

What Can Be Done to Solve the Unmet Clinical Need of Hepatocellular Carcinoma Patients following Lenvatinib Failure?

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Keywords

Hepatocellular carcinoma · Lenvatinib · Hand-foot skin reaction · Postprogression treatment · Beyond progression of disease

Abstract

Background/Aim: An effective postprogression treatment of lenvatinib (LEN) against unresectable hepatocellular carcinoma (u-HCC) has not been established. We aimed to elucidate the clinical role of continuing LEN beyond progression of disease (PD). **Methods:** From March 2018 to October 2020, 99

u-HCC patients, in whom PD was confirmed (male:female = 78:21, median age 72 years, Child-Pugh A = 99, Barcelona Clinic Liver Cancer stage A:B:C = 2:43:54, LEN as first-line = 55), were enrolled (stopped LEN at PD [A group], $n = 26$; continued LEN beyond PD [B group], $n = 73$). Radiological response was evaluated with RECIST 1.1. Clinical features and prognostic factors for overall survival (OS) were retrospectively investigated using inverse probability weighting (IPW) calculated by propensity score. **Results:** Median time to progression, best response, and modified albumin-bilirubin grade (mALBI) at both baseline and PD did not show significant difference between the groups. Postprogression treatment in the A group

was best supportive care in 17, sorafenib in 4, regorafenib in 3, ramucirumab in 1, and hepatic arterial infusion chemotherapy in 1. After adjusting with IPW, the B group showed better prognosis in regard to OS after PD and OS after introducing LEN than the A group (10.8/19.6 vs. 5.8/11.2 months, $p < 0.001$, respectively). In IPW-adjusted Cox hazard multivariate analysis, significant prognostic factors for OS after PD were mALBI 2b/3 at PD (HR 1.983, $p = 0.021$), decline of Eastern Cooperative Oncology Group performance status (ECOG PS) from baseline at PD (HR 3.180, $p < 0.001$), elevated alpha-fetoprotein (≥ 100 ng/mL) at introducing LEN (HR 2.511, $p = 0.004$), appearance of new extrahepatic metastasis (HR 2.396, $p = 0.006$), positive for hand-foot skin reaction (HFSR) before PD (any grade) (HR 0.292, $p < 0.001$), and continuing LEN beyond PD (HR 0.297, $p < 0.001$). **Conclusion:** When ECOG PS and hepatic reserve function permit, continuing LEN treatment beyond PD, especially in u-HCC patients showed HFSR during LEN treatment, might be a good therapeutic option, at least until a more effective drug as a postprogression treatment after LEN failure is developed.

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver and fifth most common malignancy worldwide [1]. Sorafenib (SOR) [2] and regorafenib (REG) [3] have been developed as powerful molecular targeting agents (MTAs) for patients with unresectable HCC (u-HCC), and Terashima reported that postprogression survival was highly correlated with overall survival (OS) in advanced HCC patients treated with SOR [4]. Prior to introduction of lenvatinib (LEN) in March 2018 [5], there had been no established postprogression treatment protocol for use after REG failure and no treatment established for patients who showed SOR intolerability. Since that time, LEN has been shown in clinical practice in Japan to be useful not only as first-line but also as second- and even third-line treatment [6, 7]. Nevertheless, establishment of new effective postprogression treatments are needed to obtain better improvement of prognosis for patients with u-HCC. At the time of writing, though ramucirumab (RAM) [8, 9] become approved in Japan as an additional MTA drug in June 2019, no other effective postprogression treatment after LEN failure has been established. The present study aimed to elucidate the clinical role of continuing LEN beyond first progression of disease (PD) as an alternative therapeutic method in real-world clinical practice.

Materials and Methods

This is a report of multicenter analysis results of 183 u-HCC patients with serial radiological assessment imaging data obtained from March 2018 to October 2020 at 11 different institutions (Ehime Prefectural Central Hospital, Himeji Red Cross Hospital, Okayama City Hospital, Kagawa Prefectural Central Hospital, Kagawa University Hospital, Saiseikai Niigata Hospital, Matsuyama Red Cross Hospital, Nippon Medical School Hospital, Osaka Medical College, Hamamatsu University School of Medicine Hospital, and Toyama University Hospital) (Fig. 1). After confirming no significant differences between time to progression (TTP) determined with Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [10], and modified RECIST (mRECIST) [11] in the entire cohort (see online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000513355), RECIST was used for all of the analyses. Of the 183 patients, the clinical features of 99, in whom PD was confirmed by both RECIST and mRECIST, were finally analyzed in a retrospective manner after exclusion of those in whom LEN was discontinued 1 month or more before the time of PD determined by RECIST 1.1, or those without assessment of therapeutic response with an enhanced imaging modality. The 99 patients were divided into 2 groups, those for whom LEN was abandoned at PD (A group: $n = 26$) and those who continued LEN beyond PD (B group: $n = 73$) (Fig. 1). Treatment “beyond PD” was defined as LEN treatment continued for >1 month after PD by RECIST 1.1. The first assessment of the therapeutic effect was performed using dynamic CT/MRI from 1 to 2 months after introduction of LEN, with imaging examinations performed every 2 months following the initial assessment with dynamic imaging (CT or MRI).

Basal Liver Diseases

HCC due to hepatitis C virus (HCV) was judged when anti-HCV was positive, whereas HCC due to hepatitis B virus (HBV) was judged when the HBV surface antigen was positive.

Liver Function Assessment

Child-Pugh classification [12] and albumin-bilirubin (ALBI) grade were used for assessment of hepatic reserve function. ALBI score was calculated with serum albumin and total-bilirubin values using the following formula: $\text{ALBI score} = \log_{10} \text{bilirubin } (\mu\text{mol/L}) \times 0.66 + \text{albumin } (\text{g/L}) \times -0.085$ (≤ -2.60 , ALBI grade 1; > -2.60 to ≤ -1.39 , grade 2; and > -1.39 , grade 3) [13–15]. To perform more detailed evaluations of patients with the middle ALBI grade of 2, we used a revised grading system consisting of 4 levels that included subgrading for the middle grade of 2 (2a and 2b) based on an ALBI score of -2.27 as the cutoff, which was previously developed based on the value for indocyanine green retention after 15 min of 30% [16, 17].

HCC Diagnosis and Treatment

Based on an increasing course of alpha-fetoprotein (AFP), as well as dynamic CT [18] or MRI [19, 20], contrast enhanced ultrasonography with perflubutane (Sonazoid®; Daiichi Sankyo Co., Ltd., Tokyo, Japan) [21, 22], and/or pathological findings, HCC was diagnosed. We used Barcelona Clinic Liver Cancer (BCLC) [23] and tumor node metastasis (TNM) staging, determined as previously reported in a study for TNM staging of HCC conducted by the Liver Cancer Study Group of Japan (LCSGJ) 6th edition [24] (TNM-LCSGJ), to evaluate tumor progression.

