotherapeutic options (8, 9), efforts to determine an effective treatment sequence are essential. Currently, treatment sequences with atezolizumab plus bevacizumab and subsequent lenvatinib are considered as the most powerful regimens; therefore, the concurrent sequential concept of a lenvatinib rechallenge after atezolizumab plus bevacizumab administration can be quite meaningful. Although future studies with additional case series are required, the present study has clinically important implications: it provides evidence of a potentially effective therapeutic sequence for HCC.

In conclusion, a lenvatinib rechallenge for HCC, once refractory to initial lenvatinib treatment, after an atezolizumab plus bevacizumab treatment may exert strong anti-tumor activity; however, it may be accompanied by an impaired liver function. This sequence can be a viable treatment option and requires careful monitoring of the transitions in the liver function and the patient's performance status. Further studies will be required to investigate the most appropriate treatment sequence in this era of multimodal chemotherapy.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this manuscript.

Authors' Contributions

Study conception and design: Komatsu S. Data collection: Kido M, Kuramitsu K, Gon H, Fukushima K, Urade T, So S, Yamamoto A. Article preparation and review: Yano Y, Goto T, Yanagimoto H, Toyama H, Ueda Y, Kodama Y. Supervision: Fukumoto T.

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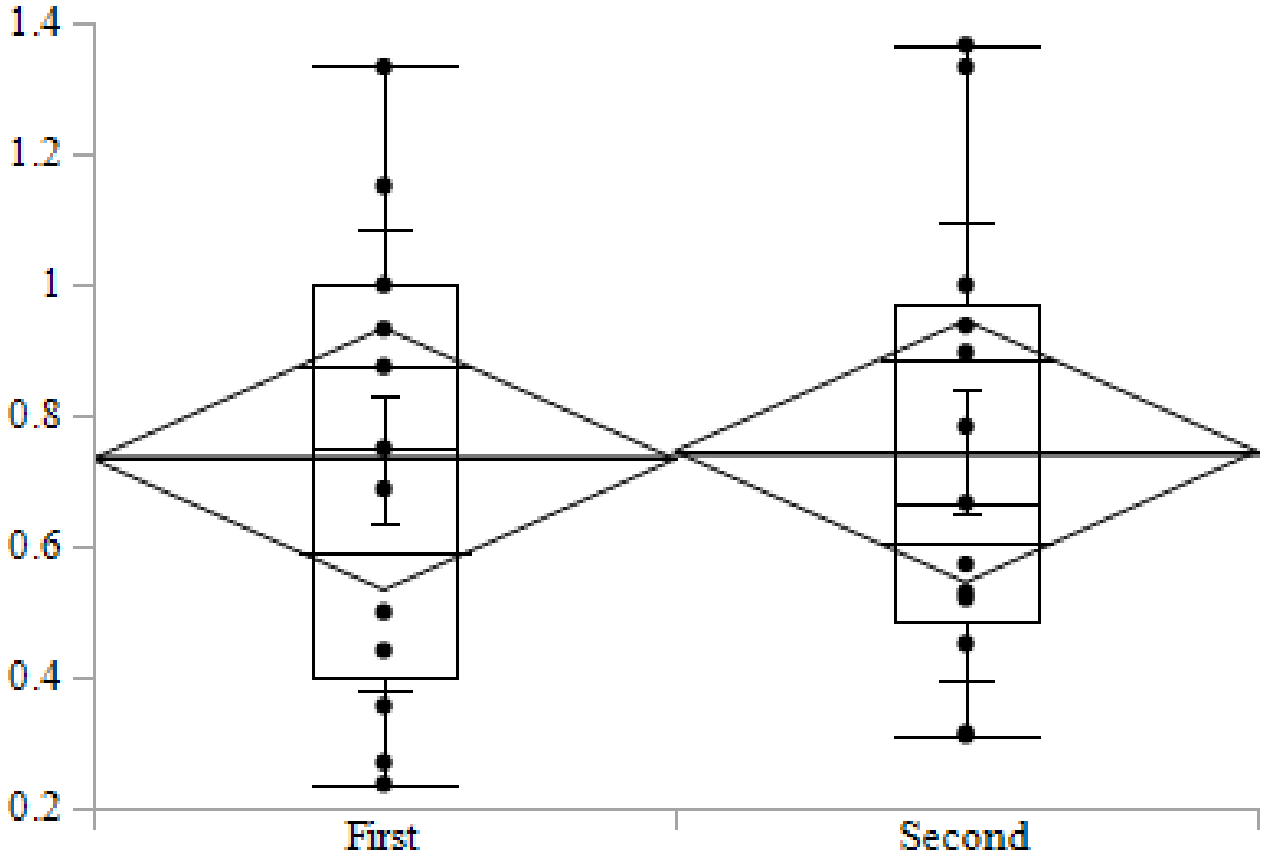
Figure legends