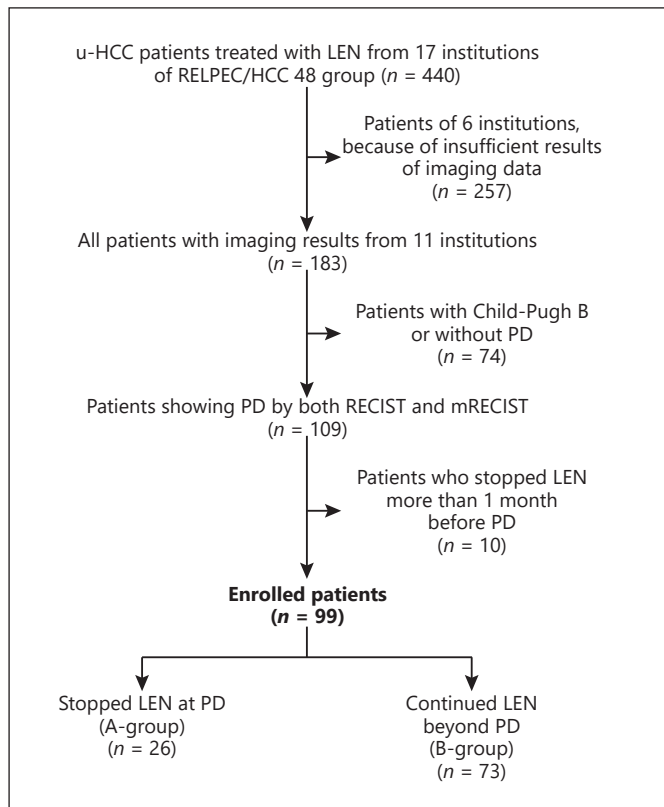


Fig. 1. Flowchart of patient enrollment. u-HCC, unresectable hepatocellular carcinoma; PD, progression of disease; LEN, lenvatinib; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

Lenvatinib Treatment and Assessment of Adverse Events

After obtaining written informed consent from each patient, LEN was started. Oral administrations at 8 mg/day were given to patients weighing <60 kg and 12 mg/day to those ≥60 kg, as much as possible, and discontinued when any unacceptable or serious adverse event (AE) is reported. When clinical tumor progression was observed, the decision to continue or discontinue LEN treatment was made at the discretion of the attending physicians. According to the guidelines for administration of LEN, the drug dose was reduced or treatment interrupted when a patient developed any grade 3 or more severe AE, or if any unacceptable grade 2 drug-related AE occurred. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 [25]. AEs of grade 3 or more were defined as severe, and the worst grade for each AE during the present observation period was recorded. If a drug-related AE was noted, dose reduction or temporary interruption was maintained until the symptom was resolved to grade 1 or 2, according to the guidelines provided by the manufacturer.

The last day of LEN treatment was defined as the day of last date of administration of LEN before a clear statement of discontinuation of LEN by attending physicians on the medical record, or the last day of administration of LEN before postprogression treat-

ments. In analysis for prognostic factors of postprogression overall survival (OS), we used clinical 17 factors described below for calculating inverse probability weighting (IPW) with propensity score.

This was a retrospective analysis of records stored in a database, and official approval was received based on the Guidelines for Clinical Research issued by the Ministry of Health and Welfare of Japan. All procedures complied with the Declaration of Helsinki. The protocol used in the present study was approved by the Institutional Ethics Committee of Ehime Prefectural Central Hospital (IRB No. 30-66).

Statistical Analysis and Calculations of Propensity Score and Inverse Probability Weighting

Continuous variables are expressed as median values (first-third quartile). Statistical analyses were performed using Welch's *t* test, Student's *t* test, Fisher's exact test, or Mann-Whitney's U test, as appropriate. Prognosis was analyzed by Cox hazard analysis, the Kaplan-Meier method, and a log-rank test.

The A- and B-group probabilities (propensity) were calculated using logistic regression analysis with a set of covariates deemed likely to have effects on OS, including patients' condition (elderly [age ≥75 years], gender, infection for chronic hepatitis virus, and history of MTA), hepatic function (Child-Pugh scores at introducing LEN and at time of PD), malignant potential of tumor (elevated AFP data [≥100 ng/mL] at time of introducing LEN and for 1 month before or after PD), BCLC stages (C or D), which include tumor burden, hepatic function, and Eastern Cooperative Oncology Group performance status (ECOG PS), at introducing LEN and at time of PD, decline of ECOG PS from baseline at time of PD, clinical features during LEN treatment (no response to LEN [best response: PD]), 4 types of PD patterns (appearance of new extrahepatic metastasis [EHM], appearance of major portal vein tumor thrombosis [Vp3 and Vp4], intrahepatic new lesion, and increasing size without new lesion), and treatment factors (starting dose of LEN [reduced dose]).

IPW was defined as $1/(\text{propensity score})$ for the A group and $1/(1-\text{propensity score})$ for the B group. Hazard ratio (HR) for OS after PD of each clinical factor and OS after introducing LEN and OS after PD were tested using IPW-adjusted Cox hazard analysis or an IPW-adjusted log-rank test, respectively [26, 27].

A *p* value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed using Easy R, version 1.53 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [28], a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Time to Progression in 183 u-HCC Patients

In all 183 u-HCC patients with imaging results from 11 institutions (male:female = 142:41, median age 73 years; Child-Pugh score 5:6:7:8:9:10 = 108:62:11:1:0:1; mALBI 1:2a:2b:3 = 59:52:68:4; BCLC 0:A:B:C:D = 1:6:81:94:1; TNM-LCSGJ I:II:III:IVa:IVb = 2:32:63:16:70) (Fig. 1), the median TTP by mRECIST was 8.4 months,

Table 1. Clinical features of u-HCC patients at first progression of disease (N = 99)

Parameters	A group (n = 26)	B group (n = 73)	p value
At introducing LEN			
Age, years ^a	73 (64–78)	72 (65–78)	0.924
Gender, male:female	19:7	59:14	0.414
Etiology, HCV:HBV:alcohol:other	16:2:0:8	30:14:12:17	0.037
BMI, kg/m ^{2a}	22.4 (20.2–25.1)	21.8 (19.1–23.9)	0.252
ECOG PS at LEN introduction, 0:1	22:4	69:4	0.201
Platelets, ≥10 ⁴ /μL ^a	13.1 (10.2–15.5)	14.2 (11.1–17.3)	0.207
AST, U/L ^a	46 (32–63)	39 (26–59)	0.118
ALT, U/L ^a	38 (22–56)	27 (19–44)	0.101
Total bilirubin, mg/dL ^a	0.8 (0.6–1.0)	0.7 (0.5–0.8)	0.023
Albumin, g/dL ^a	3.8 (3.6–4.1)	3.8 (3.5–4.1)	0.921
Prothrombin time, % ^a	86.1 (77.0–91.0)	93.0 (82.0–102.0)	0.044
eGFR, mL/min/1.73 m ^{2a}	71.0 (60.5–92.3)	72.4 (57.0–81.3)	0.534
AFP, ng/mL at LEN introduction ^a (AFP <100:≥100 ng/mL)	306.5 (11.5–1,898.3)	24.0 (3.9–473.2)	0.034 (0.108)
	(10:16)	(43:30)	
Started with reduced dose of LEN	5 (19.2%)	16 (21.9%)	1.000
Past history of SOR	15 (57.7%)	29 (39.7%)	0.167
Past history of REG	5 (19.2%)	7 (9.6%)	0.291
ALBI score at LEN introduction ^a	−2.48 (−2.30 to −2.61)	−2.57 (−2.24 to −2.79)	0.504
mALBI grade at introducing LEN, 1:2a:2b:3	7:12:7:0	34:19:20:0	0.127
Child-Pugh score, 5:6	18:8	52:21	1.0
Intrahepatic tumor size, none:<2:2–5:>5 cm (maximum)	2:2:16:6	10:22:25:16	0.043
Intrahepatic tumor, n, none:single:multiple	2:3:21	10:7:56	0.785
Positive for MVI, %	2 (7.7)	3 (4.1)	0.604
Positive for EHM, %	12 (46.2)	30 (41.1)	0.653
TNM-LCSGJ at LEN introduction, II:III:IVa:IVb	0:9:4:13	17:20:6:30	0.022
BCLC stage at LEN introduction, A:B:C	0:10:16	2:33:38	0.729
Best response (CR:PR:SD:PD) ^b	0:8:11:7	3:23:31:16	0.862
At time of PD^b			
ECOG PS at time of PD, ^b 0:1:2:3	13:8:2:3	53:17:3:0	0.015
Frequency of decline of ECOG PS from baseline, %	11 (42.3)	19 (26.0)	0.141
AFP, ng/mL ^a at time of PD ^b (AFP <100:≥100 ng/mL)	604.1 (16.2–6,227.5)	48.5 (6.1–522.4)	0.016 (0.038)
	(9:17)	(44:29)	
Delta ALBI score at time of PD ^b from baseline ^a	0.24 (−0.05–0.69)	0.25 (0.01–0.47)	0.691
ALBI score ^a at time of PD ^b	−2.18 (−2.19 to −2.64)	−2.35 (−1.94 to −2.65)	0.467
mALBI grade at time of PD, ^b 1:2a:2b:3	8:4:11:3	21:21:25:6	0.571
Child-Pugh score at time of PD, ^b 5:6:7:8:9: ≥10 (frequency of Child-Pugh class A, %)	11:5:5:2:3:0 (16, 61.5%)	37:19:8:4:3:2 (56, 76.7%)	0.612 (0.199)
TNM-LCSGJ at time of PD, ^b II:III:IVa:IVb	0:7:4:15	8:23:6:36	0.243
BCLC stage at time of PD, A:B:C:D	0:3:20:3	1:21:50:1	0.034
Postprogression treatment, BSC:SOR:REG:RAM:HAIC	17:4:3:1:1	na	na
PD pattern (appearance of new EHM:appearance of MVI: appearance of intrahepatic new lesion:increasing size without new lesion)	4:1:9:12	10:3:29:31	0.939
Period of LEN administration, months ^a	4.5 (2.2–7.5)	11.4 (6.8–16.3)	<0.001
Difference between time of LEN administration discontinuation and PD, ^b months ^a	0 (−0.4 to 0.10)	4.1 (2.3–7.3)	<0.001
Death during observation period, %	19 (73.1%)	33 (45.2%)	0.021
Observation period, months ^a	7.5 (5.5–12.2)	15.4 (10.3–21.0)	<0.001
IPW ^a	3.02 (2.19–4.29)	1.23 (1.10–1.45)	<0.001

u-HCC, unresectable hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; AST, aspartate transaminase; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; eGFR, estimated glomerular filtration rate; ALBI, albumin-bilirubin; mALBI, modified ALBI grade; MVI, major portal vein tumor thrombosis (Vp3 and Vp4); EHM, extrahepatic metastasis; BCLC, Barcelona Clinic Liver Cancer stage; EHM, extrahepatic metastasis; TNM-LCSGJ 6th, tumor node metastasis stage by Liver Cancer Study Group of Japan, 6th edition; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1; CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease; BSC, best supportive care; SOR, sorafenib; REG, regorafenib; RAM, ramucirumab; HAIC, hepatic arterial infusion chemotherapy; na, not applicable; LEN, lenvatinib; IPW, inverse probability weighting. ^aMedian values (interquartile range) are shown as numbers, unless otherwise indicated. ^bEvaluated by RECIST 1.1.

Table 2. AEs in both groups

	Before PD ^a			AEs occurred during beyond PD ^a treatment with LEN
	group A (n = 26) (grade 0:1:2:3)	group B (n = 73) (grade 0:1:2:3)	p value	group B (grade 1:2:3)
HFSR	22:2:1:1	44:13:16:0	0.019	1:2:0
Appetite loss	16:2:7:1	46:14:10:3	0.286	6:7:0
General fatigue	15:6:4:1	52:10:11:0	0.227	3:1:0
Hypertension	22:1:2:1	54:5:12:2	0.679	1:0:0
Urine protein	20:3:1:2	55:6:7:5	0.838	0:4:2
Abnormality of thyroid function	17:4:4:1	49:9:14:1	0.763	1:1:1
Diarrhea	22:3:2:1	55:11:6:1	0.639	2:3:0
Elevation of the levels of NH3	23:0:0:3	67:1:1:4	0.665	1:0:1
Hoarseness	23:3:0:0	58:13:2:0	0.754	3:0:0
Decreasing the levels of platelet count	25:0:0:1	70:0:1:2	1.000	None
Elevation of the levels of transaminase	25:1:0:0	71:1:0:1	0.603	0:3:0
Other AEs of grade 3	None	Body weight loss (n = 1) Fever up (n = 1) Neutropenia (n = 1)	1.00	Fever up (n = 3)

LEN, lenvatinib; PD, progression of disease; AE, adverse event; HFSR, hand-foot skin reaction; na, not applicable. ^a Evaluated by RECIST 1.1.

while that by RECIST was 8.1 months (online suppl. Fig. 1a, b). These results were the same as previously reported by Kaneko et al. [29], in which PD judgment by RECIST and mRECIST showed similar clinical weight in regard to prognosis. Based on the above, we used RECIST 1.1 to evaluate using common criteria, as previously reported in trials of SOR [2], REG [3], and RAM [8, 9] in the present study.