Figure 1. The ratios of the 1-month post-treatment alpha-fetoprotein level to the pretreatment alpha-fetoprotein level during the first and second lenvatinib treatments.

Figure 2. The ratios of the 1-month post-treatment serum albumin–bilirubin scores to the pretreatment serum albumin–bilirubin scores during the first and second lenvatinib treatments.

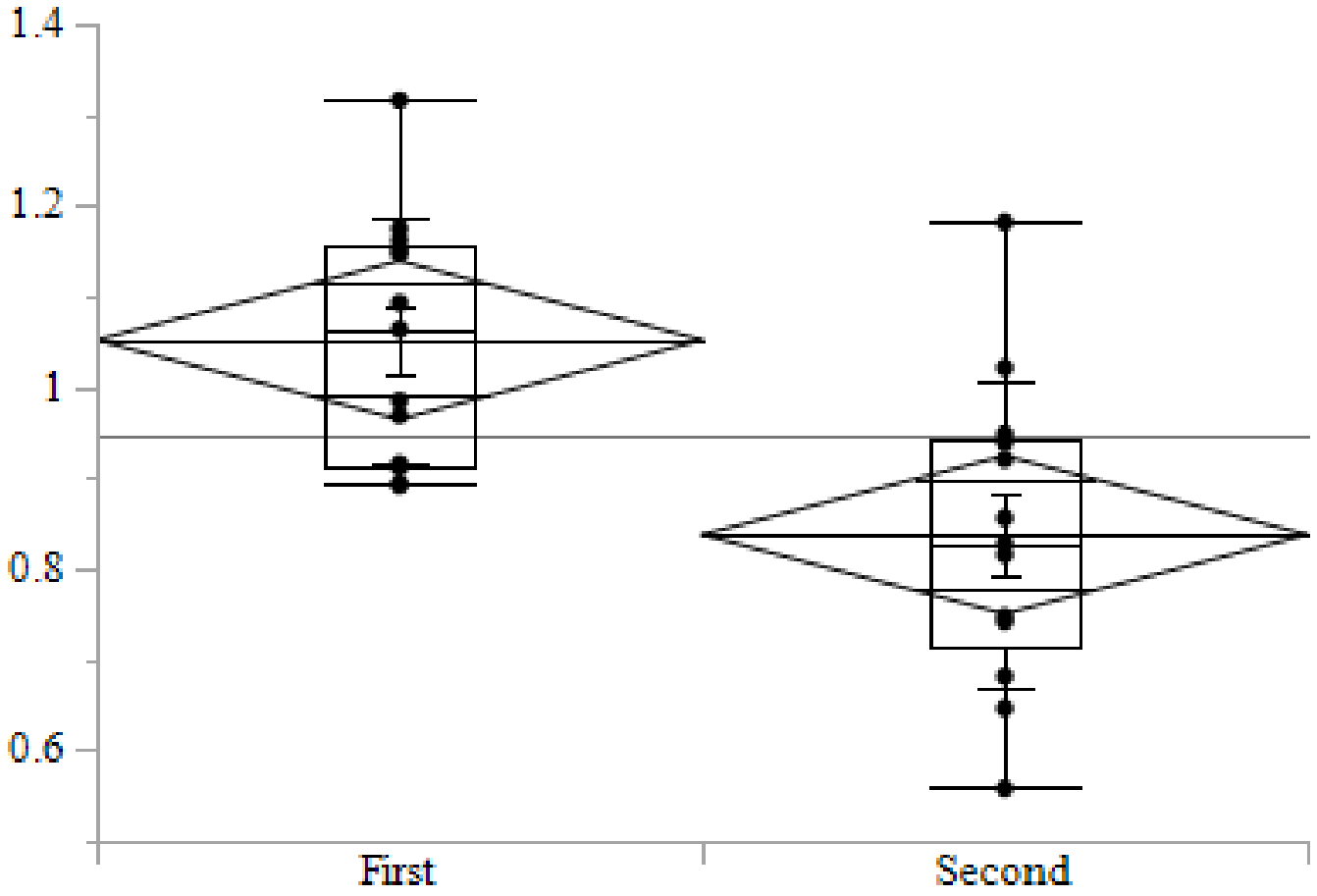
Figure 1



Lenvatinib	Minimum	Median	Maximum
First time	0.237	0.750	1.333
Second time	0.311	0.667	1.367

P = 0.9327

Figure 2



Lenvatinib	Minimum	Median	Maximum
First time	0.892	1.063	1.316
Second time	0.558	0.827	1.182

P = 0.015

Table I. Patient characteristics of all patients (before 1st lenvatinib introduction)

	No. of patients (n = 13)
Age (years)*	66.0 (46-78)
Sex, male : female	11 : 2
ECOG PS, 0 : 1	12 : 1
Etiology, HBV : HCV : NBNC	6 : 2 : 5
BCLC classification, B : C	5 : 8
Child-Pugh score, 5A : 6A	11 : 2
ALBI grade, 1 : 2	10 : 3
mALBI grade, 1 : 2a : 2b	10 : 2 : 1
AFP, ng/ml, median (range), ≤ 10 : 10<	6 : 7
PIVKAII, mAU/ml, median (range), < 40 : 40 ≤	7 : 6
Number of intrahepatic tumors, none : <10 : 10≤	5 : 5 : 3
Extrahepatic metastasis, yes : no	8 : 5
Previous TKI history before 1st lenvatinib, yes : no	1 : 12
Treatment line of 1st lenvatinib, 1st/2nd	12 : 1

Data expressed as number of patients (%) unless specified.
*values are median (interquartile range)
ECOG PS: Eastern cooperative Oncology Group performance status; HBV: hepatitis B virus; HCV: hepatitis C virus; NBNC: non B non C; BCLC: Barcelona Liver Clinic;