Clinical Characteristics of Final Analyzed Group of 99 Patients

Significant differences were observed in etiology of basal liver diseases, serum levels of total bilirubin, prothrombin time, AFP at introducing LEN, maximum size of intrahepatic tumor, TNM-LCSGJ at introducing LEN, ECOG PS at time of PD, AFP at time of PD (before or after 1-month PD), and BCLC stage at time of PD between the A and B groups (Table 1). Postprogression treatment in the A group was best supportive care in 17, sorafenib in 4, regorafenib in 3, ramucirumab in 1, and hepatic arterial infusion chemotherapy in 1 (online suppl. Table 1). Of the 9 patients, who received postprogression therapies, in the A group, 8 showed PD and 1 had no evaluation at the time of analysis. On the other hand, 6 were treated with dose-up, 59 with the same dose, and 8 with more reduced dose after PD in the B group. Except for patients received combination with other therapeutic modalities

(RFA 1, TACE 3, or HAIC 2) (n = 6) and 1 patient without following imaging data (n = 1), only 2 showed no progression after PD by the same dose, while 64 showed continuous progression.

Adverse Events

AEs during LEN treatment are shown in Table 2. Although only HFSR was more frequent in the B group than the other (grade 0:1:2:3 = 44:13:16:0 vs. 22:2:1:1. *p* = 0.019), there were no significant differences in other AEs (Table 2).

Administration Period of LEN, Relative Changes in ALBI Score, and Therapeutic Responses

There was no significant difference for TTP between the A and B groups (median 4.0 vs. 6.0 months, *p* = 0.514). The LEN administration period in the A group was shorter (median 4.5 vs. 12.6 months, *p* < 0.001) (Fig. 2a, b). Best therapeutic response by RECIST (*p* = 0.862), ALBI score at the time of PD (*p* = 0.467), frequency of Child-Pugh class A at time of PD (*p* = 0.199), decline of ECOG at time of PD from baseline (*p* = 0.141), and relative change in ALBI score from the baseline at the time of PD (delta ALBI score) (*p* = 0.691) did not show significant differences between the groups. In addition, PD patterns also did not show a significant difference between both groups (*p* = 0.939) (Table 1).

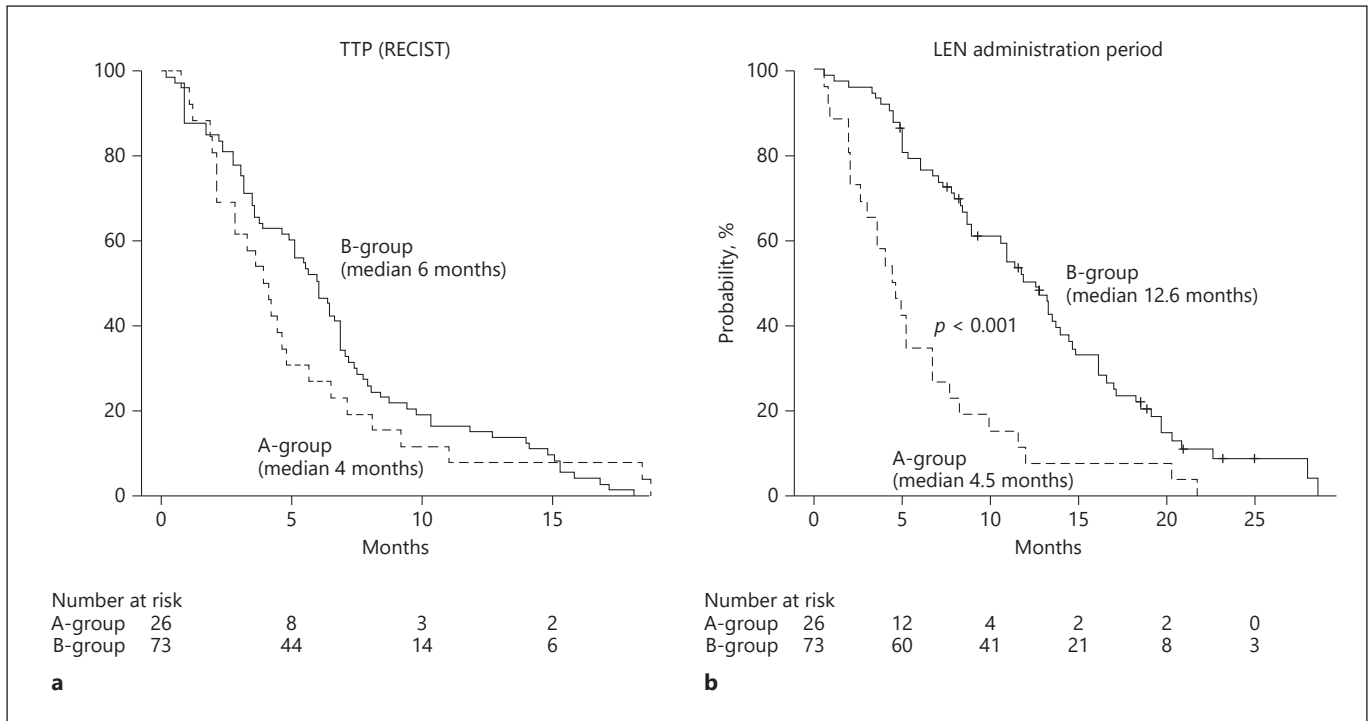


Fig. 2. a TTP shown by RECIST 1.1. **b** Period of lenvatinib administration. TTP, time to progression; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

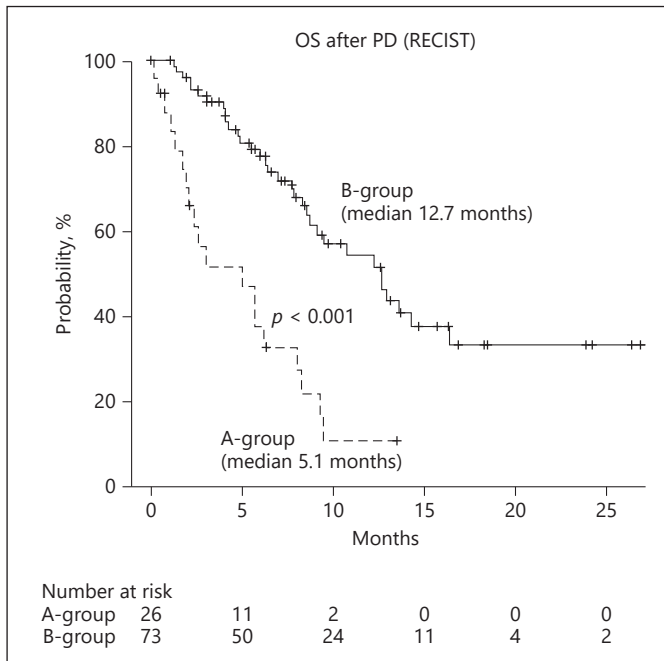


Fig. 3. OS after first PD, shown by RECIST 1.1. (A group: dotted line, B group: solid line). OS, overall survival; PD, progression of disease; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

OS after PD

Of the 99 u-HCC patients analyzed, 52 died during the observation period (A vs. B group = 73.1 vs. 45.2%, $p = 0.021$) (Table 1). OS after PD was better in the B group as compared to the A group (12.7 vs. 5.1 months, $p < 0.001$) (Fig. 3). In the A group, although when the same analysis was performed after adjusting with IPW, the B group showed better prognosis in regard to OS after PD (10.8 vs. 5.8 months, $p < 0.001$) (Fig. 4a). As a result, OS after introducing LEN was also better in the B group than the A group (19.6 vs. 11.2 months, $p < 0.001$) (Fig. 4b).

In Cox hazard univariate analysis after adjustments with IPW, prognostic factors for OS following PD were mALBI 2b or 3 at the time of PD (HR 2.160, $p = 0.008$), decline of ECOG PS from baseline at time of PD (HR 3.578, $p < 0.001$), elevated AFP (≥ 100 ng/mL) at time of introducing LEN (HR 1.804, $p = 0.047$), PD pattern (appearance of new EHM) (HR 2.105, $p = 0.013$), positive for HFSR before PD (any grade) (HR 0.370, $p = 0.002$), and continuing LEN beyond PD (HR 0.444, $p = 0.014$), while mALBI 2b or 3 at the time of PD (HR 1.983, $p = 0.021$), decline of ECOG PS from baseline at time of PD

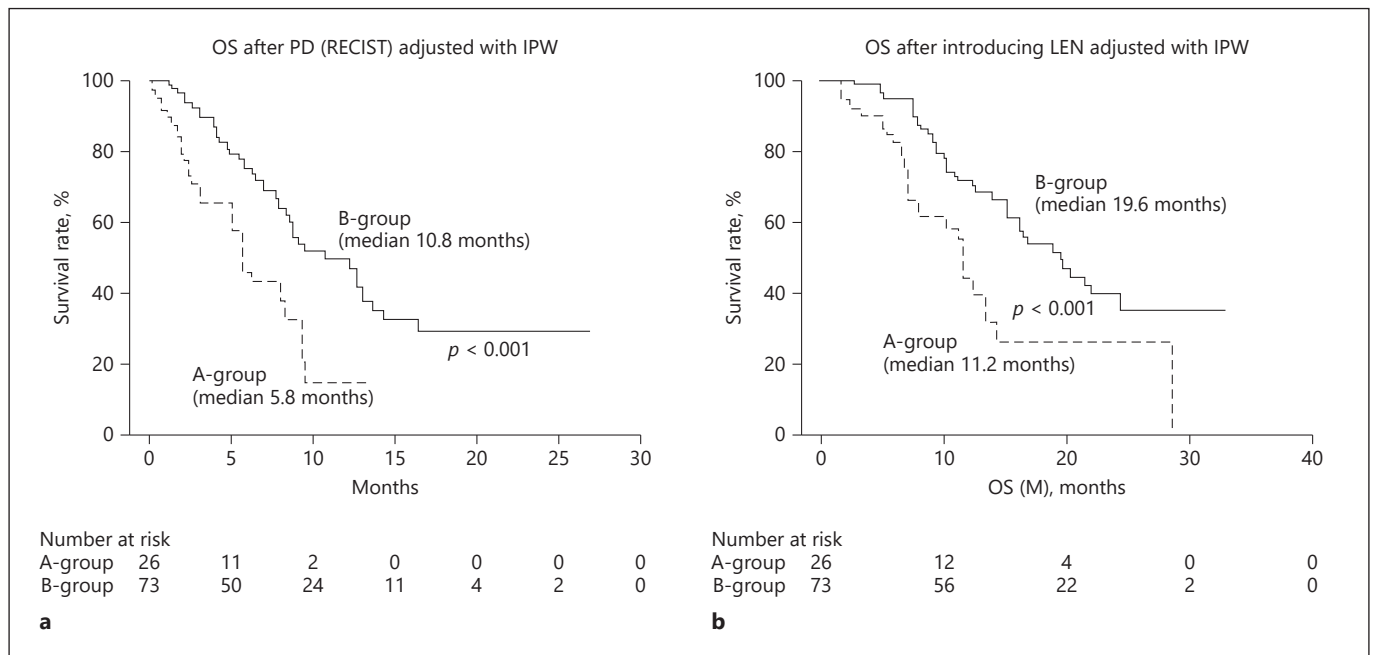


Fig. 4. OS after first PD by RECIST 1.1 following adjustment with IPW (**a**) and OS after introducing lenvatinib, adjusted with IPW (**b**) (A group: dotted line, B group: solid line). OS, overall survival; PD, progression of disease; IPW, inverse probability weighting; RECIST, Response Evaluation Criteria In Solid Tumors version 1.1.

(HR 3.180, $p < 0.001$), elevated AFP (≥ 100 ng/mL) at time of introducing LEN (HR 2.511, $p = 0.004$), PD pattern (appearance of new extrahepatic metastasis) (HR 2.396, $p = 0.006$), positive for HFSR before PD (any grade) (HR 0.292, $p < 0.001$), and continuing LEN beyond PD (HR 0.297, $p < 0.001$) were significant factors in multivariate analysis (Table 3). When OS after PD was evaluated in patients with Child-Pugh class A and ECOG PS 0/1 at time of PD, the B group showed better OS after PD than the other (MST 13.0 vs. 8.1 months, $p = 0.027$) (online suppl. Fig. 2). In the patients with Child-Pugh A and ECOG PS 0/1 at time of PD of the A group, although 8 patients, who received post progression treatments ($n = 8$), showed longer median OS than those with BSC ($n = 7$) (8.8 vs. 5.1 months, respectively), there was no significant difference statistically ($p = 0.324$). In the patients with Child-Pugh A and ECOG PS 0/1 at time of PD of the A group, although 8 patients, who received post progression treatments ($n = 8$), showed longer median OS than those with BSC ($n = 7$) (8.8 vs. 5.1 months, respectively), there was no significant difference statistically ($p = 0.324$).