ALBI: albumin-bilirubin; mALBI: modified albumin-bilirubin; TKI: tyrosine-kinase inhibitor.

Table II. Laboratory and radiological transition during each treatment

	First lenvatinib treatment			Atezolizumab plus bevacizumab treatment			Second lenvatinib treatment		
Case, Age/Sex	Pre-AFP level (ng/ml)	Proportion of AFP 1, 3 month/before	mRECIST/ RECIST	Pre-AFP level (ng/ml)	Proportion of AFP 1, 3 month/before	mRECIST/ RECIST	Pre-AFP level (ng/ml)	Proportion of AFP 1, 3 month/before	mRECIST/ RECIST
1, 46/F	653	0.44, 0.16	PR/PR	410	0.98, 0.08	SD/SD	87	0.90, 1.24	SD/SD
2, 48/M	6,234	0.69, 2.02	PR/SD	35,451	1.71, 2.05	SD/SD	72834	0.52, none	SD/SD
3, 60/M	4	0.75, 1.00	SD/SD	258	1.55, 2.94	SD/SD	758	0.31, 0.71	SD/SD
4, 65/M	3	1.00, 1.33	SD/SD	3	1.00, 1.00	PD/PD	3	0.67, none	SD/SD
5, 66/M	8	0.88, 1.00	CR/PR	10	0.5, 0.6	SD/SD	6	1.33, 1.17	SD/SD
6, 64/M	3	1.33, 2.33	SD/SD	651	1.41, none	SD/SD	883	1.37, none	PD/PD
7, 67/M	364	1.15, 1.41	SD/SD	4,103	0.95, 1.79	PR/SD	62350	0.45, none	SD/SD
8, 72/F	5,520	0.93, 4.28	SD/SD	17,128	1.16, 1.89	SD/SD	41419	0.78, 0.97	SD/SD
9, 71/M	2	0.50, 1.00	PR/SD	2	1.00, 1.00	SD/SD	2	1.00, 1.00	SD/SD
10, 71/M	93	0.24, 0.35	SD/SD	14,000	1.39, 2.13	PD/PD	29855	0.57, 0.98	PR/SD
11, 75/M	87	0.36, 0.61	SD/SD	908	0.20, 0.13	SD/SD	747	0.53, 0.79	SD/SD
12, 74/M	4	1.00, 1.25	SD/SD	9	1.11, 1.67	PD/PD	16	0.94, none	SD/SD
13, 78/M	100	0.27, 0.89	CR/CR	428	5.78, 2.46	PD/PD	3385	0.31, 1.76	SD/SD