Discussion

In the present study, clinical factors and prognosis at the time of PD in u-HCC patients treated with LEN were assessed. Interestingly, the prognosis of u-HCC patients for whom LEN treatment was discontinued after PD (A group) was significantly worse as compared to those who continued LEN beyond PD (B group), with the same result observed following adjustment with IPW. Our results showed that mALBI (2b or 3) at time of PD, decline of ECOG PS from baseline at time of PD, elevated AFP (≥ 100 ng/mL) at time of introducing LEN, PD pattern (appearance of new EHM), positive for HFSR (any grade), and continuing LEN beyond PD were significant prognostic factors for OS following PD. Although Fu et al. [30] reported that BCLC-B ($p = 0.002$) and intrahepatic PD ($p = 0.024$) were significantly correlated with post-disease progression OS in SOR treatment, BCLC stage and intrahepatic PD patterns were not significant prognostic factors in the present study. Of course, it is reasonable that malignant potential of tumors (elevated tumor marker), worse hepatic function, and decline of ECOG PS were negative prognostic factors for survival. In addition, the present results showed that AE of HFSR

Table 3. Cox hazard analysis of characteristics and prognostic factors for overall survival after PD by RECIST 1.1 adjusted with IPW in u-HCC patients ($N = 99$)

	HR	Univariate analysis 95% CI	p value	HR	Multivariate analysis 95% CI	p value
Elderly (age ≥ 75 years)	1.363	0.789–2.355	0.266			
Female gender	1.576	0.878–2.829	0.128			
Negative for hepatitis virus	1.508	0.791–2.878	0.213			
Started with reduced dose of LEN	1.262	0.610–2.610	0.531			
mALBI grade 2b/3 (ALBI score > -2.27) at introduction of LEN	1.519	0.902–2.557	0.116			
mALBI grade 2b/3 (ALBI score > -2.27) at time of PD	2.160	1.218–3.829	0.008	1.983	1.109–3.545	0.021
ECOG PS 1 at introduction of LEN	1.181	0.419–3.333	0.753			
Decline of ECOG PS from baseline at time of PD	3.578	2.010–6.365	< 0.001	3.180	1.722–5.872	< 0.001
BCLC-C at time of LEN introduction	1.323	0.754–2.323	0.329			
BCLC-C/D at time of PD	1.296	0.722–2.328	0.386			
AFP ≥ 100 ng/mL at time of LEN introduction	1.804	1.008–3.229	0.047	2.511	1.347–4.679	0.004
AFP ≥ 100 ng/mL at time of PD	1.608	0.884–2.924	0.120			
Positive for history of MTA treatment	1.275	0.726–2.237	0.398			
No response to LEN	1.444	0.853–2.444	0.172			
PD pattern, appearance of new EHM	2.105	1.173–3.777	0.013	2.396	1.291–4.449	0.006
PD pattern, appearance of MVI	0.273	0.042–1.787	0.176			
PD pattern, appearance of intrahepatic new lesion	1.047	0.610–1.797	0.868			
PD pattern, increasing size without new lesion	0.859	0.486–1.517	0.600			
HFSR (any grade) before PD	0.370	0.200–0.685	0.002	0.292	0.151–0.566	< 0.001
LEN continued beyond PD	0.444	0.232–0.848	0.014	0.297	0.163–0.541	< 0.001

u-HCC, unresectable hepatocellular carcinoma; IPW, inverse probability weighting; HR, hazard ratio; CI, confidential interval; HCV, hepatitis C virus; LEN, lenvatinib; mALBI, modified albumin-bilirubin grade; BCLC-C, Barcelona Clinic Liver Cancer stage C; AFP, alpha-fetoprotein; MTA, molecular targeting agent; EHM, extrahepatic metastasis; MVI, major portal vein tumor thrombosis (Vp3 and Vp4); HFSR, hand-foot skin reaction; PD, progression of disease.

(any grade) and continuing LEN beyond PD were positive prognostic factors for survival after first PD. Regarding HFSR, it has been reported as a positive prognostic factor for better prognosis in SOR treatment [31] as well as LEN treatment [6]. Moreover, in previous studies, Miyahara et al. [32] and Wada et al. [33] analyzed continuation of SOR treatment beyond first PD confirmation before development of second-line chemotherapy, respectively. With no present establishment of effective postprogression therapy after LEN failure and when no rapid progression is noted during LEN treatment and control of AE is obtained in u-HCC patients whose ECOG PS and hepatic function permit, our data suggest that continuation of that beyond PD might be a reasonable therapeutic option. In SOR treatment, Miyahara et al. [32] reported that the patients, who stopped SOR at PD, showed increasing tumor growth, while those who continued SOR beyond first PD did not ($p = 0.002$). Although the present database has few data concerning with growth rates of tumors, especially of the A group,

and there was a continuous tendency of PD after first PD was observed in many patients of the B group, continuing LEN beyond PD also might play a role in curbing rapid progression. Nevertheless, based on the present results, establishment of effective postprogression modalities following LEN failure is urgently needed.

There is increasing recognition regarding the clinical importance of MTA sequential treatment for improving the prognosis of u-HCC patients. Since introduction of REG as second-line treatment for SOR, it has been reported that MTA sequential treatment has a greater contribution to improving prognosis as compared to single MTA line treatment [34]. LEN was recently developed as a first-line MTA drug [5], though it also serves as a second- and even third-line treatment option in Japan [7, 35–39]. We previously reported that the total MTA administration period including LEN treatment had a good correlation with OS after introduction of the initial MTA drug (SOR in 95.2% of those patients) ($r = 0.946$, 95% CI: 0.918–0.965, $p < 0.001$), with a median OS after that in-

roduction of 46.2 months [40]. Those results suggest that SOR has effective postprogression treatment options. In contrast, no effective postprogression treatment has been established after LEN treatment failure, which is an important unmet clinical need. In the REFLECT trial, patients treated with LEN showed significantly better progression-free survival (PFS) as compared to those treated with SOR (7.4 vs. 3.7 months; HR 0.66, 95% CI: 0.57–0.77) [5]. However, even though SOR was available as a postprogression option in patients treated with LEN in that trial, LEN did not show superiority to SOR in regard to OS (median 13.6 vs. 12.3 months; HR 0.92, 95% CI: 0.79–1.06) [5]. In another study of 25 patients treated with SOR after LEN failure, a poor disease control rate shown by mRECIST (16.0%) and PFS (1.8 months) was reported [41]. A future analysis is needed to elucidate which order of sequential treatment is better, SOR followed by LEN or LEN by SOR.

A previous study found that the percentage of patients given LEN as first-line treatment and who maintained Child-Pugh A, in whom RAM was indicated, was low (approximately 20%) at the time of LEN failure [42]; thus, no conclusions could be reached regarding whether ramucirumab is an effective next-line treatment following LEN. Kuzuya reported good therapeutic usefulness following LEN failure in 12 u-HCC patients (disease control rate [DCR]: 80%) [43], whereas the results presented by our group were not similar in 28 u-HCC patients under the same situation (DCR: 42.3%) [44]. Future analysis for therapeutic effect of RAM after LEN failure will be needed. In any case, based on results of animal experimentation, Yang et al. [45] suggested that host hepatocyte but not tumor cell-derived VEGF is responsible for facilitating cancer metastasis mechanistically and proposed that nonstop persistent anti-VEGF therapy be given as treatment for humans with cancer. To improve prognosis more in u-HCC patients treated with LEN, urgent development of effective MTA drugs following LEN failure is a crucial need.

In cases with transarterial catheter chemoembolization (TACE) refractoriness [46] or those unsuitable for TACE [47], clinical consensus indicates that switching to MTA treatment should be considered. In addition to a recent clinical trend of HCC treatment based on development of MTA drugs, combination treatment with atezolizumab and bevacizumab has been approved in September 2020 as a new first-line option, as that combination resulted in better OS and PFS as compared to sorafenib (median PFS: 6.8 vs. 4.3 months, HR 0.59, 95% CI: 0.47–0.76 [$p < 0.001$]; OS at 12 months: 67.2 vs. 54.6%, HR 0.58, 95% CI: 0.42–0.79 [$p < 0.001$]) [48]. Determination of a

better order of systemic chemotherapy agents to contribute to improved prognosis will become important for u-HCC treatment in clinical practice.

The present study has some limitations. First, even though this was a multicenter analysis, it was performed in a retrospective manner. Also, the number of patients analyzed was small. Finally, there were no defined criteria used for continuing LEN treatment or determining cessation of beyond PD treatment with LEN. A future study focusing on establishment of postprogression treatment after LEN failure, especially with a larger number of patients given LEN, is needed. Since it will be difficult to perform a randomized control study, a prospective observational study at minimum should be planned in the near future.

Although LEN is a powerful drug that serves not only as a first- but also as a second- and third-line option for treatment of u-HCC in the real-world clinical practice, the present results indicate that it might be better positioned as a late-line drug in selected patients with clinical reserves, such as ALBI grade 1 liver function or a nonaggressive tumor. Furthermore, when there is no decline of ECOG PS from baseline during LEN treatment and hepatic reserve function permits, it may be better to continue LEN treatment beyond PD, especially in u-HCC patients showed HFSR during LEN treatment, at least until a more effective drug as a postprogression treatment after LEN failure is developed. In any case, urgent development of effective drugs following LEN failure is an urgent unmet clinical need.

Statement of Ethics

The protocol of the present study was approved by the Institutional Ethics Committee of Ehime Prefectural Central Hospital (IRB No. 30-66), and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Written patient consent was obtained from all patients.

Conflict of Interest Statement

Atsushi Hiraoka, MD, PhD: lecture fees from Bayer, Eisai, and Otsuka. Takashi Kumada, MD, PhD: lecture fees from Eisai. Matsutoshi Kudo, MD, PhD: advisory role with Eisai, Ono, MSD, Bristol Myers Squibb, and Roche; lecture fees from Eisai, Bayer, MSD, Bristol Myers Squibb, Eli Lilly, and EA Pharma; and research funding from Gilead Sciences, Taiho, Sumitomo Dainippon Pharma, Takeda, Otsuka, EA Pharma, AbbVie, and Eisai. None of the other authors have potential conflicts of interest to declare.

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Author Contributions

A.H., T.K., M.H., K.Ts., E.I., N.S., H.S., S.Y., H.T., Y.K., Y.H., and M.Ku. conceived the study and participated in its design and coordination. A.H., T.K., T.T., K.ka., J.T., S.F., M.A., T.I., K.Tak.,

K.Taj., H.Oc., K.K., H.Oh., K.N., A.T., T.N., N.I., K.H., T.A., M.I., S.N., K.M., K.J., and M.K. performed data curation. A.H. performed statistical analyses and interpretation. A.H. and T.K. drafted the text. All authors have read and approved the final version of the manuscript.

References

- 1 Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. *Int J Cancer*. 2001 Oct 15;94(2):153–6.
- 2 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med*. 2008 Jul 24;359(4):378–90.
- 3 Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017 Jan 7;389(10064):56–66.
- 4 Terashima T, Yamashita T, Takata N, Nakagawa H, Toyama T, Arai K, et al. Post-progression survival and progression-free survival in patients with advanced hepatocellular carcinoma treated by sorafenib. *Hepatol Res*. 2016 Jun;46(7):650–6.
- 5 Kudo M, Finn RS, Qin S, Han K-H, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet*. 2018 Feb 9;391(10126):1163–73.
- 6 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 Jul;8(8):3719–28.
- 7 Hiraoka A, Kumada T, Kariyama K, Takaguchi K, Itobayashi E, Shimada N, et al. Therapeutic potential of lenvatinib for unresectable hepatocellular carcinoma in clinical practice: multicenter analysis. *Hepatol Res*. 2019 Jan;49(1):111–7.
- 8 Zhu AX, Finn RS, Galle PR, Llovet JM, Kudo M. Ramucirumab in advanced hepatocellular carcinoma in REACH-2: the true value of alpha-fetoprotein. *Lancet Oncol*. 2019 Apr;20(4):e191.
- 9 Kudo M, Okusaka T, Motomura K, Ohno I, Morimoto M, Seo S, et al. Ramucirumab after prior sorafenib in patients with advanced hepatocellular carcinoma and elevated alpha-fetoprotein: Japanese subgroup analysis of the REACH-2 trial. *J Gastroenterol*. 2020 Jun;55(6):627–39.
- 10 Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009 Jan;45(2):228–47.
- 11 Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis*. 2010 Feb;30(1):52–60.
- 12 Pugh RN, Murray-Lyon IM, Dawson JL, Pieteroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973 Aug;60(8):646–9.
- 13 Johnson PJ, Berhane S, Kagebayashi C, Sato-mura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade. *J Clin Oncol*. 2015 Feb 20;33(6):550–8.
- 14 Hiraoka A, Kumada T, Michitaka K, Toyoda H, Tada T, Ueki H, et al. Usefulness of albumin-bilirubin grade for evaluation of prognosis of 2584 Japanese patients with hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2016 May;31(5):1031–6.
- 15 Hiraoka A, Kumada T, Kudo M, Hirooka M, Tsuji K, Itobayashi E, et al. Albumin-bilirubin (ALBI) grade as part of the evidence-based clinical practice guideline for HCC of the Japan Society of Hepatology: a comparison with the liver damage and Child-Pugh classifications. *Liver Cancer*. 2017 Jun;6(3):204–15.
- 16 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. *Liver Cancer*. 2017 Nov;6(4):325–36.
- 17 Hiraoka A, Kumada T, Tsuji K, Takaguchi K, Itobayashi E, Kariyama K, et al. Validation of modified ALBI grade for more detailed assessment of hepatic function in hepatocellular carcinoma patients: a multicenter analysis. *Liver Cancer*. 2019 Mar;8(2):121–9.
- 18 Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology*. 2005 Nov;42(5):1208–36.
- 19 Di Martino M, Marin D, Guerrisi A, Baski M, Galati F, Rossi M, et al. Intraindividual comparison of gadoxetate disodium-enhanced MR imaging and 64-section multidetector CT in the detection of hepatocellular carcinoma in patients with cirrhosis. *Radiology*. 2010 Sep;256(3):806–16.
- 20 Sano K, Ichikawa T, Motosugi U, Sou H, Muhi AM, Matsuda M, et al. Imaging study of early hepatocellular carcinoma: usefulness of gadoxetic acid-enhanced MR imaging. *Radiology*. 2011 Dec;261(3):834–44.
- 21 Hiraoka A, Ichiryu M, Tazuya N, Ochi H, Tanabe A, Nakahara H, et al. Clinical translation in the treatment of hepatocellular carcinoma following the introduction of contrast-enhanced ultrasonography with Sonazoid. *Oncol Lett*. 2010 Jan;1(1):57–61.
- 22 Hiraoka A, Hiasa Y, Onji M, Michitaka K. New contrast enhanced ultrasonography agent: impact of Sonazoid on radiofrequency ablation. *J Gastroenterol Hepatol*. 2011 Apr;26(4):616–8.
- 23 Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet*. 2018 Mar 31;391(10127):1301–14.
- 24 The Liver Cancer Study Group of Japan. *The general rules for the clinical and pathological study of primary liver cancer*. 6th ed. Tokyo: Kanehara; 2015. p. 26.
- 25 National, Cancer, Institutie. Available from: https://ctepcancer.gov/protocolDevelopment/adverse_effects.htm Accessed 2020 Jun 30.
- 26 Xie J, Liu C. Adjusted Kaplan-Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. *Stat Med*. 2005 Oct 30;24(20):3089–110.
- 27 Kim HT. Cumulative incidence in competing risks data and competing risks regression analysis. *Clin Cancer Res*. 2007 Jan 15;13(2 Pt 1):559–65.
- 28 Kanda Y. Investigation of the freely available easy-to-use software ‘EZR’ for medical statistics. *Bone Marrow Transplant*. 2013 Mar;48(3):452–8.
- 29 Kaneko S, Tsuchiya K, Kurosaki M, Kirino S, Inada K, Yamashita K, et al. Three criteria for radiological response on survival in patients with hepatocellular carcinoma treated with lenvatinib. *Hepatol Res*. 2020 Jan;50(1):137–43.
- 30 Fu SR, Zhang YQ, Li Y, Hu BS, He X, Huang JW, et al. Sorafenib continuation after first disease progression could reduce disease flares and provide survival benefits in patients with hepatocellular carcinoma: a pilot retrospective study. *Asian Pac J Cancer Prev*. 2014;15(7):3151–6.
- 31 Ogawa C, Morita M, Omura A, Noda T, Kubo A, Matsunaka T, et al. Hand-foot syndrome and post-progression treatment are the good predictors of better survival in advanced hepatocellular carcinoma treated with sorafenib: a multicenter study. *Oncology*. 2017;93(Suppl 1):113–9.
- 32 Miyahara K, Nouse K, Morimoto Y, Takeuchi Y, Hagihara H, Kuwaki K, et al. Efficacy of sorafenib beyond first progression in patients with metastatic hepatocellular carcinoma. *Hepatol Res*. 2014 Mar;44(3):296–301.