F: Female; M: male; AFP: alpha-fetoprotein; mRECIST: modified Response Evaluation Criteria in Solid Tumors; RECIST: Response Evaluation Criteria in Solid Tumors; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Table III. Transition of liver function and treatment duration during each treatment

	First lenvatinib treatment			Atezolizumab plus bevacizumab treatment			Second lenvatinib treatment		
Case, Age/Sex	Pre-ALBI score (mALBI grade)	Proportion of ALBI 1, 3 month/before	Treatment duration (month)	Pre-ALBI score (mALBI grade)	Proportion of ALBI 1, 3 month/before	Treatment duration (month)	Pre-ALBI score (mALBI grade)	Proportion of ALBI 1, 3 month/before	Treatment duration (month)
1, 46/F	-3.03 (1)	1.15, 1.03	21.7	-2.78 (1)	1.14, 1.13	9.0	-2.95 (1)	1.02, 0.85	4.2
2, 48/M	-2.73 (1)	0.89, 1.09	3.1	-2.44 (2a)	1.06, 0.92	2.8	-2.25 (2b)	0.94, none	1.2
3, 60/M	-2.52 (2a)	1.14, 1.11	29.7	-2.90 (1)	0.89, 0.67	2.8	-2.73 (1)	0.92. 0.82	3.5
4, 65/M	-2.61 (1)	1.16, 1.16	7.2	-3.26 (1)	0.90, 0.95	3.0	-3.11 (1)	0.74, none	0.9
5, 66/M	-2.64 (1)	0.89, 0.88	10.3	-1.73 (2b)	0.97, 1.03	3.0	-1.79 (2b)	0.64, 0.63	3.9
6, 64/M	-2.85 (1)	1.09, 1.06	10.6	-2.30 (2a)	1.05, 1.07	5.1	-2.82 (1)	0.68, none	1.1
7, 67/M	-2.99 (1)	1.06, 1.03	3.6	-2.16 (2b)	1.22, 1.21	4.8	-2.36 (2a)	0.85, none	1.2
8, 72/F	-2.72 (1)	1.10, 1.11	4.0	-2.53 (2a)	1.04, 1.04	3.7	-2.62 (1)	0.74, 0.73	2.8
9, 71/M	-2.64 (1)	0.96, 1.03	13.1	-2.55 (2a)	0.80, 0.75	4.8	-1.68 (2b)	0.55, 0.94	3.7
10, 71/M	-2.00 (2b)	1.31, 1.40	15.0	-2.36 (2a)	0.90, 0.92	2.8	-1.85 (2b)	1.18, 1.05	2.8
11, 75/M	-2.61 (1)	0.91, 1.00	7.4	-2.44 (2a)	1.14, 1.27	9.7	-2.30 (2a)	0.81, 0.87	4.7
12, 74/M	-2.44 (2a)	1.16, 1.11	8.7	-2.56 (2a)	0.93, 0.90	2.3	-2.30 (2a)	0.82, 0.92	2.5
13, 78/M	-2.65 (1)	0.91, 0.82	8.2	-2.26 (2b)	0.89, 0.74	2.3	-1.79 (2b)	0.93, 0.92	3.0

F: Female; M: male; ALBI: albumin-bilirubin; mALBI: modified albumin-bilirubin.