- 33 Wada Y, Takami Y, Tateishi M, Ryu T, Mikagi K, Saito H. The efficacy of continued sorafenib treatment after radiologic confirmation of progressive disease in patients with advanced hepatocellular carcinoma. *PLoS One*. 2016;11(1):e0146456.
- 34 Finn RS, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, et al. Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: additional analyses from the phase III RESORCE trial. *J Hepatol*. 2018 Aug;69(2):353–8.
- 35 Hiraoka A, Kumada T, Kariyama K, Takaguchi K, Atsukawa M, Itobayashi E, et al. Clinical features of lenvatinib for unresectable hepatocellular carcinoma in real-world conditions: multicenter analysis. *Cancer Med*. 2019 Jan;8(1):137–46.
- 36 Fuchigami A, Imai Y, Uchida Y, Uchiya H, Fujii Y, Nakazawa M, et al. Therapeutic efficacy of lenvatinib for patients with unresectable hepatocellular carcinoma based on the middle-term outcome. *PLoS One*. 2020;15(4):e0231427.
- 37 Ogasawara S, Ooka Y, Itokawa N, Inoue M, Okabe S, Seki A, et al. Sequential therapy with sorafenib and regorafenib for advanced hepatocellular carcinoma: a multicenter retrospective study in Japan. *Invest New Drugs*. 2020 Feb;38(1):172–80.
- 38 Sho T, Suda G, Ogawa K, Kimura M, Shimazaki T, Maehara O, et al. Early response and safety of lenvatinib for patients with advanced hepatocellular carcinoma in a real-world setting. *JGH Open*. 2020 Feb;4(1):54–60.
- 39 Takahashi A, Moriguchi M, Seko Y, Shima T, Mitsumoto Y, Takashima H, et al. Early tumor shrinkage as a predictive factor for outcomes in hepatocellular carcinoma patients treated with lenvatinib: a multicenter analysis. *Cancers*. 2020 Mar 23;12(3):754.
- 40 Hiraoka A, Kumada T, Atsukawa M, Hirooka M, Tsuji K, Ishikawa T, et al. Important clinical factors in sequential therapy including lenvatinib against unresectable hepatocellular carcinoma. *Oncology*. 2019;97(5):277–85.
- 41 Maruta S. Post-treatments of lenvatinib in patients with advanced hepatocellular carcinoma. *Hepatol Int*. 2020;14(Suppl 1):S234–35.
- 42 Hiraoka A, Kumada T, Fukunishi S, Atsukawa M, Hirooka M, Tsuji K, et al. Post-progression treatment eligibility of unresectable hepatocellular carcinoma patients treated with lenvatinib. *Liver Cancer*. 2020 Jan;9(1):73–83.
- 43 Kuzuya T, Ishigami M, Ito T, Ishizu Y, Honda T, Ishikawa T, et al. Initial experience of ramucirumab treatment after lenvatinib failure for patients with advanced hepatocellular carcinoma. *Anticancer Res*. 2020 Apr;40(4):2089–93.
- 44 Hiraoka A, Kumada T, Tada T, Ogawa C, Tani J, Fukunishi S, et al. Therapeutic efficacy of ramucirumab after lenvatinib for post-progression treatment of unresectable hepatocellular carcinoma. *Gastroenterol Rep*. 2020.
- 45 Yang Y, Zhang Y, Iwamoto H, Hosaka K, Seki T, Andersson P, et al. Discontinuation of anti-VEGF cancer therapy promotes metastasis through a liver revascularization mechanism. *Nat Commun*. 2016 Sep 1;7:12680.
- 46 Kudo M, Matsui O, Izumi N, Kadoya M, Okusaka T, Miyayama S, et al. Transarterial chemoembolization failure/refractoriness: JSH-LCSGJ criteria 2014 update. *Oncology*. 2014; 87(Suppl 1):22–31.
- 47 Kudo M, Han KH, Ye SL, Zhou J, Huang YH, Lin SM, et al. A changing paradigm for the treatment of intermediate-stage hepatocellular carcinoma: Asia-Pacific primary liver cancer expert consensus statements. *Liver Cancer*. 2020 Jun;9(3):245–60.
- 48 Finn RS, Qin S, Ikeda M, Galle PR, Ducreux M, Kim T-Y, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med*. 2020 May 14;382(20):1894–905